Contemporary OB/GYN

Essure tubal reversal
A novel approach

Jon I. Einarsson, MD, PhD, MPH, and Nisse V. Clark, MD

TECHNOLOGY EDITORIAL
The future of gynecologic surgery

The benefits of simulation training

ACOG COMMENTARY
Tubal ectopic pregnancy

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IN THIS ISSUE

October 2018

Volume 63 | Number 10

Our editor-in-chief looks at recent studies on induction in healthy nulliparas.

Technology Editorial

48 Gynecologic surgery’s future
Jon I Einarsson, MD, PhD, MPV

Innovation may be the main driving force for improvements in the specialty, but training and regulation also play a part.

Tech News Updates

23 Female health technology

Research reports on a women’s health market shifting towards digitalization and expanding use of genetic testing.

Peer-Reviewed

32 Simulation technology’s benefits for L&D
Shad Deering, MD

Use of simulations to train on labor and delivery is increasing and studies show it can help reduce maternal morbidity.

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The cornerstone of obstetrics is the determination of when it is better for the mother and her fetus to effect delivery. Much attention over the past decade has been focused on avoiding truly elective deliveries prior to 39 weeks because of the risks of iatrogenic prematurity. Conversely, given the increase in perinatal mortality attendant post-term gestations, it has been the longstanding policy of the American College of Obstetricians and Gynecologists (ACOG) to consider induction of labor (IOL) between 41 0/7 and 41 6/7 weeks' gestation and to recommend IOL after 42 0/7 weeks.1

However, between 39 and 42 weeks, there are multiple risks to mother and fetus associated with continuing the pregnancy. Perinatal mortality rates nadir at 39 weeks as neonatal risks from prematurity fade and rates of stillbirth grow.2 Beyond 39 weeks, pregnancies are at increased risk of placental insufficiency, preeclampsia, and macrosomia, all of which are associated with increased cesarean delivery rates, not to mention increased maternal, perinatal, and neonatal mortality and/or morbidity. These findings all suggest that elective IOL at 39 weeks could reduce adverse pregnancy outcomes and lower cesarean delivery rates compared to expectant management. While older literature did not support this thesis, recent studies suggest that this is indeed the case.

Older studies were flawed
Prior observational studies of the benefits of elective IOL were faulty because they used “spontaneous labor” as the control group. By excluding patients with subsequent post-dates and medically indicated inductions, they biased results toward lower stillbirth and cesarean delivery rates in “control” groups. Because the actual clinical choice is not between elective IOL versus spontaneous labor, but rather between elective IOL compared with expectant management, these older studies did not mirror clinical decision-making. In 2009, Caughey and associates conducted a systematic review of nine randomized clinical trials of elective IOL at either < 41 or ≥ 41 weeks compared with expectant management and noted that overall, the latter was associated with an increased cesarean delivery rate (OR 1.22; 95% CI: 1.07-1.39) but among women < 41 weeks, no significant differences were noted.3 However, the authors reported that the two studies conducted at < 41 weeks were of poor quality and not generalizable to current practice. Stock and associates conducted a large retrospective cohort study among 1.27 million Scottish women delivering between 1981 to 2007 with singleton gestations ≥ 37 weeks to compare cesarean delivery rates, perinatal mortality, and neonatal and maternal outcomes for those with elective IOL vs. expectant management.4 They noted that at 39 weeks, elective IOL was associated with decreased perinatal mortality (0.06% versus 0.18%, P < 0.001; adj OR of 0.28; 99% CI: 0.12-0.67), with a

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minimal increase in cesarean delivery rates 9.3 versus 8.4% (adj OR: 1.08, 1.00-1.16). However, the problems with these older studies include non-standardized definitions of successful induction, variable induction methods, and heterogenous populations.

Recent studies
In 2016, Walker and colleagues reported on their small clinical trial among 618 nulliparous woman ≥ 35 years with singleton pregnancies randomized to elective IOL at 39 weeks versus expectant management until spontaneous labor or medically or obstetrically indicated delivery. They observed no differences in cesarean rates (RR 0.99; 95%CI: 0.87-1.14) and no differences in operative vaginal delivery, infant deaths, or women’s experience of childbirth. The chief problem with this study was its lack of power, given the rarity of many of these adverse outcomes.

To address the issue of sample size and rare outcomes, Sinkey and associates conducted a comparative effectiveness study using a sophisticated Monte Carlo micro-simulation model to compare elective IOL at 39 weeks with expectant management including delivery for standard medical or obstetrical indications, or at 41 weeks if undelivered. They based their decision support probabilities of potential maternal and perinatal outcomes on an exhaustive review of the literature and data derived from the Consortium on Safe Labor. They also conducted sensitivity analyses based on maternal preferences for optimizing maternal versus infant health using weighted utilities. The primary objective was to determine which management strategy posed less maternal and neonatal risk. Secondary outcomes were rates of cesarean deliveries, maternal morbidity and mortality, stillbirth, neonatal morbidity and mortality, and preferences regarding the importance of maternal and perinatal health.

The authors found that elective IOL at 39 weeks resulted in lower cesarean delivery rates (13.9% versus 35.9%, P < 0.01) even among women with unfavorable cervices (8.0% versus 26.1%, P < 0.01). Conversely, there was an increase in maternal morbidity in the expectant management group (21.2% versus 16.5%, P < 0.01) as well as more stillbirths (0.13% versus 0%, P < 0.0003), neonatal deaths (0.25% versus 0.12%, P < 0.03), and neonatal morbidity (12.1% versus 9.4%, P < 0.01). These findings persisted after adjustment for maternal preferences. This decision model simulated a far larger population (> 100,000 women) than any clinical trial could hope to enroll.

Even more recently, Grobman and colleagues conducted a large prospective multicenter trial among low-risk nulliparous women with a vertex presentation who in their 38th week were randomized to either elective IOL (n=3062) at 39 0/7 to 39 4/7 weeks or expectant management (n=3044).7 No specific induction protocol was mandated. A composite of perinatal death or severe neonatal morbidity was the primary endpoint and cesarean delivery was the secondary outcome. Composite perinatal morbidity was less common in the elective IOL group than in the expectant management group (4.3% versus 5.4%; RR of 0.80; 95% CI: 0.64-1.00). In addition, cesarean delivery rates were lower in the elective IOL group (18.6% versus 22.2%; RR of 0.84; 95% CI: 0.76-0.93) as were rates of hypertension (9.1% versus 14.1%) (RR of 0.64; 95%CI: 0.56-0.74). Conversely, median labor pain scores were higher and average lengths of stay longer in the expectant management group. Subgroup analysis found no differences in results based on maternal race, age, or body mass index nor any effect from initial Bishop score. The results of the ARRIVE trial (A Randomized Trial of Induction Versus Expectant Management) add further evidence to the value of elective IOL at 39 weeks.

Take-home message
I don’t think we should be surprised by these recent studies. Term stillbirths are frequently related to placental insufficiency and cord accidents, which explains why stillbirths and neonatal morbidity stochastically increase with advancing gestational age. Simply not being in utero would reduce such risks. As for the lower cesarean delivery rates accompanying elective IOL, this may reflect a combination of: (1) fewer cesarean delivery-
Gynecologic surgery’s future
How innovation, training, and regulation all play a role

Innovation is a major component of gynecologic surgery and surgeons at all levels play a role in progressing the specialty.

As gynecologic surgery continues to evolve rapidly, it is easy to forget the origins of our specialty. Only 205 years ago, Conrad Langenbeck performed the first planned hysterectomy on record. It was a vaginal procedure done in the surgeon’s living room with no assistants and he had to use his teeth at one point to tie suture. Miraculously the patient survived, but no one believed that Dr. Langenbeck actually performed this procedure until it was confirmed at autopsy several years later.

In today’s environment, the laparotomy approach is still overutilized, but it is now gradually being replaced by laparoscopic and robotic surgery. The original minimally invasive method, the vaginal hysterectomy, is slowly on the decline despite efforts by the American College of Obstetricians and Gynecologists to turn the tide. There is no question that vaginal hysterectomy is a great minimally invasive approach, but with fewer surgeons capable of teaching this skill and a paucity of technological innovation in this space, vaginal hysterectomy has been left wanting compared with the laparoscopic approach. In this regard, other developments on the horizon, which I will discuss later, have the ability to further cement the laparoscopic minimally invasive visual approach as the primary mode of access for gynecologic surgery.

The impact of MIGS training and subspecialists
As compared with vaginal hysterectomy, one important factor tilting the scales is development of minimally invasive gynecologic surgery (MIGS) fellowship programs. Over 300 MIGS-trained subspecialists have graduated from fellowship programs since 2001, and every year 30 to 40 new MIGS-trained subspecialists pollinate the US landscape and start to operate on patients. Introduction of high-volume MIGS subspecialists is changing the landscape of gynecologic surgery, moving a large portion of the surgical volume away from generalist specialists to MIGS specialists. A similar evolution happened in gynecologic oncology a couple of decades ago with the advent of gynecologic oncology fellowships. Whether this is the ideal solution for the discipline as a whole can be argued, but it is likely that within the next 10 to 20 years, most complex benign gynecologic surgeries will be performed by subspecialists and several recent studies have...
demonstrated in multiple arenas that high-volume surgeons have better outcomes and fewer complications.

The robotic surgery landscape
Another exciting development is a new revolution in robotic surgery that we are about to witness. Until recently, Intuitive Surgical was the only game in town, but recently the Senhance surgical robotic system was launched in the United States. Other robotic systems are on the horizon, some from major players in the market such as Medtronic and J&J in collaboration with Google, but also a variety of systems from other companies. It seems evident that with increasing competition, innovation will be rapid and prices will come down. This will benefit patients and surgeons and reduce the overall cost of the healthcare system. While I have personally been critical of robotic surgery as a poor value proposition in its current iteration, I now see the possibility that in time, robotic surgery will be offered at a significantly lower cost and offer true value such as automation and greater safety for patients.

Visual improvements
Augmented visualization is also going to be something we will see increasingly in the near future.

Fluorescence-guided surgery is already in clinical use, but several companies are developing tools that incorporate augmented reality in which three-dimensional images from computed tomography or magnetic resonance imaging can be overlaid onto the surgeon’s console or monitored in real time. This can help the surgeon better determine exactly where to make an incision and see healthy tissue margins. There are also several dyes and imaging enhancements being developed for display of various tissue types on the monitor in distinct colors. In time, a surgeon will be able to see the anatomy almost as if it were in an anatomy atlas, with nerves, ureter, bowel, and muscles all in different colors on the monitor. Essentially, it will be a kind of a surgical GPS that guides the surgeon to address the correct pathology while avoiding injury to vulnerable nearby structures.

Continued innovation is the driver of this progress. Large multinational medical device companies lead the way in development of novel medical devices and equipment, but the importance of small startups should not be underestimated. Small startups are generally run by passionate and knowledgeable founders who have identified a significant unmet need and are able to move quickly through development of their devices because of their small organizational structure and the unified drive of the group. The main challenge for small startups is access to funding and it is well recognized that most of these companies will ultimately fail, often because they run out of money. However, there are inspiring success stories. One is Surbhi Sarna (now 32 years old) who was diagnosed at age 13 with ovarian cysts. Her doctors did not know if the cysts were cancerous, which inspired Ms. Sarna to found a company, nVision Medical. The company raised $17 million in venture capital and received approval from the US Food and Drug Administration (FDA) to develop a specialized device to detect ovarian cancer before being acquired by Boston Scientific for $275 million. It is obvious that Ms. Sarna is a very gifted individual to have accomplished this at such a young age, but it is nevertheless a good example of the power of the individual entrepreneurial spirit.

Navigating the regulatory system
The regulatory environment for medical devices has recently come under increased scrutiny, such as is shown in "The Bleeding Edge." In this documentary, the medical device industry is painted in a rather negative light, with the focus on (among other things) issues that are directly pertinent to women’s health, such as Essure sterilization implants, vaginal mesh, and robotic surgery. The documentary highlights some potential problems with the current regulatory system for medical devices. The 510(k) pathway enables
medical device companies to bring a device to market based on a similar device that is already on the market, called a predicate device. The problem is that sometimes the approval of that predicate device is based on a string/hierarchy of other predicate devices, meaning that the original predicate device is no longer on the market and in some cases may be outdated.

On the other hand, the 510(k) pathway enables small startups to bring their innovations to market without going through the premarket approval (PMA) process, which includes a clinical trial, a usually cost prohibitive step. In addition, even if a clinical trial is done, it may not necessarily prevent injury or issues for patients later on. An example of this is the Essure sterilization system. The device did go through the PMA process with a rigorous clinical trial, but because of the relatively short follow-up period, the problems associated with Essure were not discovered until several years after the clinical trial was completed.

The FDA’s current system for medical device approval is designed to balance the need to protect patients while continuing to encourage innovation. One obvious downfall is that the FDA’s MAUDE (Manufacturer and User Facility Device Experience) database relies on voluntary reporting from doctors, nurses, and patients while reporting is mandatory for manufacturers, importers, and device-user facilities. Consequently, there is a potential for underreporting and there is a risk for late detection of problems with medical devices, i.e., the issue is not detected by the FDA or authorities until there has been significant patient harm. There seems to be a need for a more comprehensive nationwide database to protect patients, wherein medical device complications are registered prospectively and registration is mandatory by all parties.

Take-home message
In summary, innovation in surgery is necessary if we wish to see improvements in patient safety and overall care. However, ideas alone are not the sole component. Innovation requires skilled surgeons willing to teach, less-skilled surgeons willing to learn, and a regulatory environment that properly protects patients without barriers that are too high to allow technology to evolve.

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Elective induction continued from page 10

ies for non-reassuring fetal testing again due to lower rates of placental insufficiency and cord compression; and (2) smaller infants, as fetal weight progressively increases with increasing gestational age. Macrosomia should also be less common among patients undergoing elective IOL at 39 weeks gestation. The ACOG advisory prudently notes that the obstetrician should consider a woman’s preference, available resources and ensure an adequate trial of labor is provided. From my perspective, the decision to be electively delivered at 39 weeks is an intensely personal one for mothers, and their desires should be of paramount importance. However, if a low-risk nulliparous patient whose fetus is in a vertex presentation asks me “when is the safest time for me and my fetus to deliver”, I would feel obligated to describe the outcomes of these studies.

Dr. Lockwood, editor in chief, is Senior Vice President, USF Health, and Dean, Morsani College of Medicine, University of South Florida, Tampa. He can be reached at DrLockwood@ubm.com.

FOR REFERENCES VISIT contemporaryobgyn.net/ElectiveInduction
Laparoscopic Essure tubal reversal: How we do it

With the impending withdrawal of Essure from the US market, OB/GYNs should know how to remove the device. The authors describe the traditional technique and their new approach.

by JON I. EINARESSON, MD, PHD, MPH, AND NISSE V. CLARK, MD

For over a decade, transcervical sterilization revolutionized gynecology by offering an office-based procedure for sterilization under local anesthesia. Essure® was the most successful hysteroscopic sterilization device on the market, approved for almost 16 years in the United States and with an estimated 750,000 devices sold worldwide. While Essure proved to be very effective in preventing pregnancy, recent years have seen a dramatic rise in the number of adverse events (AEs) associated with it reported to the US Food and Drug Administration (FDA). Several countries have withdrawn the product from the market and Bayer AG recently announced it will discontinue sales in the United States by the end of 2018.

A growing number of women are now seeking surgical removal of Essure due to suspected AEs such as pelvic pain, heavy bleeding, allergic reaction, and a multitude of other symptoms that may be related to the device. Essure removal is typically performed laparoscopically by removing both fallopian tubes as well as the interstitial portion of the microinsert. Many women also choose to undergo a cornual wedge resection or hysterec- tomy to ensure that the device and any fragments are completely excised.

Essure regret
Less commonly discussed is the issue of sterilization regret, a condition that affects up to 20% of sterilized women and likely some women with Essure. Traditionally, Essure sterilization is considered irreversible due to extensive scarring along a large portion of the fallopian tube. Most patients desiring pregnancy after Essure are advised to undergo in vitro fertilization (IVF), a readily-available alternative that has shown some success with Essure in situ. But what about women who desire removal of the device and restoration of fertility? For them, a procedure that removes the device and offers even a small chance of spontaneous pregnancy might be worthwhile.

Published experience with use of tubouterine anastomosis for Essure removal is limited as is literature on IVF for Essure regret.

A laparoscopic approach to device removal being tested by the authors appears to restore tubal patency, but no pregnancies have yet been recorded.
Essure reversal is uniquely challenging. The device’s polyethylene terephthalate fibers induce permanent fibrosis along almost half of the fallopian tube, including the interstitial segment. This leaves only a short segment of the distal fallopian tube available for direct attachment to the uterus. This type of procedure is termed a tubouterine anastomosis; a technique that dates back to the late 19th century (Figure 1).

Tubouterine anastomosis was first described for treating women with proximal tubal occlusion unrelated to sterilization. Proximal tubal occlusion can be caused by conditions such as chronic salpingitis, salpingitis isthmica nodosa, cornual fibroids, adhesive disease, and endometritis. Long before IVF, tubal cannulation and tubouterine anastomosis were attempted to restore tubal patency in women with proximal tubal occlusion. Tubouterine anastomosis was classically an open procedure in which fundal hysterotomy or cornual wedge resection was performed for excision of the affected fallopian tube and reimplantation of the distal fallopian tube to the uterine cornua. Conception rates following the procedure were variable, ranging from 14% to 42% in the literature.

Essure reversal
Montieth et al. are the only authors to publish their experience using tubouterine anastomosis to reverse Essure sterilization. Their technique

Essure® was the most successful hysteroscopic sterilization device on the market, with an estimated 750,000 devices sold worldwide.
uses a 5-to 10-cm laparotomy and transfundal posterior uterine incision or cornual wedge resection to reimplant the distal fallopian tubes into the uterine cornua. In a published series of 70 cases, the 12-month post-procedural conception rate was 36%.15 A more up-to-date analysis on their website reports a 38% pregnancy rate for 282 procedures performed over 9 years.16 Also reported is a 5% ectopic rate and 4% uterine rupture rate.

A new technique
We have tested a new method for Essure reversal using a laparoscopic approach that does not require a large abdominal or uterine incision. With this method, laparoscopy and hysteroscopy are performed simultaneously to remove the device and reimplant the distal fallopian tube into a new site on the uterine fundus. We present a description and video of our technique as well as our experience with three cases.

Removing the microinserts
The microinserts are identified and laparoscopic scissors are used to partially transect the fallopian tube at the distal end of the device (Figure 2). Electrosurgery is avoided to preserve as much healthy fallopian tube as possible. Once the distal end of the Essure device emerges, it is grasped laparoscopically and pulled out of the fallopian tube (Figure 3). The device uncoils and elongates as it is removed and can easily fracture. Pulling the device parallel to the tube and intermittently regrasping it near its exit from the tube can help avoid device fragmentation.

Hysteroscopic guidance
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cavitary portion of the microinsert is completely removed. We have found that a fractured device may appear to be completely removed laparoscopically, when in fact, a small portion of the proximal microinsert remains visible hysteroscopically.

**Stenting the fallopian tube**

Once both Essure microinserts are removed, semi-rigid stents are inserted into the distal fallopian tube segment laparoscopically.

**Tubouterine anastomosis**

The distal fallopian tube is brought to the uterus along the stent and the anastomosis performed. Interrupted stitches are placed circumferentially around the new tubouterine junction with knots tied intracorporeally (Figure 5). Stitches are placed until the fallopian tube is well-approximated to the uterus and the stent is no longer visible. The process is repeated on the other side and the stents are removed. At the end of the procedure, chromopertubation is used to assess tubal patency (Figure 6).

**Experience with three cases**

Three laparoscopic Essure reversal procedures were performed at Brigham and Women’s Hospital between 2017 and 2018 using this technique (Table 1). All three patients were in their 20s when they underwent Essure sterilization and later regretted the procedure. All were experiencing side effects of the Essure device and had a history of spontaneous pregnancies prior to sterilization. The three women were 27 to 35 years of age at the time of Essure reversal.

Operative time ranged from 87 to 142 minutes and estimated blood loss was minimal at 20 to 75 mL. All procedures were uncomplicated and patients were discharged home on the same day as surgery. A follow-up hysterosalpingogram was done 1 to 3 months following the procedure and showed bilateral patency in one case, unilateral patency in the other two cases. While restoration of tubal patency is promising, no pregnancies have occurred over a follow-up period of 5 to 11 months. If the patients

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are able to conceive, risk of uterine rupture may be reduced by avoiding a hysterotomy or cornual wedge resection.

**What about IVF?**

IVF is still a good option for most women who desire pregnancy after Essure, especially if the device is not causing symptoms. Literature on IVF for Essure regret is limited to a report of two cases, both of which resulted in a live birth. Several small studies have also evaluated intentional placement of Essure prior to IVF for infertile women with hydrosalpinx. In this setting, the microinserts occlude the proximal fallopian tube and prevent hydrosalphingeal fluid from spilling into the uterine cavity. A systematic review of Essure and IVF for infertile women with hydrosalpinx reported a 29% ongoing pregnancy and live birth rate. Presumably, IVF success rates for Essure regret are greater than those in women with underlying infertility.

When weighing the risks and benefits of IVF compared to Essure reversal, it is worth considering what we know about IVF and tubal reanastomosis after tubal ligation. As with any fertility procedure, tubal reanastomosis after tubal ligation is more likely to benefit younger women. A retrospective study by Boechxstaens et al. found that cumulative delivery rates were significantly greater after tubal reanastomosis compared to IVF in women younger than age 37 (72% vs. 52% over 72 months). A decision analysis by Messinger et al found that tubal reanastomosis was more cost-effective for women younger than age 41, whereas IVF was more cost-effective for women aged 41 and older.

**Important considerations**

Essure reversal with tubouterine anastomosis is technically and functionally different from tubal reversal with end-to-end anastomosis of the fallopian tube. The greater extent of tubal damage following Essure sterilization is very likely to result in lower success rates than other tubal reversal procedures. While laparoscopic Essure reversal can restore tubal patency, it is currently unknown if it can result in a normal pregnancy. Nevertheless, the opportunity to remove a device associated with symptoms may prompt younger women with Essure regret to attempt reversal despite presumably low success rates.

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**DISCLOSURES**

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

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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 are contraindicated in women who are over 35 years of age and smoke.

CONTRAINDICATIONS
Balcoltra is contraindicated in women with a high risk of arterial or venous thrombotic diseases, liver tumors (benign or malignant) or liver disease, undiagnosed abnormal uterine bleeding, during pregnancy, with breast cancer or other estrogen- or progestin-sensitive cancer (now or in the past), hypersensitivity to any of the components, or in women who are currently taking Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir (with or without dasabuvir).

WARNINGS AND PRECAUTIONS
- Discontinue Balcoltra if an arterial thrombotic event or venous thromboembolic event (VTE) occurs, and at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during prolonged immobilization. Balcoltra should not be started any earlier than 4 weeks after delivery, in women who are not breastfeeding. The use of COCs increases the risk of VTE. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions. Use COCs with caution in women with cardiovascular disease risk factors.
- If jaundice occurs, treatment should be discontinued.
- Balcoltra should not be prescribed for women with uncontrolled hypertension or hypertension with vascular disease. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. If Balcoltra is used in women with well-controlled hypertension, monitor blood pressure and stop treatment if blood pressure rises significantly.
- Women who are prediabetic or diabetic should be monitored while using Balcoltra. Alternate contraceptive methods should be considered for women with uncontrolled dyslipidemia.
- Patients using Balcoltra who have a significant change in headaches or who develop new headaches that are recurrent, persistent, or severe should be evaluated, and Balcoltra should be discontinued if indicated.
- Irregular bleeding and spotting sometimes occurs in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles on Balcoltra, check for causes such as pregnancy or malignancy.
- This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Sensitivity to tartrazine is frequently seen in patients who have aspirin hypersensitivity.

ADVERSE REACTIONS
In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg, the most common adverse reactions (incidence ≥ 2%) were headache (14%), menstrual disorders (9%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

DRUG INTERACTIONS
Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Patients should be counseled that COCs do not protect against HIV infection (AIDS) and other sexually transmitted diseases. Please see full Prescribing Information, including BOXED WARNING, for Balcoltra.

BalcoTral™ (levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets) is an oral contraceptive drug regimen containing ethinyl estradiol and levonorgestrel.

**Liver Disease**

Do not use BalcoTral in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver. Acute or chronic hepatitis may result in fulminant hepatic failure that may require liver transplantation. Women with hepatitis or severe (decompensated) cirrhosis of liver should be at an increased risk of pancreatitis when using COCs.

**Effect on Binding Globulins**

BalcoTral is contraindicated in women who currently have or have had liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver.

**High Blood Pressure**

BalcoTral is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease.

In used in women with well-controlled hypertension, monitor blood pressure and stop BalcoTral 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 with extended duration of use. This increase in blood pressure is not associated with an increase in cardiovascular events.

**Carbohydrate and Lipid Metabolic Effects**

Monitor prediabetic and diabetic women taking BalcoTral, as COCs may decrease glucose tolerance. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia. Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

**Deep Vein Thrombosis**

The risk of thromboembolic disease due to COCs gradually disappears over time or with a change to a different contraceptive product. The risk of VTE is highest during the first year of use of COCs and when COCs are used for the first time. The risk is higher in women who are not breastfeeding.

**Pregnancy**

BalcoTral is contraindicated in pregnancy because there is no reason to believe that ContinuousCombinedBalcoTral will induce or exacerbate symptoms of angioedema.

**Drug Interactions**

Consult the labeling of concurrently used drugs to obtain more information about interactions with hormonal contraceptives. Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. 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.

**Overdosage**

There have been no reports of serious ill-effects from overdose of oral contraceptives, including ingestion of more than one or two tablets. Overdosage may cause withdrawal bleeding in females and nausea. Overdosage may cause abortion in females and nausea.

The FDA-approved product labeling can be found at www.balcoltra.com, or call 1-888-632-8466

**Drug Consultation**

Consult the labeling of continuously used drugs to get more information about interactions with hormonal contraceptives.

**Serious Cardiovascular Events**

- Have uncontrolled hypertension
- Have thrombogenic valvular or rhythm diseases of the heart
- Have inherited or acquired hypercoagulopathies
- Have deep vein thrombosis or pulmonary embolism, now or in the past
- Have thrombectomy or arterial embolus
- Have thrombophilia, including antiphospholipid antibodies
- Have known or suspected hypercoagulopathy

**Other Vascular Problems**

Studies suggest a small increased relative risk of developing gallbladder disease among users. COCs may increase the risk of gallbladder disease. A history of gallbladder disease predicts an increased risk with subsequent use of COCs. A history of gallstones may resolve over time or with a change to a different contraceptive product.

**Drug Interactions**

The enzymatic activities of liver microsomal drug metabolizing enzymes may significantly affect the plasma concentrations of estrogen, progestin, and their metabolites. Drugs that induce CYP3A4 may decrease the systemic availability of levonorgestrel and ethinyl estradiol when coadministered with BalcoTral. Inhibitors of CYP3A4, such as ketoconazole, may increase plasma levonorgestrel and ethinyl estradiol concentrations.

BalcoTral has not been studied in postmenopausal women and is not indicated for use in this population.

**Carcinoma of the Breast and Cervix**

BalcoTral is contraindicated in women who currently have or have had breast cancer or breast cancer in a close relative. BalcoTral if breast cancer may be hormonally sensitive.

**Effect on Binding Globulins**

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

**Monitoring**

A woman who is taking COCs should have her blood pressure checked periodically with her healthcare provider.

**Hereditary Angiodema**

Women in hereditary angiodema, eosinophilic syndromes may induce or exacerbate symptoms of angioedema.

**Chloasma**

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 BalcoTral.

**ADVERSE REACTIONS**

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, a total of 107 healthy women of childbearing potential were enrolled and had 3780 cycles of exposure. Of these, 792 subjects had completed 1 cycle of treatment. The women ranged in age from 17 to 49 years and 87% were Caucasian.

**Common Adverse Reactions (≥ 2% of women):**

- Headache (4%), menorrhagia (8%), dysmenorrhea (7%), nausea (9%), abdominal pain (5%), breast tenderness (6%), emotional lability (5%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

- At the time of the report, 133 (3%) subjects had withdrawn from the study due to adverse events. Of these, 21 (2%) were due to headache, 13 (1%) were due to menorrhagia (1%) each. Other adverse events occurring in ≥ 1% of those who discontinued included emotional lability, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hyperleucocytosia, weight gain, dysmenorrhoea, and flatulence. All other reasons for discontinuation were reported by 3 or fewer subjects. These are all of the possible adverse reactions of BalcoTral.
Female health technology takes center stage

Digital transformation of the women’s health market is rapidly occurring through FemTech (female technology).

by Bob Kronemyer

The term FemTech was coined by Danish entrepreneur Ida Tin of Natural Cycles mobile app, the first CE-marked Class IIb medical device for use as method of contraception.

“The whole concept of FemTech can positively impact women’s health and well-being because it is not limited to a product or a service, but is rather an end-to-end solution,” said Paljit Sohal, a principal consultant at Frost & Sullivan, which is tracking the lucrative market from a research perspective. “Women’s healthcare issues are coming to the forefront with an increased focus to differentiate care provided for the healthcare issues specific to women, which no longer fit into the frameworks of men’s health.”

Sohal told Contemporary OB/GYN there is a need for inclusion of women in clinical research and trials, product development, and targeted marketing. “It will be exciting to see new applications for reproductive, maternal and general women’s health and wellness, including mental health issues, elderly care, and chronic diseases and communicable diseases,” she said.

Nearly 50 FemTech companies combined have received in excess of $1 billion in funding since 2014 and are offering interactive digital health applications for women’s health, according to Sohal. “However, major healthcare companies have only started to see the benefits of integrating FemTech into their strategy,” she said.

For example, Zimmer Biomet is scheduled to market its Gender Solutions high-flex knee, which is the first knee replacement designed specifically to fit a woman’s anatomy. Similarly, Cook Group has announced the launch of its women’s health business unit, which will address some of the most prevalent issues in women’s health globally, including infertility, chronic pelvic pain, pelvic organ prolapse, and incontinence.

Nearly 50 FemTech companies combined have received in excess of $1 billion in funding since 2014

“There is also an unmet need for accessing healthcare at affordable rates in developing markets,” Sohal said.

For instance, CareMother from India-based CareNX Innovations helps detect high-risk pregnancies in early stages through mobile monitoring tools like a health information management system. Likewise, GE Healthcare’s Vscan with dual probe is a pocket-sized portable ultrasound machine that enables women to better manage their pregnancy.

FemTech can benefit ob/gyn practices because fertility, pregnancy care, and maternal care are major areas of concern—especially for women opting for later pregnancies or at higher risk of complications. “We see various solutions already making a positive impact, such as Minerva’s endometrial ablation system for the treatment of abnormal uterine bleeding,” Sohal said.

A mobile colposcope that uses a smartphone for cervical cancer screening received approval from the US Food and Drug Administration in 2016.

Sohal said use of digital technology will help motivate patients to access and use applications for managing women’s health issues. “Women patients are playing an active role in their care delivery and are beginning to invest in their own care,” she said. “These technologies encourage patient self-management and continued engagement to manage women’s health issues. Digital technology adds value.”
The ability of women to set their own self-management or self-care goals, especially for wellness and reproductive health, “will positively benefit patients,” Sohal said.

Sohal anticipates that the rise of FemTech will promote collaboration between device, healthcare IT, and pharmaceutical companies. “A network approach will be required, though, and companies will need to continually seek new partnerships, as well as innovative business models to keep abreast of changing dynamics in the industry,” she said.

It is also critical for healthcare companies to either consider the acquisition of FemTech applications or partner with specialized FemTech companies or build their own portfolios, according to Sohal. “The end goal is to formulate a marketing strategy exclusively for FemTech,” she said. “The companies that recognize this need early on will have the first mover advantage.”

Bob Kronemyer reports no relevant financial disclosures.

Does chromosomal screening of oocytes before embryo transfer improve live birth rate?

by BOB KRONEMYER

Preimplantation genetic testing for aneuploidy (PGT-A) by comprehensive chromosome screening of select embryos for transfer did not increase the likelihood of a live birth among women of advanced maternal age who underwent a single cycle of intracytoplasmic sperm injection within 1 year, according to results of a multicenter randomized controlled trial (RCT) published in Human Reproduction (http://bit.ly/PGTAS Study).

The largest randomized trial published to date spanned nine centers in seven European countries and was led by Karen Sermon, MD, PhD, from the Research Group Reproduction and Genetics of the Vrije Universiteit Brussel (VUB) in Belgium.

The study enrolled 396 women aged 36 to 40 who were randomized to either PGT-A (205 subjects) or no PGT-A (a control group of 191 subjects).

After 1 year, both groups achieved a live birth rate of 24%.

“Given the limitations of the study, I am not surprised by the results,” said Steven Ory, MD, a reproductive endocrinologist in private practice in Margate, Florida and member of the Contemporary OB/GYN editorial board. “Finding an embryo with 46 chromosomes by PGT-A is the holy grail for success with in vitro fertilization (IVF).”

Dr. Ory said failure to produce an embryo with 46 chromosomes is the most common reason for a failed IVF cycle. “Hence, any technology that helps us improve the odds of finding such an embryo is likely to have a huge positive impact on the outcome of an IVF cycle,” he said.

However, Dr. Ory said the study highlights the limitations of applying a complex, operator-dependent technology in multiple sites. “The study’s live birth rate of 24% in both groups is significantly below what many high-performing centers have reported with PGT-A,” he said.

PGT-A, previously known as preimplantation genetic screening (PGS), has been pursued over the past 20 years. “Initially, there was a lot of excitement over an earlier technology using fluorescent in situ hybridization (FISH) to help identify abnormal embryos,” said Dr. Ory. “But when the technique was rigorously tested in randomized controlled trials, it proved to be a failure.”

The current study used a newer technology—array comparative genomic hybridization —for chromosomal analysis, which is superior to FISH in overcoming some of the previous challenges of the older technique. “FISH did not test for all of the 46 chromosomes, it was conventionally performed on 3-day-old embryos (cleavage-stage embryos) and the cells that were typically obtained did not nec-
INDICATION
SOLOSEC™ (secnidazole) 2g oral granules is a 5-nitroimidazole antimicrobial agent indicated for the treatment of bacterial vaginosis in adult women.

SELECT IMPORTANT SAFETY INFORMATION
• SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.
• Vulvo-vaginal candidiasis may develop with SOLOSEC and require treatment with an antifungal agent.
• Potential risk of carcinogenicity in patients taking single-dose of SOLOSEC to treat bacterial vaginosis is unclear. Chronic use should be avoided.
• SOLOSEC is a single-dose therapy for oral use. The entire contents of SOLOSEC packet should be sprinkled onto applesauce, yogurt or pudding and consumed once within 30 minutes without chewing or crunching the granules. SOLOSEC is not intended to be dissolved in any liquid.
• In clinical studies, the most common adverse events occurring in (≥2%) of patients receiving SOLOSEC 2g oral granules were vulvovaginal candidiasis (9.6%), headache (3.6%), nausea (3.6%), dysgeusia (3.4%), vomiting (2.5%), diarrhea (2.5%), abdominal pain (2.0%), and vulvovaginal pruritus (2.0%).

Please see Brief Summary of Prescribing Information on adjacent page.
To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-844-SOLOSEC (1-844-765-6732) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Rx Only
This Brief Summary does not include all the information needed to use SOLOSEC™ safely and effectively. See full Prescribing Information for SOLOSEC.

SOLOSEC (secnidazole) 2g oral granules

Single oral dose
Initial U.S. approval: 2017

INDICATIONS AND USAGE

SOLOSEC is a nitroimidazole antimicrobial indicated for the treatment of bacterial vaginosis in adult women.

Dosage and Administration

Administer a single 2 gram packet of granules once orally, without regard to the timing of meals. Sprinkle entire contents of packet onto yogurt, applesauce, or pudding and consume all of the mixture within 30 minutes without chewing or crunching the granules. A glass of water may be taken after the administration of SOLOSEC to aid in swallowing. SOLOSEC is not intended to be dissolved in any liquid.

CONTRAINDICATIONS

Hypersensitivity. SOLOSEC is contraindicated in patients with a history of hypersensitivity to secnidazole, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS AND PRECAUTIONS

Vulvovaginal Candidiasis. The use of SOLOSEC may result in vulvovaginal candidiasis and may require treatment with an antifungal agent.

Potential Risk for Carcinogenicity. Carcinogenicity has been seen in mice and rats treated chronically with nitroimidazole derivatives, which are structurally related to secnidazole. It is unclear if the positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of SOLOSEC to treat bacterial vaginosis. Avoid chronic use of SOLOSEC.

Drug Resistance. Prescribing SOLOSEC in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

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

The safety data described below reflect exposure to 589 patients, of whom 518 received a 2g dose of SOLOSEC. SOLOSEC was evaluated in 3 clinical trials of patients diagnosed with bacterial vaginosis: 2 placebo-controlled trials (Trial 1 n=215, Trial 2 n=189) and 1 uncontrolled safety trial (Trial 3 n=321).

All patients received a single oral dose of study medication or placebo. Trial 1 evaluated a 1g (this dose is not approved) dose (n=71) and a 2g dose (n=72) of SOLOSEC. Trial 2 evaluated a 2g dose (n=125). The population was female, aged 15 to 54 years. Patients in the placebo-controlled trials were primarily Black or African American (54%) or Caucasian (41%). There were no deaths in the trials. Two patients in Trial 3 discontinued due to vulvovaginal candidiasis in the SOLOSEC-treated arm.

Most Common Adverse Reactions

Among 197 patients treated with a single 2g dose of SOLOSEC in the 2 placebo-controlled trials, Trial 1 and 2, adverse reactions were reported by approximately 29% of patients. Table 1 displays the most common adverse reactions (≥2% in SOLOSEC-treated patients) in these 2 trials.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SOLOSEC N=197 n (%)</th>
<th>Placebo N=136 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>19 (9.6)</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (3.6)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (3.6)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (2.5)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (2.0)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>4 (2.0)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

Among the 321 patients in an uncontrolled trial, Trial 3, adverse reactions were reported in 30% of patients. Vulvovaginal candidiasis (8.4%), nausea (5.3%), vomiting (2.5%) and dysgeusia (3.4%) were the most common adverse reactions reported in this trial.

Postmarketing Experience. The following adverse reactions have been reported during use of other formulations of secnidazole 2g outside of the United States. 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. Reported adverse reactions were nausea, dysgeusia, abdominal pain, headache, and vomiting.

DRUG INTERACTIONS

Oral Contraceptives. There was no clinically significant drug interaction between secnidazole and the combination oral contraceptive, ethinyl estradiol plus norethindrone. SOLOSEC can be co-administered with combination oral contraceptives (eg, ethinyl estradiol plus norethindrone).

USE IN SPECIFIC POPULATIONS

Pregnancy. Limited available data with SOLOSEC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, there were no adverse developmental outcomes when secnidazole was administered orally to pregnant rats and rabbits during organogenesis at doses up to 4 times the clinical dose.

Lactation. Breastfeeding is not recommended. Discontinue breastfeeding for 96 hours after administration of SOLOSEC.

Pediatric Use. The safety and effectiveness of SOLOSEC in pediatric patients below the age of 18 years have not been established.

Geriatric Use. Clinical studies with secnidazole did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nitroimidazoles, which have similar chemical structures to secnidazole, have been associated with tumors affecting the liver, lungs, mammary, and lymphatic tissues in animals after lifetime exposures. It is unclear if these positive tumor findings in lifetime rodent studies of these nitroimidazoles indicate a risk to patients taking a single dose of secnidazole to treat bacterial vaginosis. Secnidazole was positive in the bacterial reverse mutation assay, but was negative for the rat micronucleus test and mouse lymphoma test.

In a rat fertility study, females were dosed for 2 weeks prior to mating until Day 7 of gestation with males that were dosed for a minimum of 28 days before cohabitation. No parental toxicity or adverse effects on mating performance, estrous cycles, fertility or conception was observed at doses of up to the maximum tolerated dose (300 mg/kg/day, approximately 1.4 times the recommended dose based on AUC comparisons).

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

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Should genomic testing be routine after stillbirth?

by BOB KRONEMEYER

State-of-the-art genetic testing shows promise in determining the cause of prenatal death and likelihood of a recurrence in future pregnancies, according to Australian researchers. Their results, with whole exome sequencing (WES) and whole genome sequencing (WGS) were published in *Human Reproduction*.

“The cause of pregnancy loss and perinatal death remains unexplained in at least 25% of cases, despite a high perinatal autopsy rate in countries such as the United States and Australia,” said Christopher Barnett, MBBS, FRACP, FCCMG, a consultant clinical geneticist and head of the Paediatric and Reproductive Genetics Unit at the Women’s and Children’s Hospital in North Adelaide, Australia. “The most common factor contributing to perinatal death is congenital abnormalities.”

Presenting at the European Society of Human Genetics conference (http://bit.ly/ESHGConference), Dr. Barnett described outcomes with WES and WGS as a way to identify genetic causes of fetal/newborn abnormalities that result in termination of pregnancy, death in utero, or in the newborn period. Using data from 43 families referred to the genetics unit, where samples were available from both parents and the fetus (the prospective cohort), and 60 from stored autopsy samples from the fetus or newborn (the retrospective cohort), researchers were able to uncover an underlying genetic cause in 23% of the prospective cohort, and have found a single promising candidate in a further 26%.

“Genomics has the potential to unlock the cause of complex congenital abnormalities in 50-60% of cases.”

Further, genetic testing enables access to preimplantation genetic diagnosis. “This is the situation where a couple’s Day 5 embryo is biopsied and tested for the previously diagnosed genetic disorder in the family,” Dr. Barnett said. “A healthy embryo without the genetic disease is then transferred and the pregnancy can continue normally.”

Bob Kronemyer reports no relevant financial disclosures.

Genomics has the potential to unlock the cause of complex congenital abnormalities in 50-60% of cases

For more information, go to HTTP://WWW.CONTEMPORARYOBGYN.NET/GENETIC-TESTING
NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

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

WARNINGS and PRECAUTIONS

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.

- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.

- Rule out pregnancy before inserting NEXPLANON.

Educate her about the risk of serious vascular events

- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events (stroke and myocardial infarction (MI)) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis (DVT), retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using the nonradioactive etonogestrel implant have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.
NEXPLANON is the only non-uterine LARC option

- Provides Up to 3 years of pregnancy prevention*
- >99% effective†
- Reversible if her plans change

Placed subdermally in the inner upper arm just under the skin

* NEXPLANON must be removed by the end of the third year and may be replaced by another NEXPLANON at the time of removal, if continued contraceptive protection is desired.
† Less than 1 pregnancy per 100 women who used NEXPLANON for 1 year.

SELECTED SAFETY INFORMATION (continued)

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

Counsel her about changes in bleeding patterns

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

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

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

Please read the adjacent Brief Summary of the Prescribing Information

INDICATION AND USAGE

NEXPLANON should not be used in women who have:

- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver disease (active or inactive), or a history of liver disease
- Undiagnosed abnormal genital bleeding
- Known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive tumors or in the family
- Allergic reaction to any of the components of NEXPLANON [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

The following information is based on experience with the etonogestrel implants (IMPLANON® [etonogestrel implant] and NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.

1. Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it is palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed until the implant is removed immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted too deeply (intramuscular or submuscular), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie in the neurovascular bundle deeper in the subcutaneous tissues. An implant inserted more deeply than subdermally (deeply implantation) may not be palpable and cannot be visualized and/or removed (see Dosage and Administration and Warnings and Precautions). NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant should be replaced after the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

2. Changes in Menstrual Bleeding Patterns

In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding patterns were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (3.3%) was reported less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3.315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are in Table 1.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotted or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>Total Days of Spotted or Bleeding</th>
<th>Treatment Days 91-100 (N = 740)</th>
<th>Treatment Days 271-320 (N = 657)</th>
<th>Treatment Days 631-720 (N = 547)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Days</td>
<td>17%</td>
<td>24%</td>
<td>16%</td>
</tr>
<tr>
<td>1-7 Days</td>
<td>10%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>8-21 Days</td>
<td>30%</td>
<td>30%</td>
<td>37%</td>
</tr>
<tr>
<td>&gt;21 Days</td>
<td>35%</td>
<td>32%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 2.

Table 2: Bleeding Patterns Using the Non-Radiopaque Etogestrel Implant (IMPLANON) During the First 2 Years of Use

<table>
<thead>
<tr>
<th>Bleeding Patterns</th>
<th>Definitions</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infrequent</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)</td>
<td>33.6</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
<td>22.2</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
<td>17.7</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than 5 bleeding and/or spotting episodes in 90 days</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Based on 3135 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion.

3. Ecotrophic Pregnancy

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON. Women should be informed that ectopic pregnancy may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the non-dominant upper arm.

4. Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (cerebral thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended that women be informed to increase the risk of venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious venous and arterial thrombotic events, including cases of pulmonary embolism (fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should be removed prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

5. Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. On rare occasions, surgery may be required.

6. Carcinoma of the Breast and Reproductive Organs

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive [see Contraindications]. Some studies suggest that the use of combination hormonal contraceptives increases the risk of breast cancer; however, other studies have not confirmed such findings. Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

7. Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops. Hepatic adenomas are associated with androgen use. A liver function test should be performed for liver assessment. Use of NEXPLANON and other progestin-only methods like NEXPLANON in women with active liver disease or liver cancer is contraindicated [see Contraindications].

8. Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after 1 year and 3.2 pounds after 2 years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for the non-radiopaque etonogestrel implant removed.

9. Elevated Blood Pressure

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

10. Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

11. Carbohydrate and Lipid Metabolic Effects

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prepubertal and diabetic women using NEXPLANON. Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

12. Depressed Mood

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

13. Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below the level of detection by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.
ADVERSE REACTIONS

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women). Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight increase</td>
<td>12.8%</td>
</tr>
<tr>
<td>Acne</td>
<td>12.3%</td>
</tr>
<tr>
<td>Depression</td>
<td>11.5%</td>
</tr>
<tr>
<td>Emotional lability†</td>
<td>8.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>6.5%</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>3.5%</td>
</tr>
<tr>
<td>Acne</td>
<td>3.3%</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.8%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2.8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.7%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>2.7%</td>
</tr>
<tr>
<td>Depression</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.5%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>1.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.3%</td>
</tr>
<tr>
<td>Pain</td>
<td>1.3%</td>
</tr>
<tr>
<td>Bruising</td>
<td>1.0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation. Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON®)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9%</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>14.5%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>13.7%</td>
</tr>
<tr>
<td>Acne</td>
<td>13.5%</td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.8%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.9%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.5%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.0%</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>9.6%</td>
</tr>
<tr>
<td>Migraine</td>
<td>9.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4%</td>
</tr>
<tr>
<td>Back pain</td>
<td>6.8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.5%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5.6%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6%</td>
</tr>
<tr>
<td>Depression</td>
<td>5.5%</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>5.4%</td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.2% of subjects. Additionally, hematomas (3.0%), bruising (2.0%), pain (1.1%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives

Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice or ketoconazole may increase the plasma concentrations of pregestin, including etonogestrel.

Human Immunoodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progesterone have been noted in cases of co-administration with HIV HCV protease inhibitors (decrease [e.g., nevirapin, ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ ritonavir, and tipranavir/ritonavir]) or increase [e.g., indinavir and atazanavir/ritonavir]) HCV protease inhibitors (increase [e.g., bupropen and tenofovir]) or non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine, efaviren]) or increase [e.g., efaviren]. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.

Effects of Hormonal Contraceptives on Other Drugs

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, ciclosporin or decrease (for example, lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

1. Pregnancy

Risk Summary

NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant (see Contraindications). Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-gential birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 μg/day).

NEXPLANON should be removed if maintaining a pregnancy.

2. Nursing Mothers

Lactation

Risk Summary

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

3. Pediatric Use

Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be the same for prepubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

4. Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

5. Hepatic Impairment

No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. The use of NEXPLANON in women with active liver disease is contraindicated (see Contraindications).

6. Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight. With time after implant insertion, it is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSE

Overdose may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY

In a 24-month carcinogenicity study in rats with subcutaneous implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.6-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling.

● Counsel women about the insertion of NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.

● Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.

● Counsel women that NEXPLANON does not protect against HIV or other STDs.

● Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information.

USP-NF84/15-IPTX-7100/019

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W056-126730/0000 05/18
Using simulation technology to improve maternal morbidity

Use of simulation technology for training on labor and delivery is increasing and studies show it can help reduce complications such as perineal lacerations and brachial plexus injury.

by SHAD DEERING, MD

Introduction
Patients expect their labor and delivery team to be prepared for complications and emergencies and they trust that hospitals are using everything available to ensure the best outcomes possible. However, maternal morbidity and mortality have increased significantly in the United States over the past two decades, with mortality increasing 26% between 2000 and 2014.1 Headlines like "United States named the ‘Most Dangerous’ developed country for women to give birth” and “Hospitals know how to protect mothers. They just aren’t doing it” continue to remind both patients and providers of these facts and emphasize the need to address this problem.2,3 While the response to this issue is broad, simulation is a critical part of the comprehensive strategy to impact maternal morbidity and mortality in obstetrics. It is already used extensively in both resident and nursing training and is becoming a key component of local, regional, and national programs being implemented to improve maternal obstetric outcomes.

Background
Obstetric simulation has been around for centuries, with its first use likely predating written history. There is archaeologic evidence showing that the Siberian Mansai created life-sized birth models from leather for teaching delivery techniques.4 In the 18th century, a French midwife, Madame du Coudray, used a leather birthing mannequin to teach obstetric delivery management.

QUICK TAKES
- Obstetric simulations can be used to train residents and also to help staff better prepare for obstetric emergencies such as postpartum hemorrhage.
- Simulators range from portable devices to full-body, multidimensional models and they can be expensive, but the long-term maintenance costs are low.

DR DEERING is Professor and Chair, Department of OB/GYN, Uniformed Services University of the Health Sciences, Bethesda, MD.
and is reported to have reduced both maternal and infant mortality.5

In modern obstetrics, simulation began to emerge in the literature in the early 2000s. While initial reports focused on its use for training medical students and residents, this quickly transitioned to staff physicians and the entire labor and delivery care team. Obstetric simulation training is now recommended by every major national professional organization in our specialty, and the American Board of Obstetrics and Gynecology has even incorporated simulation into both its certifying exam and maintenance of certification program.

Obstetric simulation as a means to improve patient outcomes is generally focused in three areas: skill acquisition, interval training, and in-situ drills.

1. **Skill acquisition:** Simulation for skill acquisition may be focused on trainees, such as medical or nursing students or residents, or be used by staff when a new procedure/technique is introduced. Often, simple task trainers are designed specifically to address a complication. Some examples include techniques for shoulder dystocia management, such as posterior arm delivery, and placement of uterine compression sutures (Figure 1).

2. **Interval training:** Interval training is meant to refresh skills and update providers on new recommendations in a manner similar to courses like the American Heart Association Advanced Cardiac Life Support (ACLS) courses. These may be done through local initiatives or with national courses such as the Emergencies in Clinical Obstetrics (ECO) Course from the American College of Obstetricians and Gynecologists (ACOG) or the Advanced Life Support Course (ALSO) from the American Academy of Family Physicians (AAFP).

3. **In-situ drills:** This refers to simulation drills that are run on actual hospital delivery and postpartum units, usually in a multi-professional manner, and can include other services such as anesthesia and the blood bank. These are important in that they provide the opportunity to practice as a team and can help identify facility or system issues that may impact patient safety and would not be found when practiced in a simulation center.

**Evidence of benefit**

While research continues into how obstetric simulation can affect patient outcomes, the benefits are increasingly clear. Simulation training has been shown to improve procedural skills, enhance team management, and reduce complications, thereby improving patient outcomes. 

Continued on page 38
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPARUEUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

DISCOVER A TREATMENT EXPERIENCE WITH SIMPLICITY AT ITS CORE

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

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

Estrogen Plus Progestin Therapy

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

TO LEARN MORE, SIMPLY VISIT IMVEXXY.COM/HCP OR CALL 1-855-351-5311 TO SPEAK TO A SALES REPRESENTATIVE AND REQUEST SAMPLES
CONTRAINDICATIONS
- IMVEXXY™ is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

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

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

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

Please see Brief Summary of the Full Prescribing Information, including the Boxed Warning, on the following pages.


*Systemic absorption may occur with IMVEXXY. The risks associated with systemic estrogen therapy should be considered.
Estrogen-Alone Therapy

Cardiovascular Disorders and Probable Dementia

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

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

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

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

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

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

The WHI estrogen plus progestin substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg)-alone, relative to placebo [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2) in full prescribing information].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.2, 5.4), Use in Specific Populations (6.8), and Clinical Studies (14.3) in full prescribing information].

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

Estrogens or 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.

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2) in full prescribing information].

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

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

INDICATIONS AND USAGE

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

DOSEAGE AND ADMINISTRATION

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

A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin [see Warnings and Precautions (5.2, 5.4, 5.11) in full prescribing information].

Use of estrogen alone in combination with a progestin, should be used with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

CONTRAINDICATIONS

IMVEXXY™ is contraindicated in women with any of the following conditions:

• Unopposed estrogen in menopausal women without a uterus, or a uterus, or a history of breast cancer

• Known or 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 myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg) relative to placebo [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2) in full prescribing information].

• Use of estrogen-alone therapy in combination with a progestin, should be used with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

WARNINGS AND PRECAUTIONS

Risks from Systemic Absorption

IMVEXXY™ is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY™ in full prescribing information. The use of IMVEXXY™ in full prescribing information. An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of cardiovascular disorders and probable dementia 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 1.10, and the absolute risk was 19 versus 17 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. [see Clinical Studies (14.2) in full prescribing information].

Consistent with the WH 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 (treatment). 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 been found significant in estimating 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 therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WH estrogen plus progesterone 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 to 3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.7

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk of ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95 percent confidence interval [CI] 1.32 to 1.50), there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with current use and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WH, 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-years8 (see Use in Specific Populations (8.8), and Clinical Studies (14.3) in full prescribing information).

In the WHIMS estrogen plus progesterone ancillary study of WH, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years8 (see Use in Specific Populations (8.8), and Clinical Studies (14.3) in full prescribing information).

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progesterone ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women.8 (see Use in Specific Populations (8.8), and Clinical Studies (14.3) in full prescribing information).

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 leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order 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 dysfunction, 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

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 progesteron should be considered.

Hereditary Angioides

Exogenous estrogens may exacerbate symptoms of angioides in women with hereditary angioides.

Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiommas and should be used with caution in women with these conditions.

Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

Drug Laboratory Test Interactions

Accelerated hypercoagulable state, prolonged prothrombin time, and platelet aggregation time, increased platelet count, increased factors II, VII, antithrombin III, procoagulant activity, IX, XII, XI-V, X complex, and beta-thromboglobulin; decreased levels of antithrombin III; decreased antithrombin III activity, increased levels of fibrinogen and fibrinogen activity; increased plasminogen and activity.

Increased thyroid-binding globulin (TBS) levels leading to increased circulating total thyroid hormone 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 TBS. Free T4 and T3 concentrations are unaffected. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

Other binding proteins may be elevated in serum, for example, corticosterone binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating cortisoloids and sex steroids, respectively. Free hormone concentrations, such as testosteron and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/rein substrate, alpha-1-antitryptsin, ceruloplasm). Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subtraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.

Impaired glucose tolerance.

ADVERSE REACTIONS

In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEEXXY incidence > 3 percent and greater than placebo was headache.

DRUG INTERACTIONS

No drug-drug interaction studies have been conducted with IMVEEXXY.

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, rifabutin and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

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

Geriatric Use

There have been no sufficient numbers of geriatric women involved in clinical studies utilizing IMVEEXXY to determine whether these over 65 years of age differ from younger subjects in their response to IMVEEXXY.

The Women’s Health Initiative Studies

In the WH 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 [see Clinical Studies (14.2) in full prescribing information].

In the WH estrogen plus progesterin 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 [see Clinical Studies (14.2) in full prescribing information].

The Women’s Health Initiative Memory Study

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 progesterin when compared to placebo [see Warnings and Precautions (5.4), and Clinical Studies (14.3) in full prescribing information].

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[see Warnings and Precautions (5.4), and Clinical Studies (14.3) in full prescribing information].

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

See FDA-approved PATIENT COUNSELING INFORMATION

Based on: NYX-2009
Revised: 05/2018
outcomes, there is already evidence that demonstrates its potential. Some examples of these include:

**Umbilical cord prolapse:** In one study, a labor and delivery unit implemented multi-professional simulation training for umbilical cord prolapse. They then reviewed the care and outcomes of actual cord prolapse cases for six years before and after training. The group found that not only did the diagnosis-to-delivery interval decrease from 25 to 14.5 minutes ($P < 0.001$) but the teams also were much more likely to perform recommended maternal interventions after training (82% after training vs 34% before, $P < 0.001$). In addition, Apgar scores < 7 at five minutes were not seen in any of the 28 cases of cord prolapse that occurred after the program began. An additional report from Denmark showed similar findings for a reduction in diagnosis-to-delivery interval for emergency cesarean deliveries.

**Postpartum hemorrhage:** The California Maternal Quality Care Collaborative (CMQCC) developed a comprehensive quality improvement toolkit for obstetric hemorrhage based on the National Partnership for Maternal Safety Consensus Bundle and focused on readiness, recognition and prevention, response and reporting/systems improvement. The CMQCC bundle was introduced and implemented in 99 hospitals within the collaborative and the outcomes of women who experienced obstetric hemorrhage were compared with those at 48 hospitals who did not implement the hemorrhage bundle. Unit-based simulation drills for obstetric hemorrhage that included both a standardized stage-based emergency management checklist and debriefings were part of the education and implementation bundle. The team found a 20.8% reduction in severe maternal morbidity when a hemorrhage occurred in a hospital that had implemented the bundle, compared to only a 1.2% reduction in hospitals that did not implement the bundle ($P < .0001$). In another study, a multi-professional training program for postpartum hemorrhage done in Norway demonstrated that after simulation training was implemented, there was a significant decrease in the rate of blood transfusion (12% vs 21%, $P < .01$) and uterine curettage (6% vs 11%, $P < .01$).

**Forceps:** As the rate of operative delivery, especially with forceps, has decreased, simulation has emerged as a way to provide opportunities for training and practice. In one residency program, a simulation training curriculum for operative delivery was implemented and the residents trained until they achieved mastery-level performance on the simulator. During the study period, more than 6000 forceps deliveries were performed and after training, there was a 26% reduction in incidence of third- and fourth-degree lacerations in forceps deliveries.

**Shoulder dystocia:** The best evidence for improved outcomes in obstetrics with simulation is related to management of shoulder dystocia. In the United Kingdom, Draycott et al implemented a training program for personnel involved in labor and delivery management. This training was mandatory and used a relatively inexpensive hybrid birthing simulator to teach and allow practice of the basic maneuvers for management of a shoulder dystocia delivery. After implementing this training, the group found that use of McRobert’s maneuver dramatically increased during ac-
A Small but Fine Difference
Minilaparoscopic Instruments from KARL STORZ
tual deliveries from 29.3% to 87.4% and there was a decrease in head-to-body delivery time from three minutes to two minutes. Neonatal outcomes also improved and risk of neonatal injury at births complicated by shoulder dystocia decreased from 9.3% to 2.3% post-training with risk of brachial plexus injury falling from 7.4% to 2.3%. In a follow-up study, the same group found that not only was the improvement sustained over 12 years, but in the final year of the study period, there were no brachial plexus injuries in over 560 deliveries complicated by shoulder dystocia. These findings were replicated in the United States as well.

In 2011, Grobman et al implemented a simulation-based shoulder dystocia training program that showed a similar decrease in incidence of brachial plexus injury after deliveries complicated by shoulder dystocia, from 10.1% to 4.0% ($P < 0.001$).

Teamwork & communication: In addition to technical skills, communication and teamwork are key to achieving optimal outcomes in obstetrics and it has been reported that communication failures are part of the root cause of over 70% of sentinel events on labor and delivery units. Because of this, programs have been developed to teach these skills to teams on labor and delivery. Simulation has been studied as a method to improve the effectiveness of this teamwork training. Riley et al reported their results with a three-hospital trial in which they used one hospital as a control (no intervention), a second that received standardized TeamSTEPPS didactics only and a third hospital that had TeamSTEPPS didactics followed by simulation exercises for obstetric emergencies based on actual cases from that hospital. The team evaluated the Weighted Adverse Outcomes Score (WAOS), which is a weighted measure that adjusts for severity of events at every delivery, and found that while there was no improvement at the control or didactics-only hospitals, the simulation-trained hospital had a 37% decrease in perinatal morbidity.

Simulation technology and implementation

Many obstetric simulator options are available, and more are being developed. There are task trainers that allow for practicing regular deliveries or specific procedures, such as episiotomy repair or cesarean hysterectomy (Figure 2). For obstetric emergencies, there are hybrid models in which an actor plays the part of the patient and uses a lower torso mannequin for practicing emergencies such as shoulder dystocia and full-size female mannequins that include the ability to palpate pulses and administer intravenous medications. Cost for these devices varies, from approximately $750 for some very basic birthing trainers, to hybrid simulators.
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in the $5,000 to $7,000 range, to full-body, high-fidelity mannequins that can be over $80,000 (Figures 3 and 4). While these dollar figures may sound high, birthing simulators can be used for years and in general, costs are minimal for maintenance or consumables that need to be replaced after training.

When planning to purchase a simulator, it is important to begin with a review of both who you will be training and what your learning objectives are as well as what kind of support you will have to run simulations. For example, if you have dedicated simulation-operating specialists to help run your simulations, then a full-body, high-fidelity birthing simulator with integrated physiology and vital signs may work. If you need something more portable that can be used by multiple providers who need a less complicated model, a hybrid simulator may be more appropriate.

Even though simulation training is encouraged by many national organizations and health care systems, there is often a disconnect between recognizing it is needed and having the expertise to implement a program. First, simulation training is a significant shift away from the typical lecture style of education that providers typically use. It is also more labor-intensive to run and requires a higher faculty-to-student ratio to be effective. Providers may also feel as if they will be put on the spot and potentially “fail” in front of their team and peers. Successful implementation requires support from leadership as well as an upfront understanding that simulation training is meant to educate and improve team performance and outcomes, not single out individual mistakes. Debriefing after training must emphasize this as well.

Recognizing the importance of simulation in our specialty and the challenges of implementation, ACOG created the Simulation Working Group in 2008, which has expanded to represent 24 institutions and every ACOG district across the country (https://www.acog.org/About-ACOG/ACOG-Departments/Simulations-Consortium). This group works to create and offer simulation-based training for education and patient safety initiatives and serves as a resource for both ACOG and providers across the country who are interested in implementing simulation training.

Current initiatives

Given the mounting evidence that obstetric simulation can improve outcomes, it is not surprising that its use continues to increase. At present, many hospitals and institutions are using obstetric simulation to teach basic and emergency skills, practice teamwork and communication, and test new units to identify any potential facility or system issues before opening.
Savings for Physicians’ Alliance of America (PAA) Members

Physicians’ Alliance of America is a nonprofit national healthcare Group Purchasing Organization (GPO) that uses the purchasing power of physicians in all 50 states (and D.C.) to negotiate discounts and preferred terms for the goods and services private practices use every day.

For more information:

PAA
1.866.348.9780
Physall.com

LILETTA
1.855.LILETTA (1.855.545.3882)
LILETTAHCP.com
for patients. In 2016, the US Military Healthcare System (MHS) began mandating obstetric simulation training for all providers, physicians, and nurses, at all 50 of their hospitals that offer maternity care across the world. This requirement includes monthly team drills on labor and delivery units and all providers must take either the Emergencies in Clinical Obstetrics (ECO) course or the Advanced Life Support in Obstetrics (ALSO) course every two years.

There are also many national initiatives in place and being developed as well. Besides the CQMCC, which was discussed previously, some additional training opportunities include:

- **Emergencies in Clinical Obstetrics (ECO) course**
  This course was created by the ACOG Simulation Working Group and includes short, focused didactic sessions followed by hands-on simulation practice for four common obstetric emergencies: shoulder dystocia, postpartum hemorrhage, breech vaginal delivery, and umbilical cord prolapse (Figure 6). The course is multidisciplinary and teaches technical skills and also emphasizes teamwork and communication. It is offered at the ACOG Annual Clinical Meeting and District meetings as well as other institutions.

- **Advanced Life Support in Obstetrics (ALSO) course**
  The ALSO course has been around for more than 25 years and was created by the AAFP. It is now a one-day course with 20 different topics, including common obstetric emergencies, and it combines didactics with hands-on simulation practice.

- **Practicing for Patients**
  The Patient Safety Council for Women’s Health Care has worked closely with the AIM team to create the Practicing for Patients initiative as a resource for any hospital to run in-situ drills for postpartum hemorrhage. This program is modeled directly on the AIM postpartum hemorrhage bundle and features a full online instruction manual that includes demonstration videos with everything needed to implement drills at a hospital. It also has a list of commonly used obstetric simulators that can be used to simulate hemorrhage. All of these resources are available for free on the Patient Safety Council’s website.

- **Society for Maternal Fetal Medicine (SMFM) Obstetric Critical Care Courses**
  SMFM has offered simulation-based courses for obstetric emergencies and critical care since 2012 (Figure 7). These courses address topics such as obstetric hemorrhage, sepsis, hypertensive emergencies and maternal cardiac arrest. SMFM courses are offered at the SMFM annual meeting as well as at stand-alone courses such as the one held every year in conjunction with Banner Health and the University of Arizona, where over 400 providers go through focused didactics followed by high-fidelity immersive team simulations.

**Conclusion**

In the final analysis, it is clear that obstetric simulation has been successfully used to improve maternal morbidity in several areas. It is not, however, a stand-alone solution, but rather, an important part of the overall response to the challenge of managing and improving care when obstetric complications occur. Future studies will continue to refine where and how obstetric simulation can best be used to affect patient safety. While there are always obstacles to implementation and culture change, the benefits of simulation training for practicing obstetric emergencies is worth the effort and a list of resources is included on page 46 to assist those interested.

**DISCLOSURES**

The opinions expressed herein are those of the author and do not reflect the official policy or position of the Department of the Navy, the Department of the Army, the Department of the Air Force, the Department of Defense, or the United States Government.

**FOR REFERENCES VISIT**

contemporaryobgyn.net/SimulationTech
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ACOG Emergencies in Clinical Obstetrics Course (ECO)
Included in the course are units on breech vaginal delivery, umbilical cord prolapse, shoulder dystocia, postpartum hemorrhage, and teamwork and communication during obstetric emergencies.
https://www.acog.org/Education-and-Events/ECO-Course

ACOG Obstetric Simulation Curricula
This course includes several up-to-date learning objectives for obstetric and gynecologic surgeries and also includes formative simulations for shoulder dystocia, eclampsia, and breech delivery.
https://www.acog.org/About-ACOG/ACOG-Departments/Simulations-Consortium/OB-GYN-Simulations-Curricula

California Maternal Quality Care Collaborative
Toolkits include: The role of medical simulation, an updated obstetric hemorrhage toolkit, and various scenarios for simulations and drills to improve the training and response of physicians for medical emergencies.
https://www.cmqcc.org/resource/role-medical-simulation
https://www.cmqcc.org/resources-tool-kits/toolkits/ob-hemorrhage-toolkit
http://mail.ny.acog.org/website/Optimizing_Hemorrhage/Simulation_Drills.pdf

Advanced Life Support in Obstetrics (ALSO)
An evidence-based, interprofessional, and multidisciplinary training program that encourages a standardized team-based approach among physicians, residents, nurse midwives, registered nurses, and other members of the maternity care team.
https://www.aafp.org/cme/programs/also.html

Practicing For Patients
Communication between labor and delivery team members is vital but they rarely practice together. This program focuses on team-based training for simulated medical emergencies on their actual unit.
https://safehealthcareforeverywoman.org/patient-safety-tools/practicingforpatients/

Practicing for Patients - Postpartum Hemorrhage in-situ Drill Program
An upcoming postpartum hemorrhage manual. Sign up to receive notifications regarding its release.

TEDx Talk: Why Doctors Should Play with Dolls.
Shad Deering, MD, discusses how we train the inexperienced physician in an emergency and whether it is ever acceptable to let them “practice” when there is a life on the line.
https://www.youtube.com/watch?v=ruNft5sWUg

Round-up of authoritative sources for further reading.

We want to hear from you. Have you tried simulation training before? Did you find it beneficial? Tell us about your experience and share with your colleagues what worked and what didn’t. What kind of training did you do? Did you do it on your own or with your delivery team? How could it be improved? Email us your thoughts at COGeditorial@ubm.com
There are thousands of gene variations that cause a higher risk of cancer. With comprehensive, affordable genetic insights, she can make screening and prevention decisions that make a difference—today and for years to come.

This moment matters.
TUBAL ECTOPIC PREGNANCY  

Ectopic pregnancy is defined as a pregnancy that occurs outside of the uterine cavity. The most common site of ectopic pregnancy is the fallopian tube. Most cases of tubal ectopic pregnancy that are detected early can be treated successfully either with minimally invasive surgery or with medical management using methotrexate.

However, tubal ectopic pregnancy in an unstable patient is a medical emergency that requires prompt surgical intervention. The purpose of this document is to review information on the current understanding of tubal ectopic pregnancy and to provide guidelines for timely diagnosis and management that are consistent with the best available scientific evidence.

COMMENTARY

Comprehensive management approach for ectopic pregnancy

by ANTHONY N. IMUDIA, MD

The interim update of the ACOG Practice Bulletin on Tubal Ectopic Pregnancy\(^1\) provides a review of information on the current understanding of tubal ectopic pregnancy and offers comprehensive guidelines for timely diagnosis and management options. Compared to the previous publication, the current bulletin provides comprehensive management options for ectopic pregnancy by incorporating new guidance on pregnancy of unknown location and on surgical management of ectopic pregnancy, as well as revised guidance on use of hCG levels for diagnosis.

ACOG recommends not using serum hCG values alone to diagnose an ectopic pregnancy and that they be correlated with the patient’s history, symptoms, and ultrasound findings. If the concept of the hCG discriminatory level is to be used as a diagnostic aid in women at risk of ectopic pregnancy, the value should be conservatively high (eg, as high as 3500 mIU/mL) to avoid the potential for misdiagnosis and possible interruption of an intrauterine pregnancy that a woman hopes to continue.

Overall, in this Practice Bulletin, ACOG is advocating use of a comprehensive approach and more conservative guidelines to avoid the potential for misdiagnosis, possible interruption of an intrauterine pregnancy or unnecessary medical treatment that could lead to teratogenicity in surviving pregnancies.

While this Practice Bulletin specifically and clearly emphasizes the importance of discussion of risks versus benefits with patients in determining treatment method, there are also other logistical issues that may arise and affect decisions about treatment. Most ectopic pregnancies are managed in the outpatient setting and with minimal variation in the team involved. However, depending on individual hospital and office setup, if different laboratories and/or hCG assays are used for trending hCG levels, it is possible that these inter-assay/laboratory variabilities in hCG values could significantly affect
Can the locum tenens process be simplified?
Will my malpractice be paid for?
When will my travel itinerary be confirmed?
When will the job I want become available?
Will everything be taken care of?

It already is.
Most cases can be treated with minimally invasive surgery or with methotrexate. But tubal ectopic pregnancy in an unstable patient is a medical emergency requiring prompt surgical intervention.

the clinical decision-making process. In addition, the issue concerning insured and uninsured patients deserves special consideration. It has been shown that there exists substantial insurance-related variation in treatment. Uninsured women and Medicaid recipients were less likely to receive treatment with methotrexate and were less likely to undergo salpingostomy. In the same article, the authors also discuss the disparity in that black and Hispanic women were less likely to receive tube-conserving surgery.

Some of the recent changes that have facilitated a more conservative approach in treatment of tubal ectopic pregnancy include wider availability of methotrexate, use of early sonography and management of pregnancy of unknown location with uterine aspiration to distinguish between early intrauterine pregnancy loss and ectopic pregnancy. These factors are leading to earlier diagnosis of the disease and subsequent growth in medical management in the outpatient setting. When indicated, surgical management with laparotomy. It is important to note that ACOG recommends that the decision to perform a salpingostomy or salpingectomy for treatment of ectopic pregnancy be guided by the patient’s clinical status, her desire for future fertility, and the extent of damage to the fallopian tube.

There has been a decline in rates of salpingostomy compared to salpingectomy. Although cumulative rates of intrauterine pregnancy and recurrence of ectopic pregnancy in patients who had salpingostomy versus salpingectomy are not statistically significantly different in randomized controlled trials, the move towards salpingectomy is increasing. This is likely due to a combination of many factors, including patient history, intraoperative findings, physician preference and comfort with the procedure as well as increased availability of in vitro fertilization. As the number of salpingostomies being performed nationwide continues to decrease, it is possible that over time, younger physicians will become unskilled in performing the procedure and the frequency could drop even more drastically. Furthermore, recent publications favoring opportunistic salpingectomy for risk reduction of ovarian cancer may be leading physicians towards complete tubal removal whenever feasible.

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

REFERENCES
How doctors can create medical technology

Developing a device is not easy, but the personal and financial benefits can be great.

by HEIDI MOAWAD, MD

Physicians who use medical devices for diagnosis and therapeutic patient care in day-to-day practice often notice unmet patient care needs that could be filled with new devices or technology.

There are many steps between having an idea and creating a viable product. Some physicians have made the leap and have developed their own medical technology, rather than waiting for products to appear on the market. Often, doctors whose work is heavily procedural are the ones who develop devices, but primary care physicians have created their own devices as well.

The process is not easy, nor is it impossible. Important steps for physicians who are planning to develop medical devices include securing funding, making prototypes and templates, testing the technology, getting a patent, obtaining regulatory approval, and marketing the product.

Research demand and competition

While ideas are plentiful, a physician may not have a strong sense of the true size of the market or whether there are similar products already available or in development.

Sam Slishman, MD, an emergency care physician in San Luis Obispo, Calif., developed the Slishman Traction Splint which he started working on in 1999 during his residency. He says getting started requires research to see whether your concept for a device is truly original and whether there is a need.

“You really have to soul search and Google search to know whether your idea merits a patent and whether you are willing to do what it takes,” he advises.

Michael Gorn, MD, a pediatrician in Austin, Texas, who developed the Quickloop Abscess Treatment Device agrees.

“First you have to do a patent search and research the market size for your invention,” he says.

New York City-based internist Jennifer Meller, MD, co-founded Navimize, a digital health company focused on reducing patient wait times. She surveyed patients to get feedback about the demand and value of her product.

“Lots of doctors have great ideas, but not every great idea is something that other people are willing to pay

DR. MOAWAD is a neurologist and author of Careers Beyond Clinical Medicine. Dr. Moawad teaches at Case Western Reserve University and John Carroll University in Cleveland, Ohio and manages nonclinicaldoctors.com.
for,” she explains. Getting input from seasoned professionals played an important role right from the beginning.

Meller, who was working on an MBA when she decided to start her company, teamed up with Kavita Mangal, a woman in her class at Wharton whose background is in technology. “We began by networking and talking to healthcare industry leaders,” she explains. While Meller’s product is specifically focused on patient wait times, an area in which there are not necessarily specialized experts, they spoke to hospital administrators and leaders who work on patient satisfaction.

Clear up conflicts of interest

Employed physicians often have specifications in their contracts that stipulate whether intellectual property belongs to the employer or to the physician.

Gorn advises physicians to carefully examine and discuss proprietary details with employers before starting a project. He explains that employer buy-in is a mixed bag, which can help defray costs, but can take away from a physician’s profit and control.

Gorn explains that he talked to his employer about collaboration, and when they agreed not to work together on his project, he was able to verify in writing that his invention belonged to him. Gorn explains that when working without the benefit of a partnership from a hospital system or a university, physicians need to secure funding for building prototypes, getting a patent, and going through the regulatory approval process, which can be costly and time-consuming, depending on the complexity of the device.

Get funding

The cost of creating and testing medical technology can run between hundreds of thousands of dollars to millions of dollars, according to these innovators, and the cost of a patent runs in the tens of thousands of dollars, according to data provided by the US Patient and Trademark Office.

Gorn went to medical technology conferences to understand the process when he was getting started, and this helped direct him to funding sources. “Startup accelerator programs are private entities, many associated with investment groups,” he explains.

Doctors can obtain funding from friends and family, angel investors, and grants. Grants can award money, and some are also designed to provide free services, such as financial guidance or marketing advice. Doctors can look for grants on university websites, state and federal government websites, and sometimes through non-profits or private companies.

Meller and Gorn both initially funded projects themselves, then raised more from friends and family. It takes a long time for a business venture to become profitable. “We are now working on raising a round of seed funding, which will allow us to hire a sales and marketing team, bring on some developers, as well as pay ourselves a salary,” says Meller.

Getting a patent

As physicians talk with investors, engineers, and legal advisors, there is a concern that someone could steal an idea. Slishman advises doctors to apply for a provisional patent early in the process.

“For very little cost you can essentially purchase ‘patent pending’ status for a year. It’s a great way to protect yourself as you talk with folks about ideas,” he says. Legal website Upcounsel.com notes this cost as around $1500 without the assistance of an attorney.

Gorn warns that if a company or individual does steal an idea, the legal expenses of trying to sue the company that stole your idea can add up after you hire attorneys, take time away from your work, produce all of your supporting evidence, and pay for court fees.

Creating and testing the product

Creating the product is where the highest cost comes in. When doctors share the intellectual property and potential profits with a university or a

CONTINUED ON PAGE 56

Read more about technology and simulation training on PAGE 32
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All physician practices have representatives ("Reps") from various manufacturers knocking on their doors. This can include Reps from companies selling pharmaceuticals, durable medical equipment, imaging devices, lab services, and more. These Reps often play an important role in keeping physicians updated on the availability and proper use of products. Other times, Reps can integrate themselves into physician practices in a manner that is inappropriate and noncompliant with the law.

There are many instances in which Rep interaction in the practice and with patients can be troubling. Here are three issues for your practice to consider regarding how Reps are welcomed into your practice:

1. **Make time for Reps, but don’t let physicians’ schedules become the victim.**

Reps are salespeople and will continue to call and visit until you see them. Reps may demand interaction with the physician instead of practice staff, which can disrupt schedules and upset patients. Interaction with Reps rarely takes the 5 minutes they promise.

   Consider setting a certain day of week and/or time of day when Reps can schedule an appointment or see a physician, and then stick with your chosen approach. Aggressive Reps will continue to push, so standing firm can help set boundaries as well as control the practice flow more consistently.

2. **Use lunch as a time to meet with representatives.**

Reps can still sponsor practice lunches if there is an educational component involved. This can mean a meal for the office and a less interrupted day while still learning about new products. Be sure to track the Rep’s visits, keep a copy of attendees on file and gather any information you can about the cost of the lunch. Do not accept any gifts in any form from the Rep.

   Remember, all meals and items provided will be tracked—and reported in dollar amount—in accordance with the Physician Payments Sunshine Act. This information is available to the public. You can search the CMS listing of such payments by physician at https://openpaymentsdata.cms.gov/. Manufacturers that do not appear to be reporting such lunches when required should be a source for concern, and the practice should discontinue any further interaction with them.
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Consider Reps’ interactions with physicians and staff.

Some Reps interact more with physicians and their staff than others. Many device manufacturers and specialty drug Reps almost embed themselves into physician practices. They may be present during surgical procedures or meeting directly with patients. Every physician needs to determine whether a Rep’s involvement with a patient is appropriate based on the facts involved.

Unfortunately, I have been involved in many cases where a Rep’s role in the practice was overreaching and inappropriate. Some examples include Reps performing services that should be performed by practice staff. This can raise questions about “free” services and possible kickback concerns. Reps completing patients’ prescriptions and prior authorization forms, including medical necessity statements, also create concerns. Physicians can be lax about receiving prescriptions/forms before signing and assume they’ve been completed by practice staff. This does not always turn out to be the case. If the physician has signed off on documents that may be inaccurate or inappropriate, it can be difficult to later prove the truth of what occurred.

While Reps from many manufacturers can help physicians to learn about new products, it is important for physicians to understand their motives and to draw a professional line in the sand. Reps do not work for the practice and should not be integrated into the office or allowed free access to data, forms, patients, or other practice resources. Many Reps are paid based on each sale, prescription, or order they generate. This means that Reps’ goals and what is best for physician practices—and their patients—are not always aligned.

Creating technology

big company, the high cost, while still an issue, may not be an impediment to progress.

But, when a doctor attempts to fund manufacturing a product, budgetary constraints can delay development. “I probably spent $50,000 to $100,000 over a decade in prototyping, flights, trade shows, and websites,” Slishman says.

Now, he works with a company, Rescue Essentials, which creates and markets his product.

Meller started by constructing a plan, and then testing it. “We built an MVP—minimum viable product—which was a very basic, manual electronic blueprint of what we wanted to ultimately build. We’ve spent the last 18 months building the product, piloting, and are now gearing up for sales/marketing,” she explains.

And after the value of the product is established to potential customers, the selling begins. Meller’s company just recently signed a contract with an EHR company to integrate software, and they are talking with hospitals about pilot programs.

Gorn explains that when a manufacturer buys a product, the physician inventor can negotiate payment terms, such as royalties, which, based on his information gleaned from technology conferences, can run between 2% and 15% of the product’s net profits.

Overall, creating medical technology is not an easy feat, and doctors who have done it put a great deal of work into the process.

According to Gorn, the time devoted to creating a new product is similar to the time a doctor spends at a full-time job. After that, physicians who have invented new products have the benefit of being able to use the product in their own clinical work, as well as having income generated from sales of the product.

What was your experience with creating technology? Tell us about what you created and how it changed your practice.

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**YOUR MONTHLY MUST READS**

- **AHRQ report underscores disparities in maternal mortality**
  - A new report shows that over a 10-year period in the United States, rates of severe maternal morbidity increased and age, race, and income, all played a role in disparities in specific related trends.

- **Are female sterilization rates and cognitive disability linked?**
  - Female sterilization is one of the most common forms of contraception but wide variation exists in the demographics of women undergoing such procedures.

- **How often are opioids dispensed to women after vaginal delivery?**
  - A recent study found that opioid dispensing after vaginal delivery may represent a source of overprescription in the United States.

- **Does delivery mode in twin pregnancies impact maternal morbidity rates?**
  - As twin pregnancies have become increasingly frequent, the issues of patient safety and planned delivery mode have become more important.

- **How do race and ethnicity impact HPV vaccine completion rates?**
  - A recent study looked at the role race and ethnicity play in HPV completion rates in an integrated health care system and why HPV vaccine coverage in the United States remains low.

- **Can marijuana pass into mother’s milk?**
  - A new study shows that women who use marijuana and breastfeed may be passing along to their babies more than just nutrients with their breastmilk.
Telehealth and the law: The challenge of reimbursement

by JOHN D. FANBURG, JD, AND JONATHAN J. WALZMAN, JD

Technological advances continue to expand the healthcare delivery marketplace. Through technology, more and more providers are trying to cash in on telehealth. As with any other business, the healthcare industry is driven by profitability.

In healthcare, profitability is generally driven by reimbursements from government payers such as Medicare and Medicaid, private insurers such as Blue Cross and Aetna, and, to a smaller degree, self-pay patients. When it comes to telemedicine services, the primary factor affecting reimbursements is legal policy.

Under the Medicare program, which covers approximately 15 percent of Americans, telehealth services are typically reimbursable only if they are provided for beneficiaries who live in certain rural or underserved areas, and usually require the beneficiary who is receiving the telehealth services to be physically located at certain “originating sites,” such as practitioners’ offices, hospitals, rural health clinics, and nursing homes. Medicare publishes a list of procedures, which are designated by billing codes, that Medicare will pay for if all of the required conditions are met. Medicare also has additional rules that must be followed in order for telehealth services to be reimbursable, such as limitations on the type of technology that may be used and what type of practitioner may provide covered telehealth services.

If a telehealth service is covered under the Medicare rules, both the remote practitioner and the originating site may be entitled to bill for the service. The remote practitioner is entitled to bill for the professional service that is provided, and the originating site is entitled to bill for a facility fee. When submitting claims to Medicare for telehealth services, each provider must add a billing code modifier to identify the service as a telehealth service. The fee is subject to applicable deductibles and coinsurance. Additionally, Medicare fee schedule reimbursement for telehealth services are not necessarily on par with the fees payable for similar in-person services.

Reimbursement for telehealth services provided for non-Medicare patients is dependent upon the jurisdiction where the patient is located while receiving the services. Most states have legal policy governing telehealth services, and there is a lack of uniformity with regard to state telehealth guidance, including in the areas of site-of-service requirements and the types of technology that may be used. And perhaps even more importantly, there is also variation regarding whether private insurers are obligated to reimburse for telehealth services.

Most states require private insurers to cover telehealth services. However, state laws vary regarding the amount that private payers must reimburse. Some states require private insurers to reimburse for telehealth services in most jurisdictions, insurance companies have great discretion in determining how much to pay telehealth services.
“on par” with, ie at the same rates that the insurer would have paid if the same service was provided to the patient in person. Other states, like New York, require private payers to cover telehealth services, but either do not require or are silent with respect to parity for reimbursement. Some states have some form of reimbursement requirement for telehealth services that does not quite equate to on-par reimbursement. Yet other states have no requirement for private payers to cover any telehealth services.

Like other types of healthcare, telemedicine profitability is driven primarily by payers, including Medicare, Medicaid, and private insurance companies. Even within the same jurisdiction, the laws and rules relating to each of these types of healthcare payers can be vastly different, which can create great difficulties for providers, especially providers delivering telehealth services from different states. In most jurisdictions, insurance companies have great discretion in determining how much to pay telehealth services, or even whether to pay at all. It is up to each provider to become aware of reimbursement rules for services they will provide for patients in another state before those services are provided.

Can a digital employee transform the revenue cycle?

by JORDAN ROSENFELD

When Valerie Barckhoff, a principal at tax advisory firm Windham Brannon, in Atlanta, Ga., got a first look at what artificial intelligence (AI) can do for simplifying revenue cycle processes, she said: “I became ridiculously geeky excited at the possibilities.”

AI is incredibly good at breaking down repetitive processes, she says, which is what revenue cycle management is all about. “A lot of what we do in the revenue cycle is predictable and repeatable and we’re just hiring some entry level staff to do the work because it needs to get done.”

Windham Brannon piloted a program to create a digital employee for a client hospital to work on what she calls “my biggest pain point,” precertifications, notices sent to payers alerting them that patients want to have a healthcare service. “We were doing a poor job of initiating and obtaining the pre-cert and patients were getting delayed or rescheduled, or we were getting denials because we didn’t pre-cert properly.”

She partnered with the cardiology department to create a digital employee they’ve named “LIA” (for Learned Intelligence Applied) that has a login just like any other employee. “She can get the schedule. She gets procedure information and diagnoses, and can log into the payer portal and initiate the pre-cert,” Barckhoff says.

The benefits of having a digital “employee” that, like all AI programs, learns as it goes and gets smarter as it receives more data, is that it can take on some of the mundane and repetitive work out of employees’ schedules.

While a live staff person still has conversations with payers, the virtual employee helps with follow-ups and pulling back information.

Barckhoff believes this is just the beginning of what the AI can do, and sees it as a crucial way to free up employees from burdensome tasks.

There’s no way any revenue cycle operation can touch every claim that comes through,” she says.

She envisions that the digital employee will free up time so that real employees can go after the low dollar claims that practices rarely get to follow up on, typically leading to a high-volume back log.

Because AI programs learn as they go, the virtual employee can be programmed with a confidence rate to free it up to do tasks. For example, it can be trained to pull specific records and input them into the medical record. Additionally, an AI assistant can help with scheduling. “We’re expecting to have to reschedule [fewer] patients because of administrative issues,” she says.

The response she’s received from executives has been overwhelmingly positive, so she urges physicians to be the drivers of this technology within their medical groups or hospitals—once they receive access to this technology.

“I think this is truly revolutionary for the revenue cycle,” she says.
Reliance on technology

Discovery
In our expert’s opinion, liability was certain. There was a possible causation defense, ie, that oxytocin administration didn’t necessarily cause or contribute to fetal demise, but a successful causation defense was impaired by the “opts” of the case and by the note from the attending at the follow-up visit inferring a causative link between the order for oxytocin and the fetal demise.

The expert found several departures regarding the issuing of preset electronic orders. He found error in the computer system used at the hospital to generate orders for obstetrical patients as well as human error. First, the expert could not understand why a postpartum order was generated by the computer instead of an antepartum order. He wondered why the patient was marked as a postpartum patient at 11 weeks’ gestation. We know it was a postpartum order because the documented indication for the order was: “for uterine atony or heavy uterine bleeding.” Additionally, the Medication Audit Report reads: “hang bag immediately after placental delivery.” He also couldn’t understand why there was no computer warning to alert the staff that this was a postpartum order at 11 weeks’ gestation.

Another point of departure was the lack of human intervention to delete the oxytocin order from the order set. The expert pointed to the fact that there was a debriefing immediately after the procedure, which commonly occurs in the operating room. The expert was concerned that despite this debriefing, just moments later, the order for oxytocin was verified. The expert also wondered if the nurses involved in the procedure were obstetrical nurses and if they were not, if they simply were not familiar with oxytocin. Despite any lack of knowledge by the nurses, neither the resident nor the attending altered the order.

Regarding causation, the defense could have attempted to prove that there were insufficient receptors in the uterus at 11 weeks’ gestation and therefore the oxytocin did not cause the miscarriage. The expert provided a medical article regarding the concentration and distribution of oxytocin receptors in myometrial and decidual tissues obtained at cesarean delivery or hysterectomy during pregnancy. Myometrial receptor concentration was low at 13 to 17 weeks but had risen about twelvefold by 37 to 41 weeks. These results are consistent with a functional role of endogenous oxytocin in the activation of the human uterus during pregnancy and parturition. In addition, the expert was aware of two out-of-state physicians who might be able to testify that the receptors, which start to appear at 13 weeks, increase as gestation advances. This might have assisted in mitigating damages, if it could be shown that this was a risk of the procedure and could happen even if the oxytocin was not administered. The expert was still cautious, citing the “opts” of the case, errors in the hospital chart, and that the attending’s note could easily be “the nail in the coffin.”

Outcome
The case settled prior to trial given the damning entries in the record by the attending and the obvious error in the “postpartum” orders. Whether the case could be defended on causation was ultimately moot given the requirement that a jury would essentially have had to first forgive the admitted errors before accepting that “they didn’t cause the injury.”

This case is a prime example of the potential benefits of technology backfiring. While electronic medical records can expedite documentation requirements and assist practitioners in making and keeping accurate contemporaneous records, they cannot be used without oversight. Auto-population, in particular, has been an issue in many cases we’ve handled, whether it be that the system automatically changed dates of entries to “current date;” or “old” records with current complaints or diagnoses were autopopulated; or, as in this case, the system “automatically” entered an order that was neither relevant nor appropriate to the issue at hand. Technological advancements can be a boon in myriad ways, but in our experience, they cannot be implemented without proper oversight and risk assessment by practitioners, or mistakes that should be avoided will invariably be made.
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OB/GYN Opening - McLeod Health

Join established & mature practice with existing patient base in a thriving area. Great schedule, 1:5 call! McLeod Regional Medical Center, a Regional Perinatal Center for northeastern SC, houses the regions only NICU and PICU with spacious labor and delivery suites, excellent pre-term labor and high risk pregnancy care. High risk gynecologic surgery performed here with access to daVinci Si and daVinci Xi robots.

Competitive Salary! Paid Vacation Time, Health Benefits, Physician Retirement plans, Paid Malpractice, CME allowance, Signing Bonus and Relocation Allowance!

McLeod Health is a private, non-profit institution founded in 1906 with nearly 850 physicians and 8,500 employees and 7 hospital campus locations with over 900 beds system wide. The 16 county area McLeod serves has a population of more than one million. McLeod Regional Medical Center is a 565 bed tertiary care and teaching facility.

We are a constantly growing community with a bustling downtown, 1-hour drive to the beach and 2 hours to Charleston, SC. Affordable lifestyle, low traffic and crime, coupled with great amenities and schools make Florence an excellent place to work and live!
Please email Ashley Watson at Ashley.watson@mcleodhealth.org or call at 843-777-7299

UTAH

Intermountain is frequently referenced nationally as one of the leaders in delivering high quality/low cost healthcare.
Intermountain Healthcare needs OB/GYNs in multiple cities throughout Utah. Contact: Physician Recruiting, 800-888-3134, physicianrecruit@mail.org, http://physicianjobsutah.org
Did reliance on technology contribute to fetal demise?

An oxytocin order entered in an EMR was the key to this case.

Facts
The patient was evaluated at 10 weeks, 2 days’ gestation for abdominal cerclage. She had a history of two prior vaginal cerclages resulting in pre-term deliveries with fetal demise. A bedside sonogram at the prenatal visit was positive for fetal heart rate (FHR) and fetal movement. Surgery was scheduled for the following week.

At the preoperative visit, the defendant obstetrician documented the risks, including fetal loss, and that the patient understood the risks, including another mid-trimester loss. The woman consented to the cerclage and signed an informed consent form.

The patient was admitted to the defendant hospital for abdominal cerclage with placement of mesh at 11 weeks, 5 days. At the conclusion of the procedure, a positive FHR was noted. The patient was transferred to the recovery room in stable condition. Six minutes after the procedure, preset electronic post-partum orders that included oxytocin were entered and the drug was started. The orders were e-signed by the resident, authorized by the attending, and oxytocin was started by a nurse. The time was not documented in the chart but was captured in the medication audit report.

At 9:16 pm that evening, the resident’s note stated that at approximately 2:24 pm, he was called to evaluate the patient for increased vaginal bleeding. The patient was informed she was having a spontaneous abortion.

Earlier in the afternoon the patient had been noted to have vaginal bleeding and on evaluation was noted to have a spontaneous abortion of an 11 week fetus with placenta remaining in situ. She was counseled regarding these findings and the need for dilation and curettage to remove the placenta, which had remained within the uterus.

Two weeks later, the patient returned to see the attending for a follow-up visit. At that visit, the attending wrote:
“The patient was given Pitocin in the recovery room after her first procedure and this medication was wrongly given...the combination of Pitocin after uterine manipulation likely expedited the loss. This type of error is taken seriously. The nursing staff and the resident were re-educated. The order set will be changed so that this medication is not automatically part of the orders.”

Andrew I. Kaplan, Esq is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation.
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