MDEDGE.COM/OBGMANAGEMENT | VOL 30, NO 5 | MAY 2018

OBG MANAGEMENT

Nitrous oxide for labor pain

Pearls from experience

William Camann, MD

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 nonradiopaque etonogestrel implant have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.

NEXPLANON — 1 ARM IMPLANT provides up to 3 years of pregnancy prevention*

Nexplanon®
(etonogestrel implant) 68mg
Radiopaque

(Actual implant shown;
actual implant size is 4cm)

>99% effective†

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.

MERCK

Nexplanon®

(etonogestrel implant) 68mg

BRIEF SUMMARY (For full Prescribing Information, see package insert.)

Women should be informed that this product does not protect against HIV infection (the virus that causes AIDS) or other sexually transmitted diseases.

INDICATION AND USAGE

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The efficacy of NEXPLANON does not depend on daily, weekly or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON. A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant 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 there in the neurovascular bundle deeper in the subcutaneous tissues. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult or impossible *[see Dosage and Administration and Warnings and Precautions]*. NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant must be removed by the end of the third year and may be replaced by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have

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

WARNINGS AND PRECAUTIONS

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

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 unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

   If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the inner 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 there in the neurovascular bundle deeper in the subcutaneous tissues. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

   Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

   There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal.

   If at any time the implant cannot be palpated, it should be localized and removal is recommended.

   Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

2. **Changes in Menstrual Bleeding Patterns**

   After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of the future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy.

   In clinical studies of the non-radiopaque etonogestrel implant, reports of changes in bleeding pattern were the most common reason for stopping treatment (11.1%). Irregular bleeding (10.8%) was the single most common reason women stopped treatment, while amenorrhea (0.3%) was cited less frequently. In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the non-radiopaque etonogestrel implant are shown in Table 1.

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

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

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

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

Bleeding Patterns	Definitions	%†
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting more than 14 days in 90 days	17.7
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion

† % = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

3. **Ectopic Pregnancies**

   As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

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 (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed. There have been postmarketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

   Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Consider removal of the NEXPLANON implant in case of long-term immobilization due to surgery or illness.

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 occasion, 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 might increase the incidence of breast cancer; however, other studies have not confirmed such findings. Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors. Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

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 combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON. The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated *[see Contraindications]*.

8. **Weight Gain**

   In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

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 sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not respond adequately to antihypertensive therapy, NEXPLANON should be removed.

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 prediabetic and diabetic women using NEXPLANON. Women who are being treated for hyperlipidemia should be followed closely if they elect to use NEXPLANON. Some progestins may elevate LDL levels and may render the control of hyperlipidemia more difficult.

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 sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

Nexplanon®
(etonogestrel implant) 68mg

14. **Fluid Retention**
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

15. **Contact Lenses**
Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

16. ***In Situ* Broken or Bent Implant**
There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety *[see Dosage and Administration]*.

17. **Monitoring**
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

18. **Drug-Laboratory Test Interactions**
Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS

In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

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

Adverse Reactions	All Studies N = 942
Bleeding Irregularities*	11.1%
Emotional Lability†	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression‡	1.0%

*Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
†Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
‡Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

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

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

Adverse Reactions	All Studies N = 942
Headache	24.9%
Vaginitis	14.5%
Weight increase	13.7%
Acne	13.5%
Breast pain	12.8%
Abdominal pain	10.9%
Pharyngitis	10.5%
Leukorrhea	9.6%
Influenza-like symptoms	7.6%
Dizziness	7.2%
Dysmenorrhea	7.2%
Back pain	6.8%
Emotional lability	6.5%
Nausea	6.4%
Pain	5.6%
Nervousness	5.6%
Depression	5.5%
Hypersensitivity	5.4%
Insertion site pain	5.2%

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives

Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding.

Some drugs or herbal products that may decrease the effectiveness of HCs include efavirenz, phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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

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

Effects of Hormonal Contraceptives on Other Drugs

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

USE IN SPECIFIC POPULATIONS

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-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 µg/day). NEXPLANON should be removed if maintaining a pregnancy.

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 well-established; however it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

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 postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

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 and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the *in vitro* Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the *in vivo* mouse micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION *See FDA-Approved Patient Labeling.*

- Counsel women about the insertion and removal procedure of the NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. A USER CARD and consent form are included in the packaging. Have the woman complete a consent form and retain it in your records. The USER CARD should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.
- Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.
- Counsel women that NEXPLANON does not protect against HIV 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.

USPI-MK8415-IPTX-1705r019
Revised: 05/17

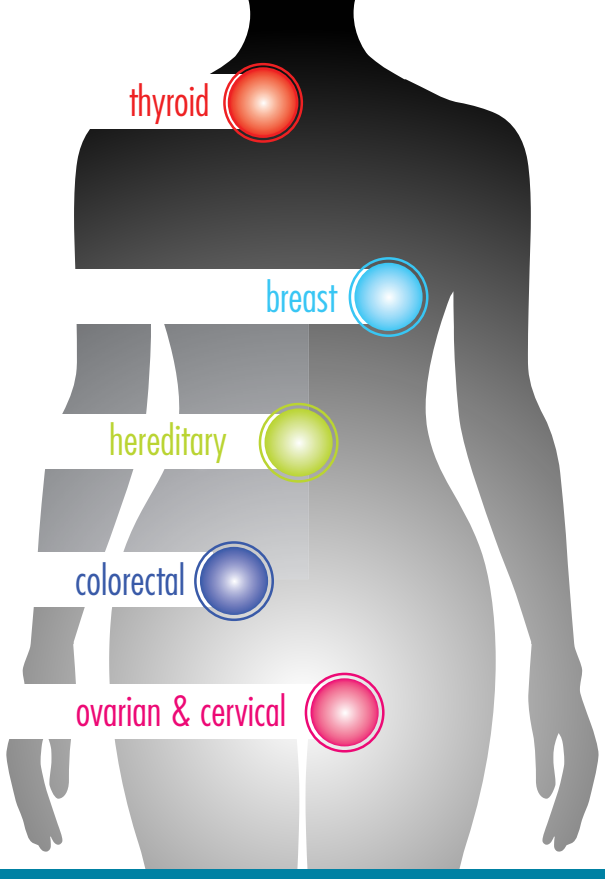
MERCK

#1 IN READERSHIP!*

OBG MANAGEMENT
mdedge.com/obgmanagement

Enhancing the quality of women's health care and the professional development of ObGyns and all women's health care clinicians

*Source: Kantar Media, Medical Surgical Study December 2017, Obstetrics/Gynecology Combined Office & Hospital Readers.



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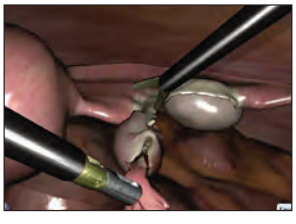
See what's ON THE WEB! page 7



Surgery simulators
SS6

$$NPV = \sum_{t=1}^{T} \frac{C_t}{(1+r)^t} - C_o$$

Net Present Value
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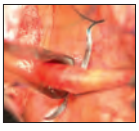

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Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.

Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

Important Safety Information for Makena® (hydroxyprogesterone caproate injection)

- Do not use Makena in women with any of the following conditions:
  - Current or history of thrombosis or thromboembolic disorders
  - Known or suspected breast cancer, other hormone-sensitive cancer or history of these conditions
  - Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
  - Cholestatic jaundice of pregnancy
  - Liver tumors, benign or malignant, or active liver disease
  - Uncontrolled hypertension
- Makena should be discontinued if thrombosis or thromboembolism occurs
- Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil

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- Women receiving Makena should be monitored if they:
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  - Have conditions that may be affected by fluid retention, such as preeclampsia, epilepsy, cardiac or renal dysfunction
  - Have a history of clinical depression; Makena should be discontinued if depression recurs
  - Develop jaundice; consider whether benefit of use warrants continuation
  - Develop hypertension
- Certain pregnancy-related fetal and maternal complications or events were numerically increased in Makena-treated subjects as compared to placebo subjects, including miscarriage (2.4% vs. 0%) and stillbirth (2% vs. 1.3%), admission for preterm labor (16% vs. 13.8%), preeclampsia or gestational hypertension (8.8% vs. 4.6%), gestational diabetes (5.6% vs. 4.6%), and oligohydramnios (3.6% vs. 1.3%)
- In a study where the Makena intramuscular injection was compared with placebo, the most common adverse reactions reported with Makena intramuscular injection (reported incidence in ≥2% of subjects and higher than in the control group) were: injection site reactions (pain [35%], swelling [17%], pruritus [6%], nodule [5%]), urticaria (12%), pruritus (8%), nausea (6%), and diarrhea (2%)
- In studies where the Makena subcutaneous injection using auto-injector was compared with Makena intramuscular injection, the most common adverse reaction reported with Makena Auto-Injector use (and higher than with Makena intramuscular injection) was injection site pain (10% in one study and 34% in another)

Please see brief summary of full Prescribing Information on the following page.

Reference: 1. Makena® (hydroxyprogesterone caproate injection) prescribing information, AMAG Pharmaceuticals, 2018.

Makena®
hydroxyprogesterone caproate injection

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please consult full prescribing information.

INDICATIONS AND USAGE
Makena is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity.
Limitation of use: While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. **It is not intended for use in women with multiple gestations or other risk factors for preterm birth.**

CONTRAINDICATIONS
Do not use Makena in women with any of the following conditions:
- Current or history of thrombosis or thromboembolic disorders
- Known or suspected breast cancer, other hormone-sensitive cancer, or history of these conditions
- Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
- Cholestatic jaundice of pregnancy
- Liver tumors, benign or malignant, or active liver disease
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

Thromboembolic Disorders
Discontinue Makena if an arterial or deep venous thrombotic or thromboembolic event occurs.

Allergic Reactions
Allergic reactions, including urticaria, pruritus and angioedema, have been reported with use of Makena or with other products containing castor oil. Consider discontinuing the drug if such reactions occur.

Decrease in Glucose Tolerance
A decrease in glucose tolerance has been observed in some patients on progestin treatment. The mechanism of this decrease is not known. Carefully monitor prediabetic and diabetic women while they are receiving Makena.

Fluid Retention
Because progestational drugs may cause some degree of fluid retention, carefully monitor women with conditions that might be influenced by this effect (e.g., preeclampsia, epilepsy, migraine, asthma, cardiac or renal dysfunction).

Depression
Monitor women who have a history of clinical depression and discontinue Makena if clinical depression recurs.

Jaundice
Carefully monitor women who develop jaundice while receiving Makena and consider whether the benefit of use warrants continuation.

Hypertension
Carefully monitor women who develop hypertension while receiving Makena and consider whether the benefit of use warrants continuation.

ADVERSE REACTIONS
For the most serious adverse reactions to the use of progestins, see *Warnings and Precautions.*

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.
In a vehicle (placebo)-controlled clinical trial of 463 pregnant women at risk for spontaneous preterm delivery based on obstetrical history, 310 received 250 mg of Makena and 153 received a vehicle formulation containing no drug by a weekly intramuscular injection beginning at 16 to 20 weeks of gestation and continuing until 37 weeks of gestation or delivery, whichever occurred first. Certain pregnancy-related fetal and maternal complications or events were numerically increased in the Makena-treated subjects as compared to control subjects, including miscarriage and stillbirth, admission for preterm labor, preeclampsia or gestational hypertension, gestational diabetes, and oligohydramnios (Tables 1 and 2).

Table 1 Selected Fetal Complications

Pregnancy Complication	Makena n/N	Control n/N
Miscarriage (<20 weeks)[1]	5/209	0/107
Stillbirth (≥20 weeks)[2]	6/305	2/153

[1]N = Total number of subjects enrolled prior to 20 weeks 0 days
[2]N = Total number of subjects at risk ≥20 weeks

Table 2 Selected Maternal Complications

Pregnancy Complication	Makena N=310 %	Control N=153 %
Admission for preterm labor[1]	16.0	13.8
Preeclampsia or gestational hypertension	8.8	4.6
Gestational diabetes	5.6	4.6
Oligohydramnios	3.6	1.3

[1]Other than delivery admission

Common Adverse Reactions:
The most common adverse reaction with intramuscular injection was injection site pain, which was reported after at least one injection by 34.8% of the Makena group and 32.7% of the control group. Table 3 lists adverse reactions that occurred in ≥2% of subjects and at a higher rate in the Makena group than in the control group.

Table 3 Adverse Reactions Occurring in ≥2% of Makena-Treated Subjects and at a Higher Rate than Control Subjects

Preferred Term	Makena N=310 %	Control N=153 %
Injection site pain	34.8	32.7
Injection site swelling	17.1	7.8
Urticaria	12.3	11.1
Pruritus	7.7	5.9
Injection site pruritus	5.8	3.3
Nausea	5.8	4.6
Injection site nodule	4.5	2.0
Diarrhea	2.3	0.7

In the clinical trial using intramuscular injection, 2.2% of subjects receiving Makena were reported as discontinuing therapy due to adverse reactions compared to 2.6% of control subjects. The most common adverse reactions that led to discontinuation in both groups were urticaria and injection site pain/swelling (1% each).

Pulmonary embolus in one subject and injection site cellulitis in another subject were reported as serious adverse reactions in Makena-treated subjects.

Two clinical studies were conducted in healthy post-menopausal women, comparing Makena administered via subcutaneous auto-injector to Makena administered as an intramuscular injection. In the first study, injection site pain occurred in 3/30 (10%) of subjects who used the subcutaneous auto-injector vs. 2/30 (7%) of subjects receiving intramuscular injection. In the second study, injection site pain occurred in 20/59 (34%) of subjects who used the subcutaneous auto-injector vs. 5/61 (8%) of subjects receiving intramuscular injection.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Makena. 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.
- *Body as a whole*: Local injection site reactions (including erythema, urticaria, rash, irritation, hypersensitivity, warmth); fatigue; fever; hot flashes/flushes
- *Digestive disorders*: Vomiting
- *Infections*: Urinary tract infection
- *Nervous system disorders*: Headache, dizziness
- *Pregnancy, puerperium and perinatal conditions*: Cervical incompetence, premature rupture of membranes
- *Reproductive system and breast disorders*: Cervical dilation, shortened cervix
- *Respiratory disorders*: Dyspnea, chest discomfort
- *Skin*: Rash

DRUG INTERACTIONS
In vitro drug-drug interaction studies were conducted with Makena. Hydroxyprogesterone caproate has minimal potential for CYP1A2, CYP2A6, and CYP2B6 related drug-drug interactions at the clinically relevant concentrations. *In vitro* data indicated that therapeutic concentration of hydroxyprogesterone caproate is not likely to inhibit the activity of CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. No *in vivo* drug-drug interaction studies were conducted with Makena.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary: Makena is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Fetal, neonatal, and maternal risks are discussed throughout labeling. Data from the placebo-controlled clinical trial and the infant follow-up safety study did not show a difference in adverse developmental outcomes between children of Makena-treated women and children of control subjects. However, these data are insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the Makena-treated women received the drug during the first trimester of pregnancy. In animal reproduction studies, intramuscular administration of hydroxyprogesterone caproate to pregnant rats during gestation at doses 5 times the human dose equivalent based on a 60-kg human was not associated with adverse developmental outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
Data: *Animal Data* Reproduction studies of hydroxyprogesterone caproate administered to various animal species have been reported in the literature. In nonhuman primates, embryolethality was reported in rhesus monkeys administered hydroxyprogesterone caproate up to 2.4 and 24 times the human dose equivalent, but not in cynomolgus monkeys administered hydroxyprogesterone caproate at doses up to 2.4 times the human dose equivalent, every 7 days between days 20 and 146 of gestation. There were no teratogenic effects in either strain of monkey.
Reproduction studies have been performed in mice and rats at doses up to 95 and 5, respectively, times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to hydroxyprogesterone caproate.

Lactation
Risk Summary: Low levels of progestins are present in human milk with the use of progestin-containing products, including hydroxyprogesterone caproate. Published studies have reported no adverse effects of progestins on the breastfed child or on milk production.

Pediatric Use
Makena is not indicated for use in women under 16 years of age. Safety and effectiveness in patients less than 16 years of age have not been established. A small number of women under age 18 years were studied; safety and efficacy are expected to be the same in women aged 16 years and above as for users 18 years and older.

Hepatic Impairment
No studies have been conducted to examine the pharmacokinetics of Makena in patients with hepatic impairment. Makena is extensively metabolized and hepatic impairment may reduce the elimination of Makena.

Oncofertility in women: Time for a national solution

The authors propose a multifaceted approach to raise awareness of oncofertility services and break down barriers to access for reproductive-age women with a cancer diagnosis

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Fertility preservation and sexual health are main concerns in reproductive-age cancer survivors. Approximately 1% of cancer survivors are younger than age 20 and up to 10% are estimated to be younger than age 45.[1] For many of these survivors, a cancer diagnosis may have occurred prior to their completion of childbearing.

Infertility or premature ovarian failure has been reported in 40% to 80% of cancer survivors due to chemotoxicity-induced accelerated loss of oocytes.[2] Most gonadotoxic chemotherapeutic agents cause DNA double-strand breaks that cannot be adequately repaired, eventually leading to apoptotic cell death.[3] Therefore, any chemotherapeutic agent that induces apoptotic death will cause irreversible depletion of ovarian reserve, since primordial follicles cannot be regenerated.

Alkylating agents, such as cyclophosphamide, have been shown to be most cytotoxic, and young cancer survivors who have received a combination of alkylating agents and abdominopelvic radiation—such as those with Hodgkin's lymphoma—are at higher risk. Other poor prognostic factors for fertility include a hypothalamic-pituitary radiation dose greater than 30 Gy, an ovarian-uterine radiation dose greater than 5 Gy, summed alkylating agent dose score of 3 to 4 for each agent, and treatment with lomustine or cyclophosphamide.[4]

In general, a woman's age (which reflects her existing ovarian reserve), type of therapeutic agents used, and duration of therapy impact the post-treatment viability of ovarian function. Despite conflicting information in published literature, medical suppression by gonadotropin-releasing hormone agonists is not effective.

Fertility preservation options in the United States include egg, embryo, and ovarian tissue banking and ovarian transposition and ovarian transplantation.[5]

Oncofertility: Maximizing reproductive potential in cancer patients

In 2006, Dr. Teresa Woodruff of the Feinberg School of Medicine at Northwestern University coined the term *oncofertility*. Oncofertility is defined by the Merriam-Webster dictionary as "a field concerned with minimizing the negative effects of cancer treatment (such as chemotherapy or radiation) on the reproductive system and fertility and with assisting individuals with reproductive impairments resulting from cancer therapy."

Recognition of the many barriers to fertility preservation led to the establishment of the Oncofertility Consortium, a multi-institution group that includes Northwestern University, the University of California San Diego, the University of Pennsylvania, the University of Missouri, and Oregon Health and Science University. The Consortium facilitates collaboration between biomedical and social scientists, pediatricians, oncologists, reproductive specialists, educators, social workers, and medical ethicists in an effort to assess the impact of cancer and its treatment on future fertility and reproductive health and to advance knowledge. The Consortium also is a valuable information resource on fertility preservation

The authors report no financial relationships relevant to this article.

TABLE Programs that offer financial assistance for fertility treatments

Program	Services offered
Heartbeat Fertility Preservation Program (Walgreens Pharmacy and Ferring Pharmaceuticals) https://www.walgreens.com/topic/specialty-pharmacy/fertility-preservation.jsp	• Free medications for egg and embryo freezing for women newly diagnosed with cancer • Excludes Medicaid
LIVESTRONG Fertility https://www.livestrong.org/we-can-help/livestrong-fertility	• Financial assistance for newly diagnosed men and women who are seeking to bank sperm, eggs, or embryos prior to cancer treatment • $45 million spent, over 680 clinics
Team Maggie for a Cure http://www.teammaggieforacure.org/	• Financial assistance to young women and men for the purpose of preserving eggs and sperm • Denial by insurance carriers prior to consideration of application
The Samfund http://www.thesamfund.org/	• Scholarships to young adult cancer survivors for a wide range of cancer-associated costs, including storage of eggs, embryos, and sperm and expenses for fertility treatment
Tinina Q. Cade Foundation https://www.cadefoundation.org/	• Up to $10,000 to infertile families; fertility treatments and adoption • Combination of Savannah grant and family building grant

options for patients, their families, and providers.[6]

The oncofertility program at Northwestern University was established as an interdisciplinary team of oncologists, reproductive health specialists, supportive care staff, and researchers. Reproductive-age women with cancer can participate in a comprehensive interdisciplinary approach to the management of their malignancy with strict planning and coordination of care, if they wish to maintain fertility following treatment. Many hospitals and health care systems have established such programs, recognizing that the need to preserve fertility potential is an essential part of the comprehensive care of a reproductive-age woman undergoing treatment. When a cancer diagnosis is made, prompt referral to a fertility specialist and a multidisciplinary approach to treatment planning are critical to mitigate the negative impact of cancer treatment on fertility and the potential risk of ovarian damage.

Barriers to oncofertility care

Timely referral to fertility specialists may not occur because of lack of a formal oncofertility program or unawareness of available therapeutic options. In some instances, delaying cancer treatment is not feasible. Additionally, many other factors must be considered regarding societal, ethical, and legal implications. But most concerning is the lack of consistent and timely access to funding for fertility preservation by third-party payers. Although some funding options exist, these require both patient awareness and effort to pursue (**TABLE**).

National legislation does not include provision for this aspect of women's health, and as of 2017 insurance coverage for oncofertility was mandated only in 2 states, Connecticut and Rhode Island. In New York, Governor Cuomo directed the Department of Financial Services to study how to ensure that New Yorkers can have access to oncofertility services, and legislation is pending in the New York state legislature.[7]

Recently, Cardozo and colleagues reported that 15 states currently require insurers to provide some form of infertility coverage.[8] By contrast, RESOLVE: The National Infertility Association, reports information on fertility coverage and the status of bills by state on its website (https://resolve.org). For example, in California, Hawaii, Illinois, and Maryland, bills have been proposed and are in various stages of assessment. Connecticut and Rhode Island mandate coverage. As always, details matter. Cardozo and colleagues eloquently point out limitations of coverage based on age and definition of infertility, and potential financial impact.[8]

An actuarial consulting company called NovaRest prepared a document for the state of Maryland in which the estimated expected number of "cases" would amount to 1,327 women and 731 men aged 10 to 44.[9] These individuals might require oncofertility services.

Oncofertility efforts are moving in the right direction

Lucia DiVenere, MA

Drs. Ursillo and Chalas bring attention to an important issue. As technology advances, so do treatment and coverage needs, and so does the need for ongoing physician and patient education.

In 1990, the US Congress passed the Breast and Cervical Cancer Mortality Prevention Act to help ensure that low-income women would have access to screening for these diseases. It took 10 years before Congress passed the Breast and Cervical Cancer Prevention and Treatment Act so that women detected with breast or cervical cancer could be treated. A curious delay, I know.

Today, we seem to be in a similar situation regarding fertility preservation. Cancer treatment is advanced, coverage is available. Fertility-related treatment is now possible, but coverage is nearly absent.

In my research for this commentary, I learned (a little) about ovarian transplantation and translocation. Even that little was enough to see that we live in an amazing new world. Drs. Ursillo and Chalas put out an important call for physicians to learn, to teach their patients, and, especially, to consider fertility preservation options before (when possible) initiating cancer treatment. It also is imperative to consider fertility preservation in young patients who have not yet reached their fertile years. Cancer treatment begun before fertility preservation may mean future irreversible infertility.

They also call for insurers and public programs to cover fertility and fertility preservation as "essential in the comprehensive care" of cancer patients. To the American College of Obstetricians and Gynecologists (ACOG), that means a federal policy that would ensure public and private coverage for every woman, no matter where she lives, her income level, or her employer.

In many ways, this is a difficult time in public policy related to women's health. With ACOG's leadership, our physician colleague organizations and patient advocacy groups are fighting hard to retain women's health protections already in law. At this moment, opportunities are rare for consideration of expansion. But a national solution is the right solution.

Until we reach that goal, we support state efforts to require private health insurers to cover fertility preservation. As Drs. Ursillo and Chalas point out, only 2 states require private insurers to cover fertility preservation treatment. State-by-state efforts are notoriously difficult, unique, and inequitable to patients. Patients in some states simply are luckier than patients in other states. That is not how to solve a health care problem.

As is often the case, employers—in this case big, cutting-edge companies—are leading the way. Recently, an article in the *Wall Street Journal* (February 7, 2018) described companies that offer fertility treatment coverage to attract potential employees, such as Pinterest, American Express, and Foursquare. This is an important first step that we can build upon, ensuring that coverage includes fertility protection and then leveraging employer coverage experience to influence coverage more broadly.

Big employers may help us find our way, showing just how little inclusion of this coverage relates to premiums; by some estimates, only 0.4%. That is a small investment for enormous results in a patient's future.

My takeaways from this thoughtful editorial:

- Physicians should educate themselves about fertility preservation options.
- Physicians should educate their patients about the same.
- Physicians should consider these options before initiating treatment.
- We all should advocate for our patients, in this case, national, state, and employer coverage of fertility treatment, including preservation.

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The author reports no financial relationships relevant to this article.

NovaRest estimated that clients could experience up to a 0.4% increase in insurance premiums annually if this program was offered. Similar estimates are reported by other states. In Kentucky and Mississippi, such bills "died in committee." The American Society for Reproductive Medicine (ASRM) is actively lobbying with partners, including the Coalition to Protect Parenthood After Cancer, to advocate for preservation of fertility.

We need a joint effort

Most recent statistics support an increase in cancer survivorship over the past decade.[10] This trend likely will continue thanks to greater application of screening and more effective therapies. The use of targeted therapy is on the rise, but it is not applicable for most malignancies at this time, and its effect on fertility is largely unknown. Millennials now constitute the largest group in our population, and delaying childbearing to the late second and third decades is now common. These medical and societal trends will result in more women being interested in fertility preservation.

The ASRM and other organizations are lobbying to support legislation to mandate coverage for oncofertility on a state-by-state basis. Major limitations of this approach include inability to address

CONTINUED ON PAGE 28

How does oral contraceptive use affect one's risk of ovarian, endometrial, breast, and colorectal cancers?

Oral contraceptives (OCs) are associated with a decreased risk of ovarian and endometrial cancers across multiple modifiable lifestyle characteristics. There may be an **increased risk of breast cancer** with OC use.

FAST TRACK

OC use was associated with a significantly decreased risk of ovarian cancer and a decreased risk of endometrial cancer—regardless of smoking status, alcohol use, BMI, and physical activity

Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers [published online January 18, 2018]. JAMA Oncol. doi:10.1001/jamaoncol.2017.4942.

EXPERT COMMENTARY

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Hormonal contraception (HC), including OC, is a central component of women's health care worldwide. In addition to its many potential health benefits (pregnancy prevention, menstrual symptom management), HC use modifies the risk of various cancers. As we discussed in the February 2018 issue of OBG MANAGEMENT, a recent large population-based study in Denmark showed a small but statistically significant increase in breast cancer risk in HC users.[1,2] Conversely, HC use has a long recognized protective effect against ovarian and endometrial cancers. These risk relationships may be altered by other modifiable lifestyle characteristics, such as smoking, alcohol use, obesity, and physical activity.

The authors report no financial relationships relevant to this article.

Details of the study

Michels and colleagues evaluated the association between OC use and multiple cancers, stratifying these risks by duration of use and various modifiable lifestyle characteristics.[3] The authors used a prospective survey-based cohort (the NIH-AARP Diet and Health Study) linked with state cancer registries to evaluate this relationship in a diverse population of 196,536 women across 6 US states and 2 metropolitan areas. Women were enrolled in 1995–1996 and followed until 2011. Cancer risks were presented as hazard ratios (HR), which indicate the risk of developing a specific cancer type in OC users compared with nonusers. HRs differ from relative risks (RR) and odds ratios because they compare the instantaneous risk difference between the 2 groups, rather than the cumulative risk difference over the entire study period.[4]

Duration of OC use and risk reduction

In this study population, OC use was associated with a significantly decreased risk of ovarian cancer, and this risk increased with longer duration of use (**TABLE**). Similarly, long-term OC use was associated with a decreased risk for endometrial cancer. These

TABLE Risks of developing any cancer with OC use

Hazard ratio (95% confidence interval) for cancers by duration of OC use[3]				
Type of cancer	**Incidence in US women[a]**	**1–4 years of OC use**	**5–9 years of OC use**	**10+ years of OC use**
Ovarian	11.7[17]	0.82 (0.69–0.97)	0.72 (0.59–0.88)	0.60 (0.47–0.76)
Endometrial	25.7[18]	0.79 (0.70–0.90)	0.84 (0.73–0.97)	0.66 (0.56–0.78)
Breast	124.9[19]	1.04 (0.98–1.10)	1.02 (0.96–1.09)	1.04 (0.97–1.11)
Colorectal	35.1[20]	0.94 (0.85–1.05)	0.97 (0.86–1.10)	1.03 (0.91–1.18)

Abbreviation: OC, oral contraceptives.

[a]Per 100,000 women per year. These rates are age adjusted and are based on 2010–2014 data from the Surveillance, Epidemiology, and End Results Program.

effects were true across various lifestyle characteristics, including smoking status, alcohol use, body mass index (BMI), and physical activity level.

There was a nonsignificant trend toward increased risk of breast cancer among OC users. The most significant elevation in breast cancer risk was found in long-term users who were current smokers (HR, 1.21 [95% confidence interval (CI), 1.01–1.44]). OC use had a minimal effect on colorectal cancer risk.

The bottom line. US women using OCs were significantly less likely to develop ovarian and endometrial cancers compared with nonusers. This risk reduction increased with longer duration of OC use and was true regardless of lifestyle. Conversely, there was a trend toward a slightly increased risk of developing breast cancer in OC users.

CONTINUED ON PAGE 16

WHAT THIS EVIDENCE MEANS FOR PRACTICE

According to the study by Michels and colleagues, overall, women using OCs had a decreased risk of ovarian and endometrial cancers and a trend toward a slightly increased risk of breast cancer.[3] Based on this and prior estimates, the overall risk of developing *any* cancer appears to be *lower* in OC users than in nonusers.[5,6]

Consider discussing the points below when counseling women on OC use and cancer risk.

Cancer prevention

- OC use was associated with a significantly decreased risk of both ovarian and endometrial cancers. This effect increased with longer duration of use.
- Ovarian cancer risk reduction persisted regardless of smoking status, BMI, alcohol use, or physical activity level.
- The largest reduction in endometrial cancer was seen in current smokers and patients with a BMI greater than 30 kg/m^2.

Breast cancer risk

- There was a trend toward a slightly increased risk of breast cancer with OC use of any duration.
- A Danish cohort study showed a significantly higher risk (although still an overall low risk) of breast cancer with HC use (RR, 1.20 [95% CI, 1.14–1.26]).[1]
- The differences in these 2 results may be related to study design and population characteristic differences.

Overall cancer risk

- The definitive and larger risk reductions in ovarian and endometrial cancer compared with the lesser risk increase in breast cancer suggest a *net decrease* in developing any cancer for OC users.[3,5,6]

Risks of pregnancy prevention failure

- OCs are an effective method for preventing unintended pregnancy. Risks of OCs should be weighed against the risks of unintended pregnancy.
- In the United States, the maternal mortality rate (2015) is 26.4 deaths for every 100,000 women.[7] The risk of maternal mortality is substantially higher than even the highest published estimates of HC-attributable breast cancer rates (that is, 13 incremental breast cancers for every 100,000 women using HC; 2 incremental breast cancers for every 100,000 women 35 years of age or younger using HC).[1]
- Unintended pregnancy is a serious maternal-child health problem, and it has substantial health, social, and economic consequences.[8–14]
- Unintended pregnancies generate a significant economic burden (an estimated $21 billion in direct and indirect costs for the US health care system per year).[15] Approximately 42% of unintended pregnancies end in abortion.[16]

DANA M. SCOTT, MD, AND MARK D. PEARLMAN, MD

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Study strengths and weaknesses

The effect on breast cancer risk is less pronounced than that reported in a recent large, prospective cohort study in Denmark, which reported an RR of developing breast cancer of 1.20 (95% CI, 1.14–1.26) among all current or recent HC users.[1] These differing results may be due to the US study population's increased heterogeneity compared with the Danish cohort; potential recall bias in the US study (not present in the Danish study because pharmacy records were used); the larger size of the Danish study (that is, ability to detect very small effect sizes); and lack of information on OC formulation, recency of use, and parity in the US study.

Nevertheless, the significant protective effect against ovarian and endometrial cancers (reported previously in numerous studies) should be a part of totality of cancer risk when counseling patients on any potential increased risk of breast cancer with OC use. ●

FAST TRACK

When counseling patients on any potential risk of breast cancer with OC use, also discuss OCs' significant protective effect against ovarian and endometrial cancers

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UPDATE Cervical disease

Mark H. Einstein, MD, MS
Dr. Einstein is Professor and Chair, Department of Obstetrics, Gynecology and Women's Health, and Assistant Dean, Clinical Research Unit, Rutgers New Jersey Medical School, Newark, New Jersey. He is coauthor of the 3 articles on ASCCP colposcopy guidelines that are cited and discussed in this Update on cervical disease.

Dr. Einstein has advised, but does not receive an honorarium from any companies. In specific cases his employer has received payment for his consultation from Photocure, Cynvec, Papivax, and PDS Biotechnologies. If travel is required for meetings with any industry, the company pays for Dr. Einstein's travel-related expenses. Also, his employers have received grant funding for research-related costs of clinical trials that Dr. Einstein has been the overall principal investigator or local principal investigator for the past 12 months from Astra Zeneca, Pfizer, and Inovio.

Recent updates include ASCCP guidelines for performing colposcopy and data on cervical cancer screening adherence and cervical cancer prevention with vaccination

In this Update, I outline important findings from several studies published in the past year. First and foremost, what are best practices for performing colposcopy in the United States? The American Society for Colposcopy and Cervical Pathology (ASCCP) released guidelines addressing such practices. Second, what are the implications of repeated negative screening and patients' acceptance of extended screening intervals? A recent observational cohort study and a large study of Kaiser Permanente's practices since 2003 shed light on these questions. Last, where do we stand with HPV vaccination? Two studies shed light on the efficacy of vaccination against human papillomavirus (HPV), and subsequent cervical intraepithelial neoplasia (CIN) and cervical cancer.

IN THIS ARTICLE

ASCCP releases updated quality guidelines for performing colposcopy

Khan MJ, Werner CL, Darragh TM, et al. ASCCP colposcopy standards: Role of colposcopy, benefits, potential harms, and terminology for colposcopic practice. J Low Genit Tract Dis. 2017;21(4):223–229.

Waxman AG, Conageski C, Silver MI, et al. ASCCP colposcopy standards: How do we perform colposcopy? Implications for establishing standards. J Low Genit Tract Dis. 2017;21(4):235–241.

Wentzensen N, Schiffman M, Silver MI, et al. ASCCP colposcopy standards: Risk-based colposcopy practice. J Low Genit Tract Dis. 2017;21(4):230–234.

In October 2017, the ASCCP released a set of standards on the role and performance of colposcopy that represents best practices in women's health care in the United States. The work of these groups comprised a

literature search, a national survey of ASCCP members, public comment, and expert consensus, and addressed:

- establishment of a common understanding of 1) the **benefits** of colposcopy in health maintenance and risk prevention, 2) **risks** presented by the procedure, and 3) **terminology and criteria** for reporting results that reduce subjectivity in reporting
- the rationale for, approach to, and recommendations regarding **assessment of cervical precancer** at colposcopy
- both minimum and comprehensive **guidelines for the colposcopic examination**, from preprocedure evaluation to follow-up.

Each Working Group performed the analysis and produced its own report and recommendations, published sequentially in a 2017 issue of the *Journal of Lower Urinary Tract Disease*. The findings and standards that they produced 1) offer essential insight for high- and low-volume coloposcopists and 2) are intended to improve the quality of colposcopy, reduce subjectivity in reporting findings, and improve the sensitivity of the procedure. Aware of the concerns and objectives of payers and hospital credentialing committees, the ASCCP found it important to establish what would be considered US-based minimum quality standards and to present goals that providers and systems could strive to achieve.

Selected details of the 3 guideline reports

The past 6 years have brought us through a great deal of transition in the prevention of cervical precancer, with regard to screening intervals and types of screening (for example, see "HPV–cytology co-testing every 3 years lowers population rates of cervical precancer and cancer," in the 2017 "Cervical Disease Update," OBG MANAGEMENT, May 2017, page 33). The most significant change was in 2012, when American Cancer Society/ASCCP guidelines were revised to abandon screening with annual Pap testing on most patients—an effort to strike a balance between the lifesaving value of identifying precancer and the potential harm of excessive colposcopy.

If, as the US Preventive Services Task Force (USPSTF) has declared, excessive colposcopy is a *harm* of screening, then we should be adapting our practices, especially in terms of the frequency of screening, to 1) reduce the risk of unnecessarily screening and potentially triaging patients to colposcopy and 2) bring the highest standards of performance and reporting to colposcopic practice (see "Why aren't you doing a Pap on me?"). In other words, "This is the way I've always done it" shouldn't characterize efforts to detect disease, when the data are clear that doing less might be more beneficial for our patients. Adherence to extended screening intervals is not yet good enough to balance benefit and risk of harm, as Rendle and colleagues showed in an article this year in *Preventive Medicine* (discussed in the next section of this "Update"). We need to do better.

Here is a limited encapsulation of the 3 wide-ranging reports on the ASCCP colposcopy recommendations:

Role of colposcopy; benefits, potential harms, terminology (Khan et al; Working Group 1). The authors provide reinforcement: The strategic benefit of colposcopy is clear—a

"Why aren't you doing a Pap on me?"

Adherence to extended screening intervals means fewer colposcopies and less exposure to risk of attendant harm. But adherence is not purely mechanical: It can be intertwined with how patients feel about the care we provide and about their safety. When a patient moves from years of annual Pap testing to less frequent screening, she might express her concern by challenging your expertise.

In my practice, I have a simple, 1-minute conversation with the patient that is important to wedge into our discussion of her care. I explain that increasing the frequency of screening is only going to increase the chance that I will perform a colposcopy but not increase the chance that I will identify cancer. I conclude by reassuring her that I do not want to harm her, or to cause her anxiety, pain, cramping, or bleeding—or require her to spend time away from work or show her family that she is suffering. Patients are reassured and happy after that, I find. This is a patient-centered discussion that providers need to have if they hope to establish and maintain adherence to recommended screening intervals.

MARK H. EINSTEIN, MD, MS

FAST TRACK

New ASCCP guidelines strive to improve the quality of colposcopy, reduce subjectivity in reporting findings, and improve procedure sensitivity

TABLE 1 Which findings of the colposcopic exam should be documented? ASCCP comprehensive criteria[3,a,b]

- Cervix visibility (ie, fully visualized or not fully visualized)
- *Squamocolumnar junction visibility (ie, fully visualized or not fully visualized)*
- *Acetowhitening (yes or no)*
- *Lesion(s) present (acetowhite or other) (yes or no)*
- Lesion visualized (ie, fully visualized or not fully visualized)
- Location of lesion(s)
- Size of lesion(s)
- Vascular changes
- Other features of lesion(s)
  - Color
  - Contour
  - Borders
  - Lugol's iodine uptake
- *Colposcopic impression (ie, normal or benign; low grade; high grade; cancer)*

[a]ASCCP encourages providers to aim for comprehensive reporting of findings, but recognizes that the variability of practice nationwide makes it necessary to offer a set of core (minimum) criteria. The distinction largely regards a more detailed description of findings (eg, annotated images).

[b]Core (minimum) criteria, derived from comprehensive criteria, appear in *italic font*.

"drastic" reduction in excisional procedures by limiting them to patients in whom cervical cancer precursors have been confirmed or who present a high risk of occult invasive cervical cancer. Furthermore, the rate of adverse events for colposcopy—including significant bleeding and infection—is low.

Nevertheless, the potential for harm exists when an unskilled provider performs colposcopy; the Working Group emphasizes that proficiency comes with training *and* experience. Even in skilled hands, however, anxiety and the discomfort of a speculum examination and from acetic acid, as well as cramping and pain, might dissuade some women from receiving regular cervical screening subsequently. The authors cite research showing that educational interventions can help soothe anxiety about colposcopy and potential findings,[1,2] although consensus is lacking on the value of such interventions.

The Working Group 1) developed recommended terminology for reporting findings in colposcopy practice in the United States and 2) defined the *comprehensive* documentation of the procedure as comprising cervix and squamocolumnar junction visibility; acetowhitening; presence of a lesion; lesion visibility, size and location of lesion(s); vascular changes; other features; and colposcopic impression (**TABLE 1**).[3] Minimum criteria for reporting colposcopy results were also proposed, extracted from the comprehensive standards.

Risk-based colposcopy practice (Wentzensen et al). Women referred to colposcopy present with a range of underlying risk of precancer. Assessing that risk at the colposcopy visit allows the provider to modify and individualize the procedure. Risk can be estimated by referral screening tests (eg, cytology, HPV testing) performed in conjunction with the colposcopic impression. As opposed to a lack of standards for a minimum number of biopsies, the Working Group recommends that, as a standard, multiple targeted biopsies (≥2, as many as 4) are needed to improve detection of prevalent precancers. Colposcopic impression alone is not enough to diagnose precancerous cells. Let's face it: Our eyes with a colposcopic magnification of 15X do not make a microscope.

Implementing the Working Group's recommendations is expected to lead to improved detection of cervical precancers at colposcopy and to provide stronger reassurance of negative colposcopy results. Regarding biopsy of lesions, ASCCP did not find added benefit to taking random (nondirected) biopsies for women at low risk for precancer. The sensitivity of biopsy is increased by taking multiple biopsies of suspicious lesions, based on a risk-based approach detailed in the ASCCP guidelines. So, depending on underlying risk (estimated from screening and triage tests), *colposcopy practice can be adapted in a useful manner to account for differences in risk*:

- When risk of precancer is very high, for example, immediate treatment might reduce cost and prevent the patient from being lost to follow-up. When risk is very low, consider expectant management (serial cytology and HPV testing) with limited need for biopsy. In a setting of intermediate risk, the Working

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CONTINUED FROM PAGE 20

Group proposes, "multiple biopsies of acetowhite lesions lead to increased detection of precancer."

- Perform multiple biopsies that target all areas characterized by 1) acetowhitening, 2) metaplasia, and 3) higher abnormalities.
- Do not perform nontargeted biopsies on patients at the lowest end of risk who have been referred to colposcopy—ie, those with cytology that is less than HSIL; no evidence of HPV types 16/18; and a normal colposcopic impression (ie, no acetowhitening or metaplasia, or other visible abnormality).
- Immediate excision *without* biopsy confirmation or colposcopy with multiple targeted biopsies is acceptable in nonpregnant women 25 years and older whose risk of precancer is very high (≥2 of the following: HSIL cytology, HPV 16- or HPV 18-positive (or both), and high-grade colposcopy impression). Endocervical sampling should be conducted according to ASCCP's 2012 management guidelines. If biopsies do not show precancer, manage the patient using ASCCP's 2012 management guidelines, the Working Group recommends.

TABLE 2 Recommendations for comprehensive colposcopy practice[4]

Precolposcopy evaluation
Evaluate and document *at least:*
• Indications for colposcopy
• History of cervical cytology, colposcopy, treatment
• Parity
• Contraception
• Pregnancy status
• Hysterectomy status
• Smoking history
• HIV status
• HPV vaccination status
• Informed consent
Examination
• Vulva and vagina grossly
• Cervix with multiple magnifications after application of 3% to 5% acetic acid
Documentation[a]
• Cervix visibility (fully/not fully visualized)
• SCJ visibility (fully/not fully visualized), and whether cervical manipulation is needed, to completely visualize the SCJ, eg, using an applicator stick or endocervical speculum
• Colposcopic findings
– Acetowhitening present (yes/no)
– Lesion(s) present (yes/no)
– Document extent of any lesion(s) visualized (fully/not fully), size and location, and description (color, contour, border, vascular changes)
• Colposcopic impression (benign–normal/LSIL/HSIL/cancer)
Biopsy
• Biopsy at the SCJ and document location (if indicated)
• Document whether ECS performed and method: curette vs brush or both
Postprocedure
• Document how patient will be notified of results and management plan

Abbreviations: ECS, endocervical sampling; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCJ, squamocolumnar junction.

[a]Use a diagram or photograph; annotate if possible; import into electronic medical record.

How do we perform colposcopy? Implications for establishing standards (Waxman et al; Working Group 3). To serve as a guide to standardizing colposcopy across the United States, the authors defined and delineated 6 major components (and their constituent parts) of a *comprehensive* colposcopy:

- precolposcopy evaluation
- the examination
- use of colposcopy adjuncts
- documentation
- biopsy sampling
- postcolposcopy procedures.

The constituent parts of these components are laid out in **TABLE 2**.[4] A set of components for a minimum colposcopy procedure is drawn mostly from the comprehensive protocol.

The Working Group acknowledges that, in the United States, "the accuracy and reproducibility of colposcopy with biopsy as a diagnostic tool are limited." Why? Three contributing factors, the authors write, might be the absence of practice recommendations for colposcopy-biopsy procedures; of measures of quality assurance; and of standardized terminology.

Standards arrive for practice

Minimum quality standards are becoming part of almost everything US health care providers

do—whether it is documentation, billing practices, or good care. Our work in gynecology, including colposcopy, is now being assessed as it is in much of the world, where minimum standards are already in place and guidelines must be followed. (In some countries standards require performing a minimum number of colposcopies per year to be identified as a "certified" colposcopist.)

What should be considered "minimum standards" for colposcopy in the United States? These ASCCP reports ask, and deliver answers to that question, bringing a broad range of concerns about high-quality practice into focus. Physicians and advanced-practice clinicians in this country who perform colposcopies have been trained to do so, but they have never had minimum standards by which to model and assess their performance. A procedure that has the potential to lead to additional testing for either cervical cancer, or to surveillance, should have minimum standards by which it is performed and documented in the United States as it is for much of the world that has widespread cervical cancer screening.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Guidance and recommendations developed by ASCCP offer women's health care providers a set of comprehensive and, alternatively, minimum quality standards that should be incorporated into practice across all aspects of the colposcopic exam, including precolposcopy evaluation, how to perform the procedure, how to document and report findings (**TABLE 2**), biopsy practice, establish quality control and assurance, as well as postprocedure follow-up. In taking the initiative to draw up these standards, ASCCP encourages providers to exceed the minimum requirements.

Cervical screening adherence is relatively low, but safe. Extended intervals are very safe.

FAST TRACK

The risk of invasive cervical cancer and ≥CIN3 was found to decline with each round of cotesting with HPV and cytology

Castle PE, Kinney WK, Xue X, et al. Effect of several negative rounds of human papillomavirus and cytology co-testing on safety against cervical cancer: an observational cohort study. Ann Intern Med. 2018;168(1):20–29.

Rendle KA, Schiffman M, Cheung LC, et al. Adherence patterns to extended cervical screening intervals in women undergoing human papillomavirus (HPV) and cytology cotesting. Prev Med. 2018;109:44–50.

Patients who have been screened for cervical cancer for a long time—decades, even—have a diminishing likelihood that cancer will ever be detected. Furthermore, highest-risk patients already have been triaged into further testing or procedures, such as a loop excision electrosurgical procedure or hysterectomy. Two recent studies examined the implications of repeated negative screening and patients' acceptance of extended screening intervals.

Details of the studies

Several negative rounds of cotesting (HPV and cytology) might justify changes to the screening interval. To determine the rate of detection of CIN3, adenocarcinoma in situ, and cervical cancer (≥CIN3) in routine practice after successive negative screening at 3-year intervals, Castle and colleagues looked at records of more than 990,000 women in an integrated health care system who underwent cotesting (HPV and cytology) between 2003 and 2014. They determined that the risk of invasive cervical cancer and ≥CIN3 declined with each round of cotesting; the absolute risk fell more between

first and second rounds than between second and third rounds.

At any given round of cotesting, Castle found that the ability to reassure a patient about cancer and cancer risk was similar when looking at an HPV result *alone*, whatever the cytology or HPV–cytology cotest result was. The investigators concluded that similar patterns of risk would have been seen had stand-alone HPV testing been used, instead of co-testing, (HPV testing alone might have missed a few cases of CIN3 and adenocarcinoma in situ leading to cancer). A single negative cotest was so effective at ruling out ≥CIN3 and cervical cancer that, after a second round of cotesting, they found that no interval cancer cases were detected among women who had a negative HPV result.

Women aged 50 years or older had a 5- to 6-fold lower risk after their third consecutive negative cotest than women aged 30 to 39 years had after their first negative cotest. These data support the ideas, Castle noted, that 1) assigning screening intervals based on both age and number of previous negative screens and 2) extending the screening interval even further than 3 years after 2—perhaps even after 1—negative cotests or HPV tests are worth entertaining. Screening women of this age becomes inefficient and cost-ineffective, even at 5-year intervals.

Is patients' adherence to an extended interval of cotesting reliable enough to change practice? Rendle and colleagues examined the records of more than 491,000 women (in the same integrated health care system that Castle studied) who had undergone routine cervical cancer screening between 2003 and 2015. Their goal was to determine how high adherence had become to the system's recommendation of an every-3-year screening interval—an interval that mirrors long-standing guidelines elsewhere.

In short, researchers observed increasing and relatively rapid clinical adoption of every-3-year cotesting for routine cervical screening over time; between 2003 and 2009, the cohort grew significantly less likely overall to come in early for screening. In this setting, adoption of an extended screening interval appears to run counter to earlier understanding that patients are likely to resist such extension.

Women aged 60 to 64 were most likely to screen *early* across 2 consecutive intervals. What Rendle termed a "modest" decrease in the percentage of *late* screeners (but still within a 5-year interval) was also noted during adoption of the 3-year interval.

FAST TRACK

Researchers observed increasing and relatively rapid clinical adoption of every-3-year cotesting for routine cervical screening over time

What next?

Molecular-based testing. Research, mostly outside of the United States, is taking us in the direction of molecular-based technologies as at least a component of cervical cancer screening. Today, we rely mostly on Pap tests and colposcopy, but these are subjective screens, with a human operator. With molecular testing (mostly of components of HPV), results are objective—a "Yes" or "No" finding based on clinically validated thresholds. Methods such as genotyping, $P16^{INK4a}$/Ki-67 gene product dual-stain cytology, and testing for E6 and E7 HPV mRNA transcripts are in development, and hold promise to allow us to screen safely using almost completely molecular testing, thus eliminating human error and subjectivity and enriching the population that needs further management with very sensitive and potentially specific testing.

We are being presented with the possibility that almost all aspects of screening can be done without a provider, until the patient needs treatment.

Access to screening. Research is also looking at improving access, such as self-sampling for primary screening. That includes home cervical and vaginal sampling, with specimens mailed to the laboratory, from where results and follow-up instructions as communicated to patients. The Netherlands and the United Kingdom are moving to self-sampling primary screens; the United States is not—yet. But that is the direction research is taking us.

Modified guidelines. Eyes are on the work of the USPSTF. Last year, the Task Force issued draft recommendations (https://www.uspre

ventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/cervical-cancer-screening2#clinical), followed by a comment period (now closed), for updating 2012 cervical cancer screening guidelines in a way that would trigger a major change in clinical practice. Those draft recommendations and public comments are under review; final recommendations are possible within this calendar year.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Continue to follow current screening guidelines; they are safe and effective for preventing cervical cancer. This assumes adherence to intervals, which is both the provider's and the patient's responsibility: First, less is more; too much screening ("I've always done it this way") can be harmful. Second, screening at intervals set by the guidelines is extremely safe, despite earlier reports or provider concerns that suggest otherwise.

Patients who have undergone several rounds of negative screening have a markedly diminished risk of cervical cancer. Serve them best by performing this underutilized gyn procedure: Sit on your hands.

Be aware that winds of change are blowing: What constitutes appropriate screening intervals is up for discussion this year, and molecular-based testing technologies that are under investigation have the potential to someday be a vast improvement over current good, but subjective, interpretations of results.

Last, promote primary prevention of cervical cancer with HPV vaccination in your practice to increase the percentage of protected patients. Doing so will contribute not only to their long-term health but also, at a societal level, to a herd immunity effect.[5] Any positive HPV infection in a future of a well-vaccinated population will be significant, and HPV-targeted technologies to identify the highest risk women will be the most efficient screening.

Primary prevention of cervical cancer with vaccination is critical in any cancer prevention program

Benard VB, Castle PE, Jenison SA, et al; New Mexico HPV Pap Registry Steering Committee. Population-based incidence rates of cervical intraepithelial neoplasia in the human papillomavirus vaccine era. JAMA Oncol. 2017;3(6):833–837.

Luostarinen T, Apter D, Dillner J, et al. Vaccination protects against invasive HPV-associated cancers. Int J Cancer. 2018;142(10):2186–2187.

The success story of HPV vaccination, after more than a decade of use, continued to unfold in important ways over the past year.

Safety. With tens of millions of doses delivered, we know that the vaccine is safe, and we have retreated on some of the precautions that we once took: For example, we no longer perform a routine pregnancy test before vaccination on reproductive-age women.

Efficacy. We have learned, based on what we see in Australia and Western Europe, that vaccination is highly effective. We are also starting to see evidence of efficacy in areas of the United States, even though the vaccine is voluntary and there are no school-based recommendations. And we know that herd vaccination is very effective. The 2 studies

WHAT THIS EVIDENCE MEANS FOR PRACTICE

The exciting news that the sought-out endpoint of HPV vaccination—prevention of invasive HPV-associated cervical cancer—is being realized. This should all the more energize you to:

- urge vaccination for your patients in whom it is indicated
- emphasize vaccine coverage in the young—especially for the routinely recommended age group of 11- and 12-year-olds
- strenuously reject and counter arguments made by segments of the public that HPV vaccination is neither safe nor necessary
- prepare for potential changes down the road in practice guidelines regarding screening (eg, raising the age at which screening begins) as the impact of vaccination on the health of women is felt.

described here add to our understanding of how vaccination is having an impact on endpoints.

Findings of the 2 studies

HPV vaccination has a direct impact on the precursor of cancer, CIN. Benard and colleagues examined data from the New Mexico HPV Pap Registry, a mandatory statewide surveillance system of cervical cancer screening that captured estimates of both screening prevalence and CIN since the time HPV vaccination was introduced in 2007 to 2014. The investigators examined registry data to gauge trends in the rate of CIN and to estimate the effect of HPV vaccination on that rate when adjusted for changes in screening for cervical cancer.

FAST TRACK

Registry data indicated the incidence of CIN declined significantly across all grades between 2007 and 2015 among women aged 15 to 24 years

The incidence of CIN declined significantly across all grades in 2 groups between 2007 and 2015: females aged 15 to 19 years and females aged 20 to 24 years (but not in females 25 to 29 years of age). During those years, mean uptake of HPV vaccination among females 13 to 17 years of age reached as high as 40% (in 2014).

Although a reduction in CIN2 and CIN3 precancers "are early benchmarks for achieving this aim [of reducing the rate of cancer]," the investigators note, a reduction in CIN1 is "a direct measure of reductions in HPV infections requisite to the development of almost all invasive cervical cancer."

Benard moves on to conclude that a reduction in clinical outcomes of CIN among groups who are partially vaccinated for HPV is going to change clinical practice and reduce the cost-effectiveness of clinical care that supports prevention of cervical cancer. Of greatest importance, modalities and strategies for screening, and management algorithms, are going to need to evolve as HPV vaccination and cervical screening are integrated in a rational manner. Furthermore, it might be feasible to factor in population-level decreases in CIN among cohorts who are partially vaccinated for HPV when reassessing clinical practice guidelines for cervical cancer screening.

What does this mean? As we start to eliminate HPV from the population, any positive screening result will be that much more meaningful because the outcome—cervical cancer—will be much rarer. The onus will be on providers and public health officials to re-strategize how to screen what is going to be a widely-vaccinated population; more and more, we will be looking for needles in a haystack.

How are we going to someday screen women in their 20s who were vaccinated at 11 or 12 years of age? Likely, screening will start at a later age, and screening will be conducted at longer intervals. Any finding of HPV or disease is going to be highly significant, and likely, far less frequent.

HPV vaccination protects against invasive HPV-associated cancer. Luostarinen and colleagues report proof of highly efficacious protection offered by a population-based HPV vaccination program in Finland, in the form of a decrease in the key endpoint: cases of invasive HPV-associated cancer. Examining vaccinated (3,331 females) and unvaccinated (15,665 females) cohorts in the nationwide Finnish Cancer Registry, the investigators identified 10 cases of HPV-caused cancer (8 cervical, 1 oropharyngeal, 1 vulvar) in the unvaccinated females and 0 cases in vaccinated females—a statistically significant difference.

From the evidence gathered in this first intention-to-treat trial, the investigators conclude that vaccination protects against

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invasive HPV-associated cancer—what they call "an awaited, pivotal corollary" to high vaccine efficacy against HPV infection.

Summing up

This success story continues to unfold, despite well-organized, antivaccine campaigns. The HPV vaccine has been an easy target: It is novel, it involves a sexually transmitted infection, and the endpoint of protecting against invasive HPV-associated cancer is years—decades—away. But antivaccine groups can no longer argue the point that studies have not been designed to yield evidence of the impact of the vaccine on decisive endpoints, including cervical cancer. ●

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GUEST EDITORIAL

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oncofertility unless such legislation already has been introduced, the lack of impact on individuals residing in other states, and inefficiency of regional lobbying. In addition, those who are self-insured are not subject to state mandates and therefore will not benefit from such coverage mandates. Finally, nuances in the definition of infertility or age-based restrictions may limit access to these services even when mandated.

A cancer diagnosis is always potentially life-threatening and is often perceived as devastating on a personal level. In women of reproductive age, it represents a threat to their future ability to bear children and to ovarian function. These women deserve to have the opportunity to consider all options to maintain fertility, and they should not struggle with difficult financial choices at a time of such extreme stress.

To address this important issue, a 3-pronged approach is called for:

- All providers caring for cancer patients of reproductive age must be aware of fertility preservation and inform patients of these options.
- Cancer survivors and their caretakers must assist in legislative advocacy efforts.
- Nationally mandated coverage must be sought.

A joint effort by the medical community and women advocates is critical to bring attention to this issue in a national forum and provide a solution that benefits all women.

Acknowledgement

The authors express gratitude to Erin Kramer, Government Affairs, American Society for Reproductive Medicine, and Christa Christakis, Executive Director, American College of Obstetricians and Gynecologists District II, for their assistance. ●

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OBG MANAGEMENT

SPECIAL SECTION

HIGHLIGHTS FROM THE 2018 SOCIETY OF GYNECOLOGIC SURGEONS SCIENTIFIC MEETING PART 2

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Deep infiltrating endometriosis: Evaluation and management

Deep endometriosis is successfully diagnosed with clinical signs and symptoms and specific MRI or TVUS protocols, and treatment options are available to relieve pain and optimize outcomes

Rosanne M. Kho, MD, and Mauricio S. Abrão, MD

Endometriosis affects up to 10% of women of reproductive age or, conservatively, about 6.5 million women in the United States.[1,2] There are 3 types of endometriosis—superficial, ovarian, and deep—and in the past each of these was assumed to have a distinct pathogenesis.[3] Deep infiltrating endometriosis (DIE) is the presence of one or more endometriotic nodules deeper than 5 mm. In a study at a large tertiary-care center, 40% of patients with endometriosis had deep disease.[4] DIE is associated with more severe pain and infertility.[5] In patients with endometriosis, diagnosis is commonly made 7 to 9 years after the initial pelvic pain presentation.[6] For these reasons, well-directed history taking and proper evaluation and treatment should be pursued to relieve pain and optimize outcomes.

CASE Young woman with intensifying pelvic pain

Mary is a 26-year-old social worker who presents to her ObGyn with symptoms of worsening pain during as well as outside her periods. What additional information would you want to obtain from Mary, given her chief symptom of pain?

Investigate the type of pain

It is important to ask the patient about her menstrual and sexual history, her thoughts regarding near- and long-term fertility, and the type and severity of her pain symptoms. The 5 pain symptoms specific to pelvic pain are dysmenorrhea, dyspareunia, dysuria, dyschezia, and noncyclic pelvic pain. A visual analog scale (VAS) for pain as well as pelvic pain questionnaires can be used to guide evaluation options and monitor treatment outcomes. In addition, it is of paramount importance to understand the differential diagnoses that can present as pelvic pain (**TABLE,** page SS4).

CASE Continued: Mary's history

Mary reports that she always has had painful periods and that she was started on oral contraceptive pills for pain control and regulation of her periods soon after the onset of menses, when she was 12 years old. In college, she was prescribed oral contraceptive pills for contraception. Recently engaged, she is interested in becoming pregnant in 3 years.

A year ago, Mary discontinued the pills because of their adverse effects. Now she has severe pain during (VAS score, 8/10) and outside (VAS score, 7) her monthly periods. Because of this pain, she has taken time off from work twice within the past 6 months. She has pain during intercourse (VAS score, 7) and some pain with bowel movements during her menses (VAS score, 4). Pelvic examination reveals a normal-sized uterus and adnexa as well as a tender nodule in the rectovaginal septum.

What diagnostic tests and imaging would you obtain?

Imaging's role in diagnosis

At many advanced centers for endometriosis, DIE is successfully diagnosed with specific magnetic resonance imaging (MRI) or transvaginal ultrasound (TVUS) protocols. In a recent review, MRI's pooled sensitivity and specificity for rectosigmoid endometriosis were 92% and 96%, respectively.[7] Choice of imaging for DIE depends on the skills and experience of the clinicians at each center. At a large referral center in São Paulo, Brazil, TVUS with bowel preparation had better sensitivity and specificity for deep retrocervical and

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Dr. Kho and Dr. Abrão report that they are consultants to AbbVie.

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CONTINUED FROM PAGE SS2

TABLE Differential diagnosis for pelvic pain

Organ system	Differential diagnosis	
Musculoskeletal	• Abdominal wall pain • Myofascial pain • Fibromyalgia • Coccydynia	• Pelvic floor tension myalgia • Osteitis pubis • Levator ani syndrome • Abdominal wall hernia
Urologic	• Interstitial cystitis • Nephrolithiasis	
Gastrointestinal	• Inflammatory bowel disease • Irritable bowel disease • Chronic constipation	• Chronic constipation • Chronic pseudo-obstruction
Psychologic	• Sexual abuse history • Opiate dependency	• Depression • Somatization
Gynecologic (excluding endometriosis)	• Fibroid uterus • Ovarian remnant syndrome • Pelvic inflammatory disease	• Adenomyosis • Pelvic adhesion

rectosigmoid disease compared with MRI and digital pelvic examination.[8] In addition, at a center in the United States, we found that proficiency in performing TVUS for DIE was achieved after 70 to 75 cases, and the exam took an average of only 20 minutes.[9]

Despite recent advances in imaging, most gynecologic societies still hold that endometriosis is to be definitively diagnosed with histologic confirmation from tissue biopsies during surgery. Although surgery remains the diagnostic gold standard, it does not mean that all patients with pelvic pain should undergo diagnostic laparoscopy with tissue biopsies.

The combination of compelling clinical signs, symptoms, and imaging findings (such as absence of findings for ovarian and deep endometriosis) can be used to make a presumptive nonsurgical (that is, clinical) diagnosis of endometriosis. Major societies recommend empiric medical therapy (for example, combination oral contraceptives) for the pain associated with superficial endometriosis.[10,11] When there is no response to treatment, or when a patient declines or has contraindications to medical therapy, diagnostic laparoscopy with excision of endometriosis should be considered.

CASE Continued: Diagnosis

Mary undergoes TVUS with bowel preparation, which reveals a normal uterus and adnexa and the presence of 2 lesions, a 2×1.5-cm retrocervical lesion and a 1.8×2-cm rectosigmoid lesion 9 cm above the anal verge. The rectosigmoid lesion involves the external muscularis and compromises 30% of the bowel circumference.

How would you manage the bowel DIE?

Management options: Factor in the variables

DIE can involve the ureters and bladder, the retrocervical and rectovaginal spaces, the appendix, and the bowel. Lesions can be single or multifocal. Although our institutions' imaging with MRI and TVUS is highly accurate, we additionally recommend the use of colonoscopy (with directed biopsies if appropriate) to evaluate patients who present with rectal bleeding, large endometriotic rectal nodules, or have a family history of bowel cancer.

While many studies have found that surgical resection of DIE improves pain and quality of life, surgery can have significant complications.[12] Observation is adequate for asymptomatic patients with DIE. Medical treatment may be offered to patients with mild pain (there is no evidence of a reduction in lesion size with medical therapy). In cases of surgical treatment, we encourage the involvement of a multidisciplinary surgical team to reduce complications and optimize outcomes.

Patients with DIE, significant pain (VAS score, >7), and multiple failed in vitro fertilization

treatments are candidates for surgery. When bowel endometriosis is noted on imaging, factors such as size, depth, number of lesions, circumferential involvement, and distance from the anal verge are all used to determine the surgical approach. Rectosigmoid lesions smaller than 3 cm can be treated more conservatively—for example, with shaving or anterior resection with manual repair using disk staplers. Segmental resection generally is indicated for rectosigmoid lesions larger than 3 cm, involvement deeper than the submucosal layer, multiple lesions, circumferential involvement of more than 40%, and the presence of obstructed bowel symptoms.[13,14]

In patients with DIE who present with both infertility and pain, antimüllerian hormone level and TVUS follicular count are used to evaluate ovarian reserve. As surgical treatment may further reduce ovarian reserve in patients with DIE and infertility, we counsel them regarding assisted reproductive technology options before surgery.

CASE Resolved

After thorough discussion, Mary opts to try a different combination oral contraceptive pill formulation. The pills improve her pain symptoms significantly (VAS score, 4), and she decides to forgo surgery. She will be followed up closely on an outpatient basis with serial TVUS imaging.

Individualize management based on patient parameters

Imaging has been used for the nonsurgical diagnosis of DIE for many years, and this practice increasingly is being accepted and adopted. A presumptive nonsurgical diagnosis of endometriosis can be made based on the clinical signs and symptoms obtained from a thorough history and physical examination, in addition to the absence of imaging findings for ovarian and deep endometriosis.

According to guidelines from major ObGyn societies, such as the American College of Obstetricians and Gynecologists and the European Society of Human Reproduction and Embryology, empiric medical therapy (including combination oral contraceptives, progesterone-containing formulations, and gonadotropin-releasing hormone agonists) can be considered for patients with presumed endometriosis presenting with pain.[15]

When surgery is chosen, the surgeon must obtain crucial information on the characteristics of the lesion(s) and involve a multidisciplinary team to achieve the best outcomes for the patient. ■

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What's new in simulation training for hysterectomy

Here's a rundown on hysterectomy simulation trainers that can be helpful for polishing skills and teaching (and evaluating) residents

Alicia Scribner, MD, MPH, and Christine Vaccaro, DO

Due to an increase in minimally invasive approaches to hysterectomy, including vaginal and laparoscopic approaches, gynecologic surgeons may need to turn to simulation training to augment practice and hone skills. Simulation is useful for all surgeons, especially for low-volume surgeons, as a warm-up to sharpen technical skills prior to starting the day's cases. Additionally, educators are uniquely poised to use simulation to teach residents and to evaluate their procedural competency.

In this article, we provide an overview of the 3 approaches to hysterectomy—vaginal, laparoscopic, abdominal—through medical modeling and simulation techniques. We focus on practical issues, including current resources available online, cost, setup time, fidelity, and limitations of some commonly available vaginal, laparoscopic, and open hysterectomy models.

Simulation directly influences patient safety. Thus, the value of simulation cannot be overstated, as it can increase the quality of health care by improving patient outcomes and lowering overall costs. In 2008, the American College of Obstetricians and Gynecologists (ACOG) founded the Simulations Working Group to establish simulation as a pillar in education for women's health through collaboration, advocacy, research, and the development and implementation of multidisciplinary simulations-based educational resources and opportunities.

Refer to the ACOG Simulations Working Group Toolkit online to see the objectives, simulation, and videos related to each module. Under the "Hysterectomy" section, you will find how to construct the "flower pot" model for abdominal and vaginal hysterectomy, as well as the AAGL vaginal and laparoscopic hysterectomy webinars. All content is reaffirmed frequently to keep it up to date. You can access the toolkit, with your ACOG login and passcode, at https://www.acog.org/About-ACOG/ACOG-Departments/Simulations-Consortium/Simulations-Consortium-Tool-Kit.

For a comprehensive gynecology curriculum to include vaginal, laparoscopic, and abdominal approaches to hysterectomy, refer to ACOG's Surgical Curriculum in Obstetrics and Gynecology page at https://cfweb.acog.org/scog/. This page lists the standardized surgical skills curriculum for use in training residents in obstetrics and gynecology by procedure. It includes:

- the objective, description, and assessment of the module
- a description of the simulation
- a description of the surgical procedure
- a quiz that must be passed to proceed to evaluation by a faculty member
- an evaluation form to be downloaded and printed by the learner.

Takeaway. Value of Simulation = Quality (Improved Patient Outcomes) ÷ Direct and Indirect Costs.

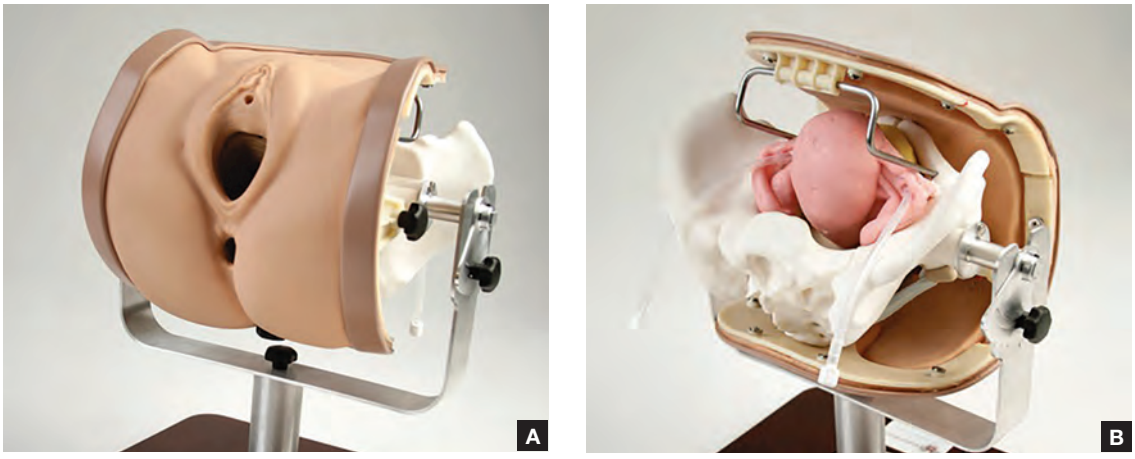
Simulation models for training in vaginal hysterectomy

According to the Accreditation Council for Graduate Medical Education (ACGME), the minimum number of vaginal hysterectomies is 15; this number represents the minimum accepted exposure, however, and does not imply competency. Exposure to vaginal hysterectomy in residency training has significantly declined over the years, with a mean of only 19 vaginal hysterectomies performed by the time of graduation in 2014.[1]

A wide range of simulation models are available

The authors report no financial relationships relevant to this article.

FIGURE 1 Front view (**A**) and back view (**B**) of the Miya Model Pelvic Surgery Training Model



Used with permission from Miyazaki Enterprises, Winston-Salem, North Carolina.

that you either can construct or purchase, based on your budget. We discuss 3 such models below.

The Miya model

The Miya Model Pelvic Surgery Training Model (Miyazaki Enterprises) consists of a bony pelvic frame and multiple replaceable and realistic anatomic structures, including the uterus, cervix, and adnexa (1 structure), vagina, bladder, and a few selected muscles and ligaments for pelvic floor disorders (**FIGURE 1**). The model incorporates features to simulate actual surgical experiences, such as realistic cutting and puncturing tensions, palpable surgical landmarks, a pressurized vascular system with bleeding for inadequate technique, and an inflatable bladder that can leak water if damaged.

Mounted on a rotating stand with the top of the pelvis open, the Miya model is designed to provide access and visibility, enabling supervising physicians the ability to give immediate guidance and feedback. The interchangeable parts allow the learner to be challenged at the appropriate skill level with the use of a large uterus versus a smaller uterus.

New in 2018 is an "intern" uterus and vagina that have no vascular supply and a single-layer vagina; this model is one-third of the cost of the larger, high-fidelity uterus (which has a vascular supply and additional tissue layers).

The Miya model reusable bony pelvic frame has a one-time cost of a few thousand dollars. Advantages include its high fidelity, low technology, light weight, portability, and quick setup.

The gynecologic surgeon and inventor, Dr. Douglas Miyazaki, has improved the vesicouterine peritoneal fold (usually the most challenging for the surgeon) to have a more realistic, slippery feel when palpated.

This model's weaknesses are its cost (relative to low-fidelity models) and the inability to use energy devices.

Takeaway. The Miya model is a high-fidelity, portable vaginal hysterectomy model with a reusable base and consumable replacement parts. It can be tailored to the learner's desired level of difficulty.

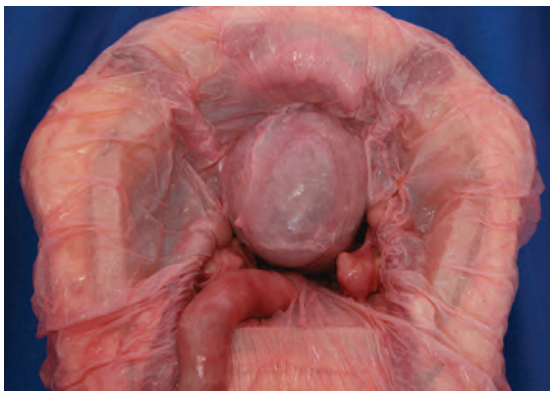
The Gynesim model

The Gynesim Vaginal Hysterectomy Model, developed by Dr. Malcolm "Kip" Mackenzie (Gynesim), is a high-fidelity surgical simulation model constructed from animal tissue to provide realistic training in pelvic surgery (**FIGURE 2**, page SS8).

These "real tissue models" are hand-constructed from animal tissue harvested from US Department of Agriculture inspected meat processing centers. The models mimic normal and abnormal abdominal and pelvic anatomy, providing realistic feel (haptics) and response to all surgical energy modalities. The "cassette" tissues are placed within a vaginal approach platform, which is portable.

Each model (including a 120- to 240-g uterus,

FIGURE 2 Abdominal view of the Gynesim Vaginal Hysterectomy Model



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bladder, ureter, uterine artery, cardinal and uterosacral ligaments, and rectum) supports critical gaps in surgical techniques such as peritoneal entry and cuff closure. Gynesim staff set up the entire laboratory, including the simulation models, instruments, and/or cameras; however, surgical energy systems are secured from the host institution.

The advantages of this model are its excellent tissue haptics and the minimal preparation time required from the busy gynecologic teaching faculty, as the company performs the setup and breakdown. Disadvantages include the model's cost (relative to low-fidelity models), that it does not bleed, its one-time use, and the need for technical assistance from the company for setup.

This model can be used for laparoscopic and open hysterectomy approaches, as well as for vaginal hysterectomy.

Takeaway. The high-fidelity Gynesim model can be used to practice vaginal, laparoscopic, or open hysterectomy approaches. It offers excellent tissue haptics, one-time use "cassettes" made from animal tissue, and compatibility with energy devices.

The milk jug model

The milk jug and fabric uterus model, developed by Dr. Dee Fenner, is a low-cost simulation model and an alternative to the flower pot model (described later in this article). The bony pelvis is simulated by a 1-gallon milk carton that is taped to a foam ring. Other materials used to make the uterus are fabric, stuffing, and a needle and thread (or a sewing machine). Each model costs approximately $5 and takes approximately 15 minutes to create. For instructions on how to construct this model, see the Society for Gynecologic Surgeons (SGS) award-winning video from 2012 at https://vimeo.com/123804677.

The advantages of this model are that it is inexpensive and is a good tool with which novice gynecologic surgeons can learn the basic steps of the procedure. The disadvantages are that it does not bleed, is not compatible with energy devices, and must be constructed by hand (adding considerable time) or with a sewing machine.

Takeaway. The milk jug model is a low-cost, low-fidelity model for the novice surgeon that can be quickly constructed with the use of a sewing machine.

Simulation models for training in laparoscopic hysterectomy

While overall hysterectomy numbers have remained relatively stable during the last 10 years, the proportion of laparoscopic hysterectomy procedures is increasing in residency training.[1] Many toolkits and models are available for practicing skills, from low-fidelity models on which to rehearse laparoscopic techniques (suturing, instrument handling) to high-fidelity models that provide augmented reality views of the abdominal cavity as well as the operating room itself. We offer a sampling of 4 such models below.

The FLS trainer system

The Fundamentals of Laparoscopic Surgery (FLS) Trainer Box (Limbs & Things Ltd) provides hands-on manual skills practice and training for laparoscopic surgery (**FIGURE 3**). The FLS trainer box uses 5 skills to challenge a surgeon's dexterity and psychomotor skills. The set includes the trainer box with a camera and light source as well as the equipment needed to perform the 5 FLS tasks (peg transfer, pattern cutting, ligating loop, and intracorporeal and extracorporeal knot tying). The kit does not include laparoscopic instruments or a monitor.

The FLS trainer box with camera costs $1,164. The advantages are that it is portable and can be used to warm-up prior to surgery or for practice to improve technical skills. It is a great tool for junior residents who are learning the basics of

FIGURE 3 FLS Trainer system (A) components (minus the monitor and instruments) and (B) the unit in use

Used with permission from Limbs & Things Ltd, Savannah, Georgia.

laparoscopic surgery. This trainer's disadvantages are that it is a low-fidelity unit that is procedure agnostic.

Notably, ObGyn residents who graduate after May 31, 2020, will be required to successfully complete the FLS program as a prerequisite for specialty board certification.[2] The FLS program is endorsed by the American College of Surgeons and is run through the Society of American Gastrointestinal and Endoscopic Surgeons. The FLS test is proctored and must be taken at a testing center.

Takeaway. The FLS trainer box is readily available, portable, relatively inexpensive, low-tech, and has valid benchmarks for proficiency. The FLS test will be required for ObGyn residents by 2020.

The SimPraxis software trainer

The SimPraxis Laparoscopic Hysterectomy Trainer (Red Llama, Inc) is an interactive simulation software platform that is available in DVD or USB format (**FIGURE 4**). The software is designed to review anatomy, surgical instrumentation, and specific steps of the procedure. It provides formative assessments and offers summative feedback for users.

The SimPraxis training software would make a useful tool to familiarize medical students and interns with the basics of the procedure before advancing to other simulation trainers. The software costs $100.

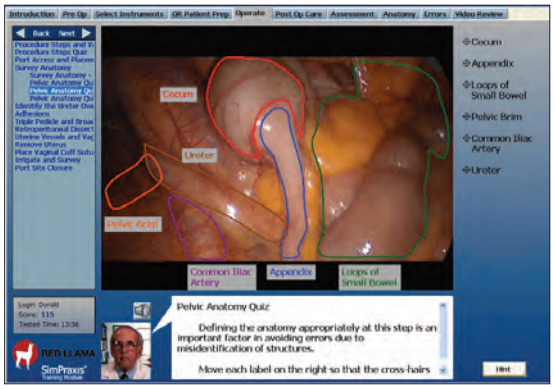
Takeaway. The SimPraxis software is ideal for novice learners and can be used on a home or office computer.

The LapSim virtual reality trainer

The LapSim Haptic System (Surgical Science) is a virtual reality skills trainer. The hysterectomy module includes right and left uterine artery dissection, vaginal cuff opening, and cuff closure (**FIGURE 5,** page SS10). One advantage of this simulator is its haptic feedback system, which enhances the fidelity of the training.

The LapSim simulator includes a training module for students and early learners and

FIGURE 4 Screenshot of the SimPraxis Laparoscopic Hysterectomy Trainer software program demonstrating pelvic structures



Used with permission from Red Llama, Inc, Seattle, Washington.

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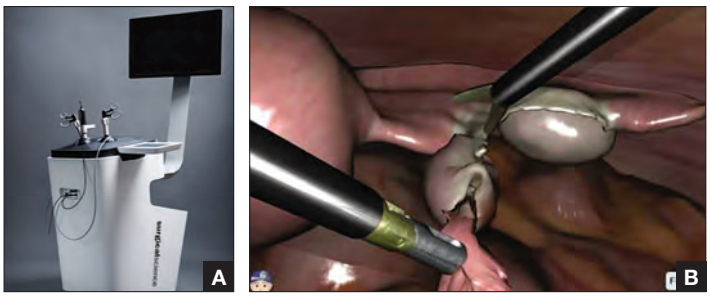
FIGURE 5 The LapSim simulator (**A**) and the LapSim hysterectomy module (**B**) in action



Used with permission from Surgical Science, Göteborg, Sweden.

modules to improve camera handling. The virtual reality base system costs $70,720, and the hysterectomy software module is an additional $15,600.

Takeaway. The LapSim is an expensive, high-fidelity, virtual reality simulator with enhanced haptics and software for practicing laparoscopic hysterectomy.

The LAP Mentor virtual reality simulator

The LAP Mentor VR (3D Systems) is another virtual reality simulator that has modules for laparoscopic hysterectomy and cuff closure (**FIGURE 6**). The trainee uses a virtual reality headset and becomes fully immersed in the operating room environment with audio and visual cues that mimic a real surgical experience.

The hysterectomy module allows the user to manipulate the uterus, identify the ureters, divide the superior pedicles, mobilize the bladder, expose and divide the uterine artery, and perform the colpotomy. The cuff closure module allows the user to suture the vaginal cuff using barbed suture. The module also can expose the learner to complications, such as bladder, ureteral, colon, or vascular injury.

The LAP Mentor VR base system costs $84,000 and the modules cost about $15,000.

Takeaway. The LAP Mentor is an expensive, high-fidelity simulation platform with a virtual reality headset that simulates a laparoscopic hysterectomy (with complications) in the operating room.

ON THE WEB: Robot-assisted laparoscopic hysterectomy simulation at **mdedge.com/obgmanagement**

Models for training in abdominal hysterectomy

In the last 10 years, there has been a 30% decrease in the number of abdominal hysterectomies performed by residents.[1] Because of this decline in operating room experience, simulation training can be an important tool to bolster residency experience.

There are not many simulation models available for teaching abdominal hysterectomy, but here we discuss 2 that we utilize in our residency program.

Adaptable task trainer

The Surgical Female Pelvic Trainer (SFPT) (Limbs & Things Ltd), a pelvic task trainer primarily used for simulation of laparoscopic hysterectomy, can be adapted for abdominal hysterectomy by removing the abdominal cover (**FIGURE 7**). This trainer can be used with simulated blood to increase the realism of training. The SFPT trainer costs $2,190.

Takeaway. The SFPT is a medium-fidelity task trainer with a reusable base and consumable replacement parts.

ACOG's do-it-yourself flower pot model

The flower pot model (developed by the ACOG Simulation Working Group, Washington, DC) is a comprehensive educational package that includes learning objectives, simulation construction instructions, content review of the abdominal hysterectomy, quiz, and evaluation form.[3] ACOG has endorsed this low-cost model for residency education. Each model costs approximately $20, and the base (flower pot) is reusable. Construction time for each model is 30 to 60 minutes, and learners can participate in the construction. This can aid in anatomy review and familiarization with the model prior to training in the surgical procedure.

The learning objectives, content review, quiz, and evaluation form can be used for the flower pot model or for high-fidelity models.

The advantages of this model are the low cost and that it provides enough fidelity to teach each of the critical steps of the procedure. The

FIGURE 6 The LAP Mentor VR simulation unit (**A**) and the Lap Mentor VR operating room (**B**) experienced via a headset

Used with permission from 3D Systems, Airport City, Israel.

disadvantages include that it is a lower-fidelity model, requires a considerable amount of time for construction, does not bleed, and is not compatible with energy devices. This model also can be used for training in laparoscopic and vaginal hysterectomy. For more information, visit ACOG's Surgical Curriculum website at https://cfweb.acog.org/scog/.

Takeaway. ACOG's flower pot model for hysterectomy training is a comprehensive, low-cost, low-fidelity simulation model that requires significant setup time.

Simulation's offerings

Simulation training is the present and future of medicine that bridges the gap between textbook learning and technical proficiency. Although in this article we describe only a handful of the simulation resources available, we hope that you will incorporate such tools into your practice for continuing education and skill development. Utilize peer-reviewed resources, such as the ACOG curriculum module and evaluation tools for abdominal, laparoscopic, and vaginal hysterectomy, which can be used with any simulation model to provide a comprehensive and complimentary learning experience.

The future of health care depends on the commitment and ingenuity of educators who embrace medical simulation's purpose: improved patient safety, effectiveness, and efficiency. Join the movement! ■

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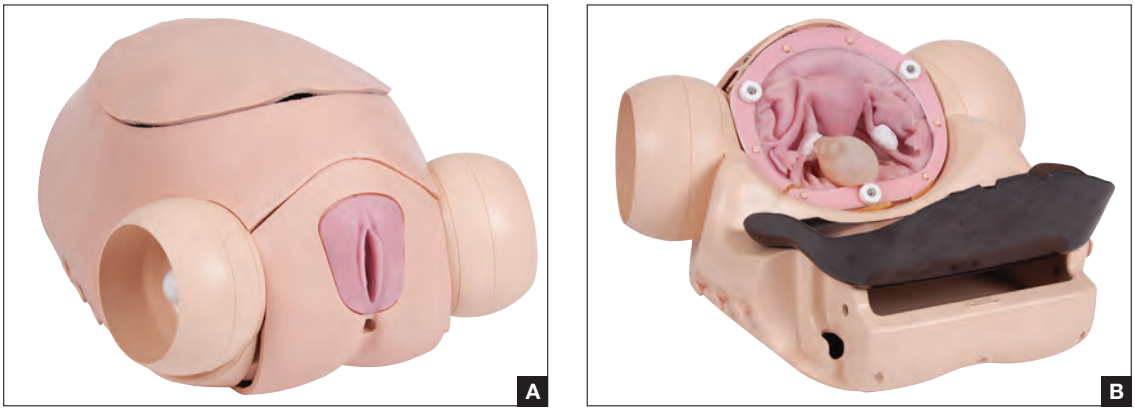
FIGURE 7 Surgical Female Pelvic Trainer model (**A**) and model (**B**) with abdominal cover removed



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Inhaled nitrous oxide for labor analgesia: Pearls from clinical experience

Nitrous oxide has minimal adverse effects when used as inhaled analgesia during labor and is economically feasible, readily available, and rapidly reversible, all without proven impact on neonatal outcomes

William Camann, MD

Nitrous oxide, a colorless, odorless gas, has long been used for labor analgesia in many countries, including the United Kingdom, Canada, throughout Europe, Australia, and New Zealand. Recently, interest in its use in the United States has increased, since the US Food and Drug Administration (FDA) approval in 2012 of simple devices for administration of nitrous oxide in a variety of locations. Being able to offer an alternative technique, other than parenteral opioids, for women who may not wish to or who cannot have regional analgesia, and for women who have delivered and need analgesia for postdelivery repair, conveys significant benefits. Risks to its use are very low, although the quality of pain relief is inferior to that offered by regional analgesic techniques. Our experience with its use since 2014 at Brigham and Women's Hospital in Boston, Massachusetts, corroborates that reported in the literature and leads us to continue offering inhaled nitrous oxide and advocating that others do as well.[1–7] When using nitrous oxide in your labor and delivery unit, or if considering its use, keep the following points in mind.

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The author reports no financial relationships relevant to this article.

A successful inhaled nitrous oxide program requires proper patient selection

Inhaled nitrous oxide is *not* an epidural (**TABLE,** page 30).[8] The pain relief is clearly inferior to that of an epidural. Inhaled nitrous oxide will not replace epidurals or even have any effect on the epidural rate at a particular institution.[6] However, the use of inhaled nitrous oxide for labor analgesia has a long track record of safety (albeit with moderate efficacy for selected patients) for many years in many countries around the world. Inhaled nitrous oxide is a valuable addition to the options we can offer patients:

- who are poor responders to opioid medication or who have high opioid tolerance
- with certain disorders of coagulation
- with chronic pain or anxiety
- who for other reasons need to consider alternatives or adjuncts to neuraxial analgesia.

Although it is important to be realistic regarding the expectations of analgesia quality offered by this agent,[7] compared with other agents we have tried, it has less adverse effects, is economically reasonable, and has no proven impact on neonatal outcomes.

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TABLE Epidural versus nitrous oxide for analgesia[8]

Epidural	Inhaled nitrous oxide
Dense pain relief	Variable pain reduction
Superior pain reduction compared with inhaled nitrous oxide	Pain is reduced but still present
No sedative effect	Significant anxiolysis
Invasive	Noninvasive
Serious side effects uncommon	No serious side effects or risks as used in labor
Laboring woman is bed bound	Woman has freedom to move about
Must have IV access and possible urinary catheter	Does not require IV access or urinary catheter
Can be converted to anesthesia for cesarean, if needed	Not possible to use for cesarean anesthesia

FAST TRACK

Inhaled nitrous oxide is patient controlled (with the patient holding a mask or mouthpiece according to her preference) and the device allows the patient to move about freely

No significant complications with inhaled nitrous oxide have been reported

Systematic reviews did not report any significant complications to either mother or newborn.[1,2] Our personal experiences corroborate this, as no complications have been associated with its frequent use at Brigham and Women's Hospital. Reported adverse effects are mild. The incidence of nausea is 13%, dizziness is 3% to 5%, and drowsiness is 4%; these rates are hard to detect over the baseline rates of those side effects associated with labor and delivery alone.[1] Many other centers have now adopted the use of this agent, with several hundred locations now offering inhaled nitrous oxide for labor analgesia in the United States.

Practical use of inhaled nitrous oxide is relatively simple

Several vendors offer portable, user-friendly, cost-effective equipment that is appropriate for labor and delivery use. All devices are structured in demand-valve modality, meaning that the patient must initiate a breath in order to open a valve that allows gas to flow. Cessation of the inspiratory effort closes the valve, thus preventing the free flow of gas into the ambient atmosphere of the room. The devices generally include a tank with nitrous oxide as well as a source of oxygen. Most devices designed for labor and delivery provide a fixed mixture of 50% nitrous oxide and 50% oxygen, with fail-safe mechanisms to allow increased oxygen delivery in the event of failure or depletion of the nitrous supply. All modern, FDA–approved devices include effective scavenging systems, such that expired gases are vented outside (generally via room suction), which prevents occupational exposure to low levels of nitrous oxide.

Inhaled nitrous oxide for labor pain must be patient controlled

An essential feature of the use of inhaled nitrous oxide for labor analgesia is that it must be considered a patient-controlled system. Patients have an option to use either a mask or a mouthpiece, according to their preferences and comfort. The patient must hold the mask or mouthpiece herself; it is neither appropriate nor safe for anyone else, such as a nurse, family member, or labor support personnel, to assist with this task.

Some coordination with the nurse is essential for optimal timing of administration. Onset of a therapeutic level of pain relief is generally 30 to 60 seconds after inhalation has begun, with rapid resolution after cessation of the inhalation. The patient should thus initiate the inspiration of the gas at the earliest signs of onset of a contraction, so as to achieve maximal analgesia at the peak of the contraction. Waiting until the peak of the contraction to initiate inhalation of the nitrous oxide will not provide effective analgesia, yet will result in sedation after the contraction has ended.

No oversight by an anesthesiologist is required

The Centers for Medicare and Medicaid Services (CMS) produced a clarification statement for definitions of "anesthesia services" (42 CFR 482.52)[9] that may be offered by a hospital, based on American Society of Anesthesiologists (ASA) definitions. CMS, consistent with ASA guidelines, does not define moderate or conscious sedation as "anesthesia," thus direct oversight by an anesthesiologist is not required. Furthermore, the definition of "minimal sedation," which is where 50% concentration delivery of inhaled nitrous oxide

would be categorized, also does not meet this requirement by CMS.

Women who use inhaled nitrous oxide for labor pain typically are satisfied with its use

The use of analog pain scale measurements may not be appropriate in a setting where dissociation from pain might be the primary beneficial effect. Measurements of maternal satisfaction with their analgesic experience support this. The experiences at Vanderbilt University and Brigham and Women's Hospital show that, while pain relief is limited, like reported in systematic reviews, maternal satisfaction scores for labor analgesia are not different among women who receive inhaled nitrous oxide analgesia, neuraxial analgesia, and those who transition from nitrous to neuraxial analgesia. In fact, published evidence supports extraordinarily high satisfaction in women who plan to use inhaled nitrous oxide, and actually successfully do so, despite only limited degrees of pain relief.[10,11] Work to identify the characteristics of women who report success with inhaled nitrous oxide use needs to be performed so that patients can be better selected and informed when making analgesic choices.

Animal research on inhaled nitrous oxide may not translate well to human neonates

A very recent task force convened by the European Society of Anaesthesiology (ESA) addressed some of the potential concerns about inhaled nitrous oxide analgesia.[12] Per their report:

> "the potential teratogenic effect of N2O observed in experimental models cannot be extrapolated to humans. There is a lack of evidence for an association between N2O and reproductive toxicity. The incidence of health hazards and abortion was not shown to be higher in women exposed to, or spouses of men exposed to N2O than those who were not so exposed. Moreover, the incidence of congenital malformations was not higher among women who received N2O for anaesthesia during the first trimester of pregnancy nor during anaesthesia management for cervical cerclage, nor for surgery in the first two trimesters of pregnancy."

There is a theoretical concern of an increase in neuronal apoptosis in neonates, demonstrated in laboratory animals in anesthetic concentrations, but the human relevance of this is not clear, since the data on animal developmental neurotoxicity is generally combined with data wherein potent inhalational anesthetic agents were also used, not nitrous oxide alone.[13] The analgesic doses and time of exposure of inhaled nitrous oxide administered for labor analgesia are well below those required for these changes, as subanesthetic doses are associated with minimal changes, if any, in laboratory animals.

No labor analgesic is without the potential for fetal effects, and alternative labor analgesics such as systemic opioids in higher doses also may have potential adverse effects on the fetus, such as fetal heart rate effects or early tone, alertness, and breastfeeding

FAST TRACK

Maternal satisfaction with labor analgesia is similar among women who receive inhaled nitrous oxide analgesia, neuraxial analgesia, and those who transition from nitrous to neuraxial analgesia

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

difficulties. The low solubility and short half-life of inhaled nitrous oxide contribute to low absorption by tissues, thus contributing to the safety of this agent. Nitrous oxide via inhalation for sedation during elective cesarean has been reported to show no adverse effects on neonatal Apgar scores.[14]

Modern equipment keeps occupational exposure to nitrous oxide safe

One retrospective review of women exposed to high concentrations of inhaled nitrous oxide reported reduced fertility.[15] However, the only effects on fertility were seen when nitrous was used without scavenging equipment, and in high concentrations. Moreover, that study examined dental offices, where nitrous was free flowing during procedures—quite a different setting than the intermittent inhalation, demand-valve modality as is used during labor—and when using appropriate modern, FDA-approved equipment, and scavenging devices. Per the recent ESA task force[12]:

> "Members of the task force agreed that, despite theoretical concerns and laboratory data, there is no evidence indicating that the use of N2O in a clinically relevant setting would increase health risk in patients or providers exposed to this drug. With the ubiquitous availability of scavenging systems in the modern operating room, the health concern for medical staff has decreased dramatically. Properly operating scavenging systems reduce N2O concentrations by more than 70%, thereby efficiently keeping ambient N2O levels well below official limits."

The ESA task force concludes: "An extensive amount of clinical evidence indicates that N2O can be used safely for procedural pain management, for labour pain, and for anxiolysis and sedation in dentistry."[12]

Two important reminders

Inhaled nitrous oxide has been a central component of the labor pain relief menu in most of the rest of the world for decades, and the safety record is impeccable. This agent has now had extensive and growing experience in American maternity units. Remember 2 critical points: 1) patient selection is key, 2) analgesia is *not* like that provided by regional anesthetic techniques such as an epidural. ●

FAST TRACK

Inhaled nitrous oxide has been used for safe labor pain relief in other countries for decades. Key to its use are patient selection and remembering that it's not an epidural.

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Two good apps for management of cervical cancer screening results

Clinical decision making made easier

Katherine T. Chen, MD, MPH

Mobile applications are useful for clinical decision making. An example is in the area of cervical cancer screening. The incidence of cervical cancer and mortality from the disease in the United States has decreased with the implementation of cervical cancer screening programs.[1] However, being up to date on the guidelines can be challenging. In 2001, the revised Bethesda system terminology for reporting cervical cytology results became available. In response, the American Society for Colposcopy and Cervical Pathology (ASCCP) developed comprehensive, evidence-based consensus guidelines to assist health care providers in managing abnormal screening results. In 2006, the guidelines were revised, and in 2012, revised again.[2]

In a search in the Apple iTunes and Google Play stores for apps useful for gynecologic oncology providers, Dr. Sara Farag, colleagues, and I identified and evaluated highly 2 cervical cancer screening apps: ASCCP Mobile and Pap Reader.[3] These apps can aid any health care provider who performs Pap smear screening and who manages screening results.

ASCCP Mobile includes follow-up guidelines regarding colposcopy results as well as guidelines for posthysterectomy and pregnant women. The app also has a clinical decision support system (an active knowledge system that uses 2 or more items of patient data to generate case-specific advice).

Pap Reader includes guidelines for postmenopausal and pregnant women and also has a clinical decision support system. Unlike ASCCP Mobile, Pap Reader is free.

The recommended cervical cancer screening apps are listed in the **TABLE** (page 38) alphabetically and are detailed with a shortened version of the APPLICATIONS scoring system, APPLI (app comprehensiveness, price, platform, literature use, and important special features).[4] I hope these apps will assist you in your management of patients who undergo Pap smear screening. ●

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The author reports being an advisory board member and receiving royalties from UpToDate, Inc.

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BUSINESS OF MEDICINE

How to decide on purchasing new medical equipment

These nonfinancial and financial tools can facilitate your analysis

David S. Kim, MD, PhD, MBA

IN THIS ARTICLE

Providing state-of-the-art health care for women often requires the use of various types of medical equipment, and decisions regarding their purchase can be complicated. With rising costs and reduced reimbursements, capital expenditures must be made with great care. Some equipment may not generate revenue but is required at a basic care-giving level: examination tables, procedure instruments, autoclaves, etc. Conversely, other equipment may not be necessary but strongly desired to offer a full complement of care. Unfortunately, sometimes a decision to buy expensive equipment is based more on a sales representative's ability to rationalize the purchase as a sound investment than on its necessity or practicality. This article focuses on tools to help you make a decision to obtain revenue-generating medical equipment.

First consideration: Nonfinancial evaluation

Nonfinancial criteria should be your first concern. They may have a greater impact on your practice than any financial consideration.

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

Does this investment align with your overall goals?

If your focus is to provide the best and most efficient obstetric care in the community, it may not make sense to purchase urodynamic equipment, even if using the equipment could be profitable.[1] If the equipment begins to distract the practice from its strategic focus, then complications from managing this new equipment might be more harmful than helpful.

What are the pros and cons of the investment?

Concern that the equipment may not be effective or may become obsolete in a few years would preclude having to consider the financial purchase in the first place.[1]

Consider a PESTLE analysis

Before starting a new project, use a PESTLE analysis to assess external factors that are political, economic, social, technological, legal, and environmental. Its purpose is to identify issues that are beyond the control of the organization and have some level of impact on the organization.[2,3]

If you are considering the purchase of a laser hair removal machine, what could be the political considerations, such as your reputation among peers or other physicians who refer patients to your practice? What are the economic (financial) considerations? How would the social (or marketing) message be communicated, and do you have the

organizational skills to implement a marketing strategy? What are the technical challenges required for maintaining this machine, and how much skill and training would be required to safely use it? What are the legal ramifications for implementing this service? Does your malpractice insurance cover it? And finally, what kind of environment (physical space) would be required?

What alternative investment opportunities might compete?

When considering a significant investment, other opportunities may no longer be feasible. Think about other ways your practice could use the money and which investment prospects would be the best fit.[1] For instance, purchasing equipment that is very time intensive may not necessarily be the most profitable decision, especially if it takes the provider away from other services with higher margins. Could investing in expensive equipment delay bringing in another provider who might have a higher financial impact?

Next stage: Financial evaluation

To begin a basic cash flow analysis of the new investment, gather your practice's financial data. Estimate the cash flow resulting from the equipment investment, including any additional expenses and revenues. Here are some steps:

1. **Identify the revenue** generated by each use of the equipment.
2. **Estimate the variable costs** (costs that increase with each incremental unit of activity). Variable costs include expenses associated with each use, such as disposable accessories. For a hysteroscope, the variable cost may be the tubing and fluid used. Some procedures, such as office hysteroscopic sterilization, require the purchase of intratubal occlusion devices.

   Also consider the cost of your time. One way to determine this is to investigate the hourly rate you would be paid if you were hypothetically hired by a third party to perform the procedure.
3. **Estimate the step costs.** Step costs are constant over a narrow range of activity but shift to a higher level with increased activity. One example is staffing costs. If the number of these procedures significantly increases, additional staffing will be required. Include the hourly pay for your medical assistants in the analysis.
4. **Determine the contribution margin.** Subtract the revenue from the sum of the variable and step costs to find the **contribution margin** (dollar contribution per unit) to your practice.[4,5]
5. **Estimate the approximate volume of procedures.** It is hard to predict future demand, but a good rule of thumb is to estimate the best, expected, and pessimistic volumes. Then average the 3 scenarios and use that figure as the anticipated volume. Multiply the volume by the contribution margin to calculate profit.

Additional financial tools

Once the basic cash flow analysis of the new investment is undertaken, add these methods to your analysis:

Net Present Value (NPV) is the difference between the present value of cash inflows and the present value of cash outflows.[6] NPV takes into consideration the time value of money, where money in the present is worth more than the same value sometime in the future due to inflation and earning capacity. NPV is used in capital budgeting to analyze the profitability of a projected investment or project.[1,4,5]

Consider the **discount rate** as the expected rate of return or cost of capital. By discounting the future cash flow each year by the discount rate, you can get the present value of cash flow. Subtract the present value of cash flow from the original investment to get the NPV for the equipment's investment. A positive value is a favorable analysis to purchase the equipment; a negative value may suggest that the equipment may be a poor investment.

The NPV can be calculated in a spreadsheet using the following NPV command formula: **NPV(rate,value1,[value2],...)**. This formula gives you the present value of cash inflows. The rate is the discount rate and the values are the series of cash flows occurring over

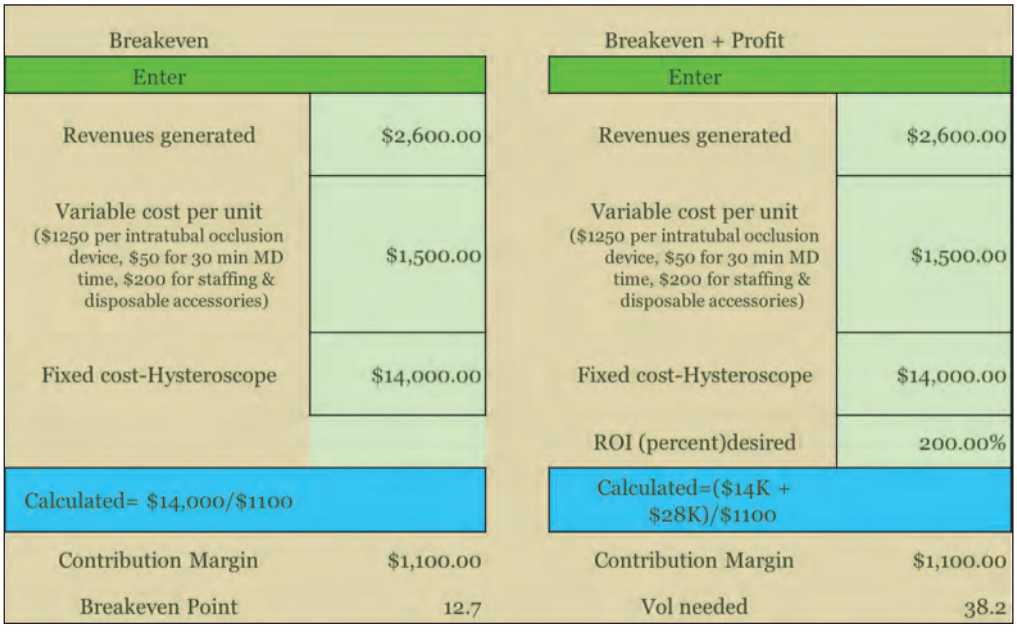
FAST TRACK

Net Present Value (NPV) is used to analyze the profitability of a projected investment or project

ON THE WEB

Additional figures are found in the web version of this article at mdedge.com/obgmanagement

FIGURE Breakeven analysis for hysteroscope purchase for use in tubal sterilization



Breakeven		Breakeven + Profit	
Enter		Enter	
Revenues generated	$2,600.00	Revenues generated	$2,600.00
Variable cost per unit ($1250 per intratubal occlusion device, $50 for 30 min MD time, $200 for staffing & disposable accessories)	$1,500.00	Variable cost per unit ($1250 per intratubal occlusion device, $50 for 30 min MD time, $200 for staffing & disposable accessories)	$1,500.00
Fixed cost-Hysteroscope	$14,000.00	Fixed cost-Hysteroscope	$14,000.00
		ROI (percent)desired	200.00%
Calculated= $14,000/$1100		Calculated=($14K + $28K)/$1100	
Contribution Margin	$1,100.00	Contribution Margin	$1,100.00
Breakeven Point	12.7	Vol needed	38.2

Abbreviations: MD, medical doctor; ROI, return on investment; Vol, volume.

FAST TRACK

Accept a project in which the internal rate of return (IRR) is greater than the required rate of return

a period of time. The NPV command formula in Excel, despite its misleading name, only gives the present value of cash flows.[7] Therefore, it is important that the present value of cash inflows is subtracted from the initial capital investment to get the NPV.

For example, a piece of equipment may require a $14,000 initial investment in Year 0. Each year the use of the equipment generates $25,300 per year through year 5. Assign a discount rate of 11%, about what you would expect for a stock market investment.

Consider other investment opportunities. The historical rate of return for a stock index fund is 11.5%.[8] Using this discount rate, you can compare whether the money would be better invested in the medical equipment or stock.

Internal rate of return (IRR) is a metric used in capital budgeting to measure the profitability of potential investments. The IRR determines if the discount rate at which the present value of expected net cash inflow is equal to the cash outlay. In other words, the IRR is the discount rate that makes the net present cash flows from a project equal zero. The decision rule related to the IRR criterion is to accept a project in which the IRR is greater than the required rate of return (cutoff rate). The formula for the IRR is the same as the NPV formula, except that the NPV is set at zero and the discount rate is calculated through iterative calculation. The IRR can be calculated in a spreadsheet using the following command formula: **IRR(values, [guess])**.[1,5,9]

The IRR is somewhat different from **return on investment** (ROI). ROI is the percent of return on the initial investment over a period of time. Each piece of equipment has a different ROI over a different time period. ROI does not take into account the **time value of money** (TVM). Incorporating the IRR (or the TVM) allows for equal comparison between 2 pieces of equipment in the analysis.[10]

If you are not comparing 2 different types of equipment for purchase, then using the cutoff of 11.5% may be helpful (the historical average stock market return). If the IRR is less than 11.5%, then in theory, it would be better to put your money in the stock market than in new equipment.[7]

Breakeven analysis calculates the volume of procedures that would be needed to break

TABLE Present value of cash flows for hysteroscopic sterilization

Years	Calculation	Result
1	$25,300 x 1/(1.11)	$22,793
2	$25,300 x 1/(1.11)^2	$20,534
3	$25,300 x 1/(1.11)^3	$18,499
4	$25,300 x 1/(1.11)^4	$16,666
5	$25,300 x 1/(1.11)^5	$15,014

even or make a profit. It can also determine if there is enough demand to meet the volume required to break even or profit. Unlike the first 2 methods, where you have to guess at future volume, this method calculates the volume required to break even, but does not specify a time period. Your practice would have to use subjective experience to determine how long it would take to reach that volume, given your patient population and the ability to reach the targeted market segment.

Fixed costs are costs that do not change with the varying volume of units of service or products sold. After calculating the contribution margin, divide the fixed costs of the equipment by the contribution margin. Then you will have the volume required to break even (**FIGURE**). Add the dollar amount of profit you would like to attain to the fixed costs, then divide that total by the contribution margin, and you'll have the volume required to meet those specifications.[1,4,5]

Even though the calculations described above relate to medical equipment, you can use this same method to analyze the cost of adding new providers or any other business development project to determine the required volume to break even on the capital outlay.

CASE New equipment requests

A new ObGyn in your practice requests that you purchase a hysteroscope so that she can start performing office-based hysteroscopic sterilization. Another partner would like to acquire urodynamic equipment instead of referring urinary incontinent patients to a urogynecologist. How do you decide what to purchase?

First calculate the contribution margins for each product. Next, since you do not know for certain the volume you might achieve for each procedure, create 3 scenarios for the best, expected, and pessimistic situations. Assume equal probability for each of these categories and average the volumes of the estimates. Even though you may keep the equipment longer, estimate the financial analysis over 5 years. In this example, we assume a discount rate of 11% for the NPV calculation for both pieces of equipment.

Calculate the IRR using a spreadsheet based on the cash flow for each piece of equipment. Say that the practice anticipates doing 23 hysteroscopic sterilizations per year. If the reimbursement is $2,600 per procedure, and the variable costs are $1,500, the contribution margin is $1,100. So 23 procedures multiplied by $1,100 equals an annual profit of $25,300. Then discount the $25,300 for each year. In this example, we use a discount rate of 11%. The **TABLE** shows the amount discounted each year.

The sum of the discounted cash flows is $93,506. However, we have to subtract the initial investment of $14,000, so the final NPV equals $79,506.

Apply the same financial NPV and IRR calculations used to assess the hysteroscope to the urodynamic equipment. From the analysis, both purchases would be financially successful. However, it appears that the urodynamic equipment is a superior investment over the hysteroscope, with a higher NPV ($115,877 vs $81,880, respectively) and IRR (336% vs 180%, respectively). This is likely due to the higher anticipated volume of use with the urodynamic equipment and lower cost of initial investment, despite having a lower contribution margin than the hysteroscope.

Caveats

For simplicity, this analysis does not account for the fact that the hysteroscope could be used for other revenue-generating procedures such as diagnostic hysteroscopy. Factoring in these potential additional services using the same hysteroscope might change the decision analysis in favor of the hysteroscope.

Remember that, although the financial

FAST TRACK

Use the same calculations to analyze the cost of adding new providers or any other business development project

analysis is very helpful in decision making, nonfinancial evaluations should also influence your choice. In this example, while there may be a financial advantage to purchasing the urodynamic equipment over the hysteroscopic equipment, nonfinancial considerations can help you decide which purchase would be a better aligned with the goals and strategies of your practice.

These tools for nonfinancial and financial analysis can be used for any investment in your practice, whether it is in medical equipment, personnel, or development of other profit centers. ●

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App REVIEW

CONTINUED FROM PAGE 33

TABLE Recommended cervical cancer screening applications

App	App comprehensiveness	Price	Platform	Literature used	Important special features
ASCCP Mobile iTunes: https://itunes.apple.com/us/app/asccp-mobile/id615585559?mt=8 Google Play: https://play.google.com/store/apps/details?id=org.asccp.mobile&hl=en	• Screening guidelines • Follow-up guidelines • Guidelines for women posthysterectomy and pregnant women	$9.99	iTunes and Google Play store	2012 ASCCP Guidelines	• Clinical decision support system • Graphics of algorithms
Pap Reader iTunes: https://itunes.apple.com/us/app/pap-reader/id664441342?mt=8	• Screening guidelines • Guidelines for postmenopausal women and pregnant women	Free	iTunes	2012 ASCCP Guidelines	• Clinical decision support system

INDEX OF ADVERTISERS

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR
ParaGard® T 380A Intrauterine Copper Contraceptive

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

ParaGard® is indicated for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies has been less than 1 pregnancy per 100 women each year.

CONTRAINDICATIONS

ParaGard® should not be placed when one or more of the following conditions exist:

1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease, or current behavior suggesting a high risk for pelvic inflammatory disease
4. Postpartum endometritis or postabortal endometritis in the past 3 months
5. Known or suspected uterine or cervical malignancy
6. Genital bleeding of unknown etiology
7. Mucopurulent cervicitis
8. Wilson's disease
9. Allergy to any component of ParaGard®
10. A previously placed IUD that has not been removed

WARNINGS

1. Intrauterine Pregnancy

If intrauterine pregnancy occurs with ParaGard® in place and the string is visible, ParaGard® should be removed because of the risk of spontaneous abortion, premature delivery, sepsis, septic shock, and, rarely, death. Removal may be followed by pregnancy loss.

If the string is not visible, and the woman decides to continue her pregnancy, check if the ParaGard® is in her uterus (for example, by ultrasound). If ParaGard® is in her uterus, warn her that there is an increased risk of spontaneous abortion and sepsis, septic shock, and rarely, death. In addition, the risk of premature labor and delivery is increased.

Human data about risk of birth defects from copper exposure are limited. However, studies have not detected a pattern of abnormalities, and published reports do not suggest a risk that is higher than the baseline risk for birth defects.

2. Ectopic Pregnancy

Women who become pregnant while using ParaGard® should be evaluated for ectopic pregnancy. A pregnancy that occurs with ParaGard® in place is more likely to be ectopic than a pregnancy in the general population. However, because ParaGard® prevents most pregnancies, women who use ParaGard® have a lower risk of an ectopic pregnancy than sexually active women who do not use any contraception.

3. Pelvic Infection

Although pelvic inflammatory disease (PID) in women using IUDs is uncommon, IUDs may be associated with an increased relative risk of PID compared to other forms of contraception and to no contraception. The highest incidence of PID occurs within 20 days following insertion. Therefore, the visit following the first post-insertion menstrual period is an opportunity to assess the patient for infection, as well as to check that the IUD is in place. Since pelvic infection is most frequently associated with sexually transmitted organisms, IUDs are not recommended for women at high risk for sexual infection. Prophylactic antibiotics at the time of insertion do not appear to lower the incidence of PID.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID.

Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

The significance of actinomyces-like organisms on Papanicolaou smear in an asymptomatic IUD user is unknown, and so this finding alone does not always require IUD removal and treatment. However, because pelvic actinomycosis is a serious infection, a woman who has *symptoms* of pelvic infection possibly due to actinomyces should be treated and have her IUD removed.

4. Immunocompromise

Women with AIDS should not have IUDs inserted unless they are clinically stable on antiretroviral therapy. Limited data suggest that asymptomatic women infected with human immunodeficiency virus may use intrauterine devices. Little is known about the use of IUDs in women who have illnesses causing serious immunocompromise. Therefore these women should be carefully monitored for infection if they choose to use an IUD. The risk of pregnancy should be weighed against the theoretical risk of infection.

5. Embedment

Partial penetration or embedment of ParaGard® in the myometrium can make removal difficult. In some cases, surgical removal may be necessary.

6. Perforation

Partial or total perforation of the uterine wall or cervix may occur rarely during placement, although it may not be detected until later. Spontaneous migration has also been reported. If perforation does occur, remove ParaGard® promptly, since the copper can lead to intraperitoneal adhesions. Intestinal penetration, intestinal obstruction, and/or damage to adjacent organs may result if an IUD is left in the peritoneal cavity. Pre-operative imaging followed by laparoscopy or laparotomy is often required to remove an IUD from the peritoneal cavity.

7. Expulsion

Expulsion can occur, usually during the menses and usually in the first few months after insertion. There is an increased risk of expulsion in the nulliparous patient. If unnoticed, an unintended pregnancy could occur.

8. Wilson's Disease

Theoretically, ParaGard® can exacerbate Wilson's disease, a rare genetic disease affecting copper excretion.

PRECAUTIONS

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. Information for patients

Before inserting ParaGard® discuss the Patient Package Insert with the patient, and give her time to read the information. Discuss any questions she may have concerning ParaGard® as well as other methods of contraception. Instruct her to promptly report symptoms of infection, pregnancy, or missing strings.

2. Insertion precautions, continuing care, and removal.

3. Vaginal bleeding

In the 2 largest clinical trials with ParaGard®, menstrual changes were the most common medical reason for discontinuation of ParaGard®. Discontinuation rates for pain and bleeding combined are highest in the first year of use and diminish thereafter. The percentage of women who discontinued ParaGard® because of bleeding problems or pain during these studies ranged from 11.9% in the first year to 2.2 % in year 9. Women complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue ParaGard®.

4. Vasovagal reactions, including fainting

Some women have vasovagal reactions immediately after insertion. Hence, patients should remain supine until feeling well and should be cautious when getting up.

5. Expulsion following placement after a birth or abortion

ParaGard® has been placed immediately after delivery, although risk of expulsion may be higher than when ParaGard® is placed at times unrelated to delivery. However, unless done immediately postpartum, insertion should be delayed to the second postpartum month because insertion during the first postpartum month (except for immediately after delivery) has been associated with increased risk of perforation.

ParaGard® can be placed immediately after abortion, although immediate placement has a slightly higher risk of expulsion than placement at other times. Placement after second trimester abortion is associated with a higher risk of expulsion than placement after the first trimester abortion.

6. Magnetic resonance imaging (MRI)

Limited data suggest that MRI at the level of 1.5 Tesla is acceptable in women using ParaGard®. One study examined the effect of MRI on the CU-7® Intrauterine Copper Contraceptive and Lippes Loop™ intrauterine devices. Neither device moved under the influence of the magnetic field or heated during the spin-echo sequences usually employed for pelvic imaging. An in vitro study did not detect movement or temperature change when ParaGard® was subjected to MRI.

7. Medical diathermy

Theoretically, medical (non-surgical) diathermy (short-wave and microwave heat therapy) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. However, a small study of eight women did not detect a significant elevation of intrauterine temperature when diathermy was performed in the presence of a copper IUD.

8. Pregnancy

ParaGard® is contraindicated during pregnancy.

9. Nursing mothers

Nursing mothers may use ParaGard®. No difference has been detected in concentration of copper in human milk before and after insertion of copper IUDs. The literature is conflicting, but limited data suggest that there may be an increased risk of perforation and expulsion if a woman is lactating.

10. Pediatric use

ParaGard® is not indicated before menarche. Safety and efficacy have been established in women over 16 years old.

ADVERSE REACTIONS

The most serious adverse events associated with intrauterine contraception are discussed in **WARNINGS** and **PRECAUTIONS**. These include:

Intrauterine pregnancy	Pelvic infection
Septic abortion	Perforation
Ectopic pregnancy	Embedment

The following adverse events have also been observed. These are listed alphabetically and not by order of frequency or severity.

Anemia	Menstrual flow, prolonged
Backache	Menstrual spotting
Dysmenorrhea	Pain and cramping
Dyspareunia	Urticarial allergic skin reaction
Expulsion, complete or partial	Vaginitis
Leukorrhea	

CooperSurgical

CooperSurgical, Inc
95 Corporate Drive
Trumbull, CT 06611

This brief summary is based on the ParaGard full prescribing information dated September 2014.

PAR-41287 01/18

ASK HER IF SHE WANTS A birth control that's HORMONE FREE

PARAGARD®
(intrauterine copper contraceptive)—
the only highly effective, reversible birth control that is *completely hormone free*[1]

- **100% hormone free**
- **94% patient satisfaction*[2]**
- **Removable whenever she decides†**
- **>99% effective for up to 10 years**

56% of women reported that they had **concerns with hormones** in their birth control‡[3]

Tell her she has a hormone-free choice—tell her about PARAGARD.

INDICATION

PARAGARD is indicated for intrauterine contraception for up to 10 years.

IMPORTANT SAFETY INFORMATION

- **PARAGARD does not protect against HIV/AIDS or other sexually transmitted infections (STI).**
- PARAGARD must not be used by women who are pregnant or may be pregnant as this can be life threatening and may result in loss of pregnancy or fertility.
- PARAGARD must not be used by women who have acute pelvic inflammatory disease (PID) or current behavior suggesting a high risk of PID; have had a postpregnancy or postabortion uterine infection in the past 3 months; have cancer of the uterus or cervix; have an infection of the cervix; have an allergy to any component; or have Wilson's disease.
- The most common side effects of PARAGARD are heavier and longer periods and spotting between periods; for most women, these typically subside after 2 to 3 months.
- If a woman misses her period, she must be promptly evaluated for pregnancy.
- Some possible serious complications that have been associated with intrauterine contraceptives, including PARAGARD, are PID, embedment, perforation of the uterus, and expulsion.

Please see the following page for a brief summary of full Prescribing Information.

CooperSurgical

*Data are from the Contraceptive CHOICE Project. The study evaluated 3- and 6-month self-reported bleeding and cramping patterns in 5011 long-acting reversible contraceptive (LARC) users (n=826, PARAGARD), and the association of these symptoms with method satisfaction. Study participants rated satisfaction with their LARC method as "very satisfied," "somewhat satisfied," or "not satisfied." For the data analyses, "satisfied" and "very satisfied" were grouped together as "satisfied."[2]

†PARAGARD must be removed by a healthcare professional.

‡Based on a September 2017 web-based survey of US women aged 18-45 years (N=300), where participants were asked about their attitudes about birth control that contains hormones. Respondents were required to be currently using birth control or have plans to use birth control in the next year. Repeat respondents within the previous 6 months were not permitted.

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PARAGARD® T380A
intrauterine copper contraceptive
Life on *Her* Terms.

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