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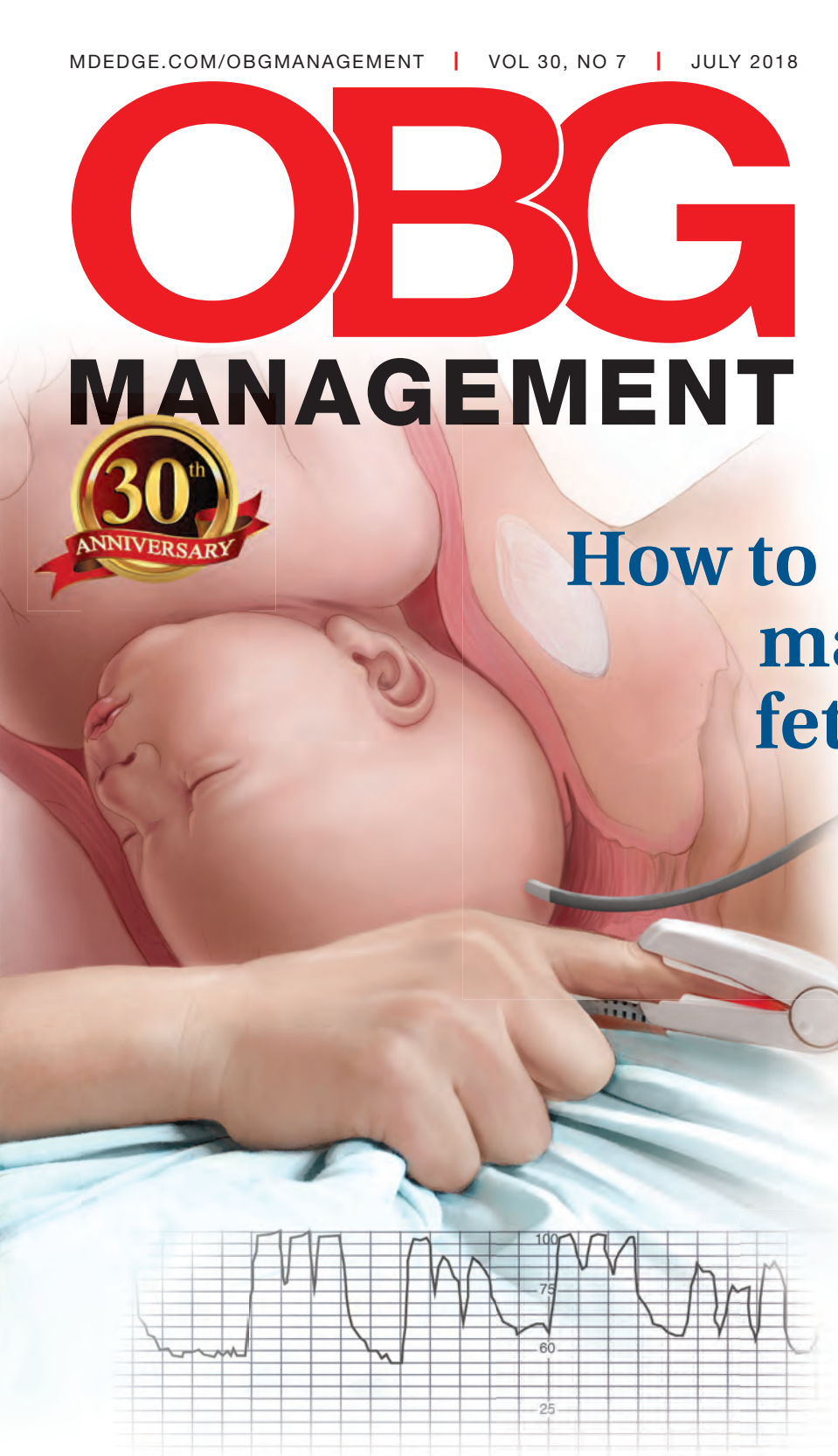
OBG MANAGEMENT

30th ANNIVERSARY

Are we ready for primary HPV testing for cervical cancer prevention?
Sarah Feldman, MD, MPH; Robert L. Barbieri, MD

Does HT increase breast cancer risk in *BRCA1* carriers?

Human trafficking—how you can help
Erin E. Tracy, MD, MPH



How to differentiate maternal from fetal heart rate on tracing

Michael G. Ross, MD, MPH

Did unsafe oxytocin dose cause uterine rupture?
Plus more Medical Verdicts

Laparoscopic hysterectomy for the very large uterus
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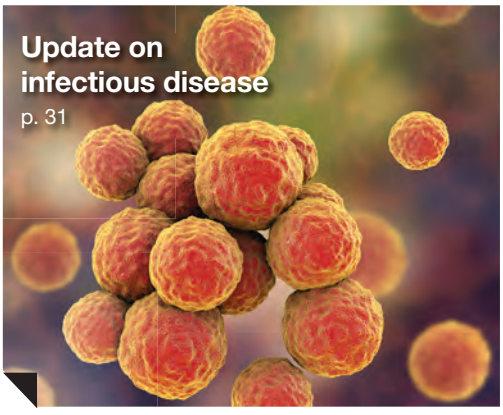

Actor portrayal

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Only INTRAROSA® converts to androgens and estrogens in a woman's body with no restrictions on duration of use[1]*

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- First and only FDA-approved, vaginal non–estrogen-based therapy[1,2]
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*Prasterone is an inactive precursor that is converted into active androgens and estrogens. The mechanism of action is not fully established.

Order samples and learn more at IntrarosaHCP.com.

Indication

INTRAROSA is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Important Safety Information

INTRAROSA is contraindicated in women with undiagnosed abnormal genital bleeding.

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

In four 12-week randomized, placebo-controlled clinical trials, the most common adverse reaction with an incidence ≥2 percent was vaginal discharge. In one 52-week open-label clinical trial, the most common adverse reactions with an incidence ≥2 percent were vaginal discharge and abnormal Pap smear.

Please see the following page for a Brief Summary of full Prescribing Information.

References: 1. Intrarosa [package insert]. Waltham, MA: AMAG Pharmaceuticals, Inc.; 2018. **2.** Archer DF, Labrie F, Bouchard C, et al. *Menopause*. 2015;22(9):950-963. **3.** Labrie F, Archer DF, Koltun W, et al. *Menopause*. 2016;23(3):243-256.

Intrarosa®
Prasterone VAGINAL INSERTS 6.5 mg

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Intrarosa®
Prasterone VAGINAL INSERTS 6.5 mg

INTRAROSA® (prasterone) vaginal inserts

Brief Summary: Consult full Prescribing Information for complete product information.

INDICATION

INTRAROSA is a steroid indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding: Any postmenopausal woman with undiagnosed, persistent or recurring genital bleeding should be evaluated to determine the cause of the bleeding before consideration of treatment with INTRAROSA.

WARNINGS AND PRECAUTIONS Current or Past History of Breast Cancer

Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. INTRAROSA has not been studied in women with a history of breast cancer.

ADVERSE REACTIONS Clinical Trials Experience

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

In four (4) placebo-controlled, 12-week clinical trials [91% - White Caucasian non-Hispanic women, 7% - Black or African American women, and 2% - "Other" women, average age 58.8 years of age (range 40 to 80 years of age)], vaginal discharge is the most frequently reported treatment-emergent adverse reaction in the INTRAROSA treatment group with an incidence of ≥ 2 percent and greater than reported in the placebo treatment group. There were 38 cases in 665 participating postmenopausal women (5.71 percent) in the INTRAROSA treatment group compared to 17 cases in 464 participating postmenopausal women (3.66 percent) in the placebo treatment group.

In a 52-week non-comparative clinical trial [92% - White Caucasian non-Hispanic women, 6% - Black or African American women, and 2% - "Other" women, average age 57.9 years of age (range 43 to 75 years of age)], vaginal discharge and abnormal Pap smear at 52 weeks were the most frequently reported treatment-emergent adverse reaction in women receiving INTRAROSA with an incidence of ≥ 2 percent. There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear (2.1 percent) in 521 participating postmenopausal women. The eleven (11) cases of abnormal Pap smear at 52 weeks include one (1) case of low-grade squamous intraepithelial lesion (LSIL), and ten (10) cases of atypical squamous cells of undetermined significance (ASCUS).

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*Source: Kantar Media, Medical Surgical Study June 2018, Obstetrics/Gynecology Combined Office & Hospital Readers.

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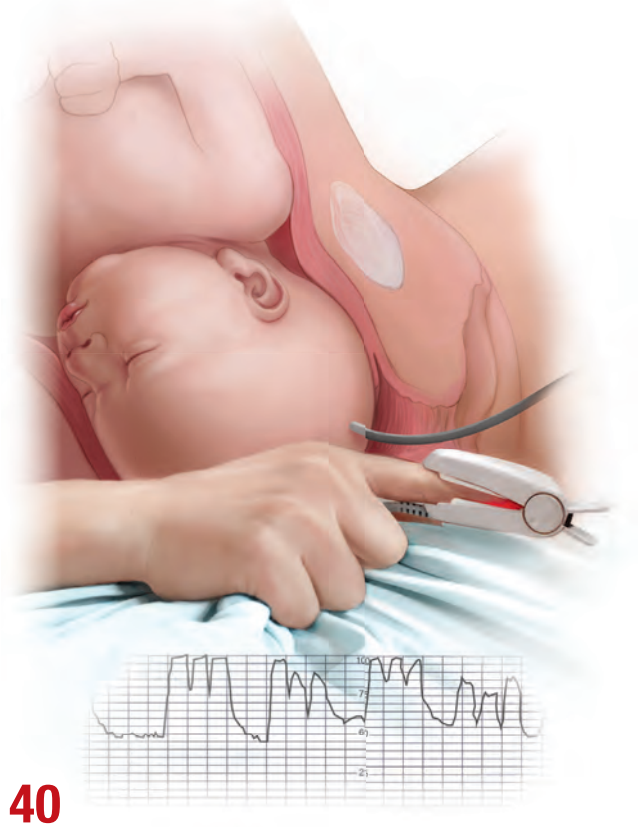
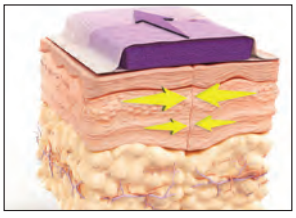
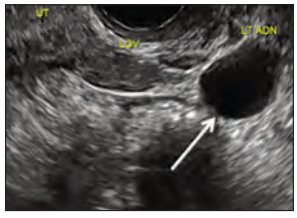


See what's ON THE WEB! page 6



Negative-pressure wound therapy **31**



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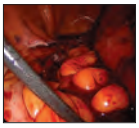

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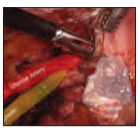

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Are we ready for primary HPV testing for the prevention of cervical cancer?

We may be at a tipping point where the iconic Pap smear is largely replaced by HPV testing for cervical cancer screening

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Cervical cancer screening represents one of the great public health successes of the 20th Century. Two physician-scientists, George Papanicolaou, MD, PhD (1883–1962), and Harald zur Hausen, MD (1936–), made extraordinary contributions to the evolution of effective cervical cancer screening programs. Dr. Papanicolaou led development of the iconic Pap smear, creating techniques for collecting specimens and using cytologic techniques to identify cervical cancer and its precursors, and Dr. zur Hausen discovered the association of human papillomavirus (HPV) infection with cervical cancer.[1,2]

Although it is but a distant memory, *in the 1930s cervical and uterine cancer caused more deaths among women than breast, lung, or ovarian cancer.* The successful deployment of Pap smear screening resulted in a decrease in cervical cancer rates in developed countries. Cervical cancer deaths remain common in many parts of the world, however. Cervical cancer screening programs can reduce cervical cancer incidence by greater than 80%.[3] In the United States between 1973 and 2006, the invasive cervical cancer age-adjusted incidence rates dropped from 10.28 to 3.97 per 100,000 women.[4]

HPV causes cervical cancer

Dr. zur Hausen dedicated his career to identifying viral causes of human cancer. In his Nobel Laureate autobiography, he reported that during his 2-year rotating residency, he loved his obstetrics and gynecology experience, but found it "physically highly demanding" and decided to focus his career in microbiology and immunology.[5] After proving that herpes simplex virus did not cause cervical cancer he began to explore the role of HPV in the disease process. He first identified HPV types 6 and 11 and showed that these agents caused genital warts. He then used low-stringency hybridization techniques to identify HPV types 16 and 18 in specimens of cervical cancer. Later, he and his colleagues proved that two HPV proteins, E6 and E7, interfere with the function of cell cycle control proteins p53 and retinoblastoma protein, resulting in dysregulated cell growth and cancer.[2] These findings permitted the development of both HPV vaccines and nucleic acid–based tests to identify high-risk oncogenic HPV (hrHPV) in cells and tissue specimens.

HPV vaccination

Dr. zur Hausen was an energetic and vocal advocate for the development and widescale deployment of HPV vaccines, including vaccination of males and females.[6] Initially his ideas were rejected by the pharmaceutical industry, but eventually, with advances in virology and vaccine development, multiple companies pursued the development of HPV vaccines, the first cancer prevention vaccines. The best approach to cervical cancer prevention is intensive population-wide HPV vaccination of both boys and girls before exposure to the HPV virus. Beyond its beneficial effect on the incidence of cervical cancer, HPV vaccination also reduces the population incidence of anal, vulvar, and oropharyngeal cancer.[7]

Instant Poll

When do you think we in the United States will transition to primary HPV screening for cervical cancer?

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

Prevention of oropharyngeal cancer is especially important for men, supporting the recommendation for vaccination of all boys.[8]

Population-wide HPV vaccination will result in a lower prevalence of cervical cancer precursors and reduce the sensitivity of cytology, thereby making primary HPV screening more attractive.[9] Based on one modelling study, universal HPV vaccination can reduce cervical cancer rates by greater than 50% over current levels, and introduction of primary HPV screening will reduce cervical cancer rates by an additional 20%.[10] In an era of widespread vaccination for HPV, screening for cervical cancer should be intensified for nonvaccinated women.[10]

Primary cervical cancer screening with cytology

Primary screening with cervical cytology alone remains an option supported by many authorities and professional society guidelines.[11] Most studies report that HPV testing has greater sensitivity than cervical cytology alone, especially for the detection of adenocarcinoma of the cervix.[12] In one Canadian study, 10,154 women were randomly assigned to HPV or cervical cytology testing. The sensitivity of HPV testing and cervical cytology for detecting cervical intraepithelial neoplasia grade 2 or 3 was 95% and 55%, respectively, with a specificity of 94% and 97%, respectively.[13] When used together the sensitivity and specificity of cotesting was 100% and 93%, respectively, but resulted in an increased number of colposcopies, which may be costly and add stress for the patient. Many countries are beginning to move away from cervical cancer screening with cytology or cotesting to programs built upon a foundation of primary HPV testing.

Primary cervical cancer screening with HPV testing

The knowledge that hrHPV is a more sensitive test for cervical cancer and its precursors, as well as the relatively lower sensitivity of cytology, is the foundation for transitioning from primary screening with cervical cytology to primary screening with HPV testing. In the Netherlands[14] and Australia[15,16] HPV testing with reflex cytology is the nationwide approach to cervical cancer screening. The basic components of the Dutch primary HPV screening program, as explained by Dr. Lai van Zulyan Mandres, are[14]:

1. Samples are collected by a general practitioner and sent to one of 5 central testing facilities for DNA testing for hrHPV.
2. If all previous samples tested negative, the screening occurs at ages 30, 35, 40, 50, and 60 years, a minimum of 5 screens per woman.
3. If there is a history of a previously positive hrHPV, the screening is intensified, with additional specimens collected at ages 45, 55, and 60 years.
4. If the sample is hrHPV negative, the patient continues screening at the standard intervals. No cytology testing is performed.
5. If the sample is hrHPV positive, reflex cytology is performed using the original collected sample. If the cytology shows no intraepithelial lesion or malignancy (NILM), another specimen is obtained for cytology within 6 months. If the second cytology specimen shows atypical squamous cells of undetermined significance (ASCUS) or a more worrisome cytology finding, the patient is sent for colposcopy. If two NILM cytology specimens have been obtained, the patient resumes primary hrHPV screening every 5 years.
6. If the specimen is hrHPV positive and cytology is ASCUS or more worrisome the patient is referred for colposcopy (**FIGURE**, page 14).[14] The Dutch estimate that primary hrHPV screening will reduce the number of cervical cytology specimens by 90% annually.

Australia also has implemented nationwide primary HPV testing for cervical cancer screening. This change was implemented following a 10-year program of universal school-based vaccination of girls and boys, and biennial cytology screening for all women. The Australian screening program initiates hrHPV testing at age 25 years and thereafter every 5 years until age 74. If the hrHPV test is positive, reflex testing for HPV types 16 and 18 are performed on the original specimen along with cervical cytology. Women who test positive for HPV 16 or 18 are immediately referred for colposcopy. If the hrHPV test is positive and reflex testing for HPV 16 and 18 is negative, cervical cytology demonstrating ASCUS, low- or high-grade squamous intraepithelial lesions, or more worrisome results trigger a referral for colposcopy. The Australian program supports testing of self-collected vaginal samples for women who are underscreened or have never been screened.[15,16]

Pros and cons of switching approaches

Deployment of new technology often yields benefits and challenges. A putative benefit of primary HPV screening is a reduction in health care costs without an increase in cervical cancer deaths. Another benefit of primary HPV screening is that it may enable self-collection of specimens for analysis, thereby increasing access to cervical cancer screening for underserved and marginalized populations of women who are not

CONTINUED ON PAGE 14

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.
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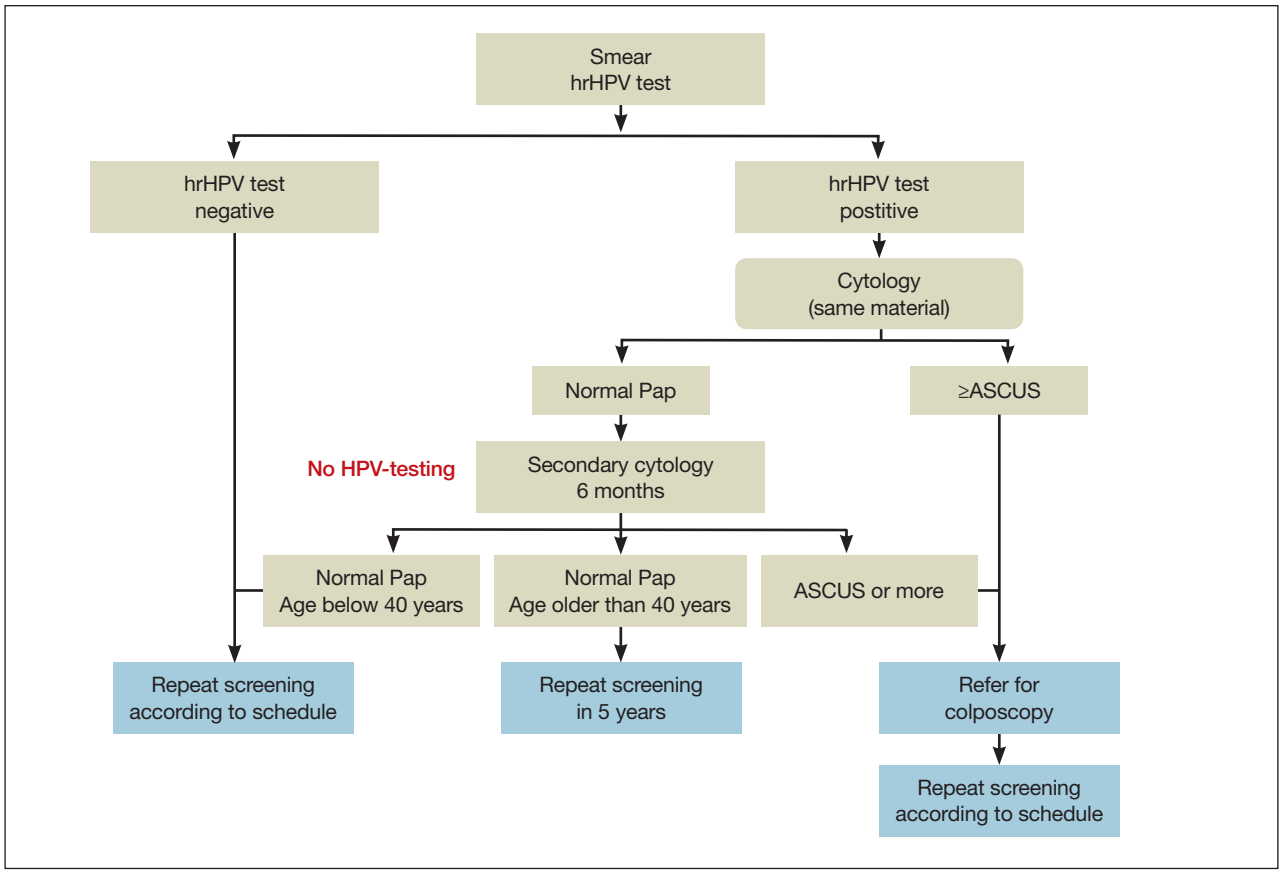
FIGURE Netherlands algorithm for cervical cancer screening[14]



Abbreviations: ASCUS, atypical squamous cells of undetermined significance; hrHPV, high-risk human papillomavirus.

currently participating in cervical cancer screening programs.[17] One challenge is that many women are unaware that hrHPV is the cause of most invasive cervical cancers. The detection of hrHPV in a woman in a long-term relationship who was previously negative for hrHPV may cause the emotions of surprise, fear, anxiety, and anger, thereby stressing the relationship.[18]

Another concern is that many women are worried about no longer receiving the familiar "Pap smear" cancer screening test in which they have tremendous faith. When Australia transitioned to primary HPV screening, more than 70,000 women signed a petition to "save women's lives" by permitting continued access to the cervical cytology testing.[19] Primary HPV testing may result in a transient increase in the number of women referred for colposcopy, potentially overwhelming the capacity of the health care system to deliver this vital service.[20,21] The HPV types that most often cause cervical cancer may vary among countries. For example, in Thailand, HPV 52 and 58 are frequently detected in women with high-grade squamous lesions, and including these subtypes in reflex genotyping may be of regional benefit.[22]

Primary cervical cancer screening with HPV testing: When will it be used widely in the United States?

In contrast to the United States, the Netherlands is a small, densely populated country that has a highly integrated health system with centralized laboratory centers, a nationwide electronic health record, and clinicians organized to perform as an integrated team. These features ensure that all lifetime tests results are available in one record, that HPV testing is highly standardized, and that clinicians will follow a prescribed care pathway. The Netherlands' health system is organized to support the successful transition, in a single step, to primary HPV testing. The United States is the third most populous country in the world, following China and India, with a diverse approach to health care, a highly mobile population, no single interoperable electronic health record, and minimal central

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MOST COMMON

PPD is the **most common** complication of childbirth.[1-6]

>50%

Without proper screening, **more than 50%** of PPD cases may go undiagnosed.[7-14]

Get a validated screening tool at **KnowPPD.com/epds**

The American College of Obstetricians and Gynecologists (ACOG) recommends screening patients at least once during the perinatal period using a standardized, validated tool.[15]

Some examples of these tools include the Edinburgh Postnatal Depression Scale (EPDS) and the Patient Health Questionnaire-9 (PHQ-9).

It only takes **~5 minutes** to know your patient's score.[15]

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SAGE THERAPEUTICS

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control of clinical practice. The United States is not organized to make a "big bang" transition to primary HPV cervical cancer screening. It is likely that the introduction of primary HPV screening will occur first in highly integrated health systems that control the clinical, laboratory, and electronic records of a large population.

The results of the ATHENA study provide a clear clinical algorithm for implementing a primary HPV screening program for cervical cancer in the United States.[23–25] Samples are collected for hrHPV testing at a specified interval, 3 or 5 years, beginning at age 25 years. Women younger than age 25 years should be screened with cytology alone. Detection of hrHPV results in reflex viral typing for HPV 16 and 18. Women with samples positive for HPV 16 and 18 are immediately referred for colposcopy. Samples positive for hrHPV and negative for HPV 16 and 18 have reflex cytology testing performed on the original HPV specimen. If cytology testing reports NILM, repeat cotesting is performed in one year. If cytology testing reports ASCUS or a more concerning result, the woman is referred for colposcopy.

Malcolm Gladwell, in his book *The Tipping Point,* identified 3 processes that help push an innovative new approach from obscurity into widespread use.[26] First, authoritative voices that can catalyze change need to consistently communicate their shared vision for the future. Second, there must be a clear message that galvanizes the many to change their approach. Third, the historical context must be supportive of the change. Over the next decade we are likely to hit a tipping point and transition from cervical cancer screening that relies on cervical cytology to an approach that prioritizes hrHPV testing. When that change will occur in the United States is unclear. But our colleagues in other countries already have transitioned to primary hrHPV testing for cervical cancer screening. ●

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Does hormone therapy increase breast cancer risk in *BRCA1* mutation carriers?

No. In a prospective study that followed 872 *BRCA1* carriers after oophorectomy for a mean follow-up of 7.6 years, the hazard ratio was 0.97 (95% confidence interval, 0.62–1.52; *P* = .89) for ever use of any type of hormone therapy versus no use. The use of estrogen therapy compared with estrogen plus progestogen therapy *reduced* the subsequent risk of breast cancer (10-year actuarial risk of breast cancer of 12% vs 22%, respectively; *P* = .04).

EXPERT COMMENTARY
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Kotsopoulos J, Gronwald J, Karlan BY, et al; Hereditary Breast Cancer Clinical Study Group. Hormone replacement therapy after oophorectomy and breast cancer risk among BRCA1 mutation carriers [published online ahead of print April 19, 2018]. JAMA Oncol. doi:10.1001/jamaoncol.2018.0211.

Prophylactic bilateral oophorectomy (BO) reduces the risk of future ovarian cancer in women who have *BRCA1* gene mutations. Women in this high-risk population may be reluctant, however, to use menopausal hormone therapy (HT) to mitigate the symptoms of surgical menopause because of concerns that it might elevate their risk of breast cancer.

To determine the relationship between HT use and *BRCA1*-associated breast cancer, Kotsopoulos and colleagues conducted a multicenter international cohort study. They prospectively followed women with *BRCA1* mutations who had undergone BO and had intact breasts and no history of breast cancer.

Dr. Kaunitz reports receiving grant or research support from Allergan, Bayer, and TherapeuticsMD and that he is a consultant to AMAG and Bayer.

Details of the study

The study included women who had a *BRCA1* mutation and considered HT use following BO. Women were excluded from the analysis if they had a prior diagnosis of breast cancer or had BO prior to study enrollment. Study participants completed a questionnaire at baseline and a follow-up questionnaire every 2 years thereafter. The primary end point was invasive breast cancer.

Among 872 participating *BRCA1* carriers, 43% (n = 377) used HT following BO. Mean duration of HT use following BO was 3.9 years, with 69% of users taking estrogen therapy alone (ET) and 19% using estrogen plus progestogen therapy (EPT). Those who used HT were younger at the time of BO compared with women who never used HT (mean age, 43.0 vs 48.4 years).

During follow-up (mean, 7.6 years; range, 0.4–22.1), invasive breast cancer was diagnosed in similar proportions of HT users

FAST TRACK

BRCA1 *carriers who undergo prophylactic oophorectomy may be reluctant to use HT for surgical menopause symptoms due to concerns it might increase their risk of breast cancer*

CONTINUED ON PAGE 21

Makena®
hydroxyprogesterone caproate injection

Now Approved!

FOR YOUR PATIENTS AT RISK FOR ANOTHER SINGLETON SPONTANEOUS PRETERM BIRTH (<37 WEEKS)

THE NEXT GENERATION OF MAKENA: ANOTHER WAY TO GET CLOSER TO TERM

Actual size

See how to use the auto-injector at **MakenaAutoInjector.com**

Makena helps give baby more time to develop[1]

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

Same Makena. Innovative Delivery Device.[1]

EFFICIENT

- Pre-filled auto-injector that is ready to use out of the box
- Administered in ~15 seconds

DISCREET

- Shorter, thinner, nonvisible needle
- Administered in the back of the upper arm—no need for patients to disrobe

ADMINISTRATION FRIENDLY

- Protective needle guard to help minimize accidental needle-sticks
- Appointment flexibility—no need for private exam rooms

Personalized patient support. Healthcare professional resources. More than Makena.

Makena Care Connection®

- Women receiving Makena should be monitored if they:
  - Are prediabetic or diabetic
  - 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.

CONTINUED FROM PAGE 17

and nonusers—10.3% and 10.7%, respectively (P = .86). The hazard ratio was 0.97 (95% confidence interval, 0.62–1.52; P = .89) for ever use of any type of hormone therapy versus no use.

When the type of HT used was examined, the 10-year actuarial risk of breast cancer was significantly lower with ET than with EPT (12% vs 22%, respectively; P = .04); this difference was more marked for women who underwent BO prior to age 45 (9% vs 24%; P = .009).

Study strengths and weaknesses

This investigation had several strengths, including the large number of *BRCA1* mutation carriers studied, the relatively long follow-up, and the detailed exposure data obtained.

The use of self-administered questionnaires for collecting information on lifetime HT use and breast cancer diagnoses may be a limitation. In addition, the HT route, regimen, and dose were not considered in the analysis, and the effect of intrauterine devices as progestational endometrial protection was not evaluated. Finally, the relationship between HT and breast cancer risk in women with intact ovaries was not evaluated. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Because women with *BRCA1* mutations have an elevated risk of ovarian cancer, risk-reducing gynecologic surgery is recommended for these women who have completed childbearing. In young women, BO without HT is associated with severe vasomotor symptoms, osteoporosis, cardiovascular disease, and cognitive decline. The clear reduction in breast cancer risk associated with ET (vs EPT) following BO suggests that in *BRCA1* carriers who have completed childbearing, hysterectomy (which precludes the need for progestogen therapy) should be considered as part of risk-reducing gynecologic surgery. Further, the findings of this prospective study in high-risk women parallels the findings of the large randomized Women's Health Initiative trial (performed in the general population of menopausal women), which found that ET (conjugated equine estrogen) reduces the risk.[1]

ANDREW M. KAUNITZ, MD

Reference

1. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310(13):1353–1368.

Have you read these related articles?

- **2018 Update on menopause**
  Andrew M. Kaunitz MD, NCMP; JoAnn V. Pinkerton, MD, NCMP; and JoAnn E. Manson, MD, DrPH, NCMP
  (June 2018)
- **Oncofertility in women: Time for a national solution**
  Lauren E. Ursillo, MD, and Eva Chalas, MD
  (May 2018)
- **How does oral contraceptive use affect one's risk of ovarian, endometrial, breast, and colorectal cancers?**
  Dana M. Scott, MD, and Mark D. Pearlman, MD
  (Examining the Evidence; May 2018)
- **Managing menopausal symptoms in breast cancer survivors**
  JoAnn V. Pinkerton, MD
  (Audiocast; May 2018)
- **Does hormonal contraception increase the risk of breast cancer?**
  Dana Scott, MD, and Mark D. Pearlman, MD
  (Commentary; February 2018)
- **Did long-term follow-up of WHI participants reveal any mortality increase among women who received HT?**
  Andrew M. Kaunitz, MD
  (Examining the Evidence; November 2017)
- **2017 Update on menopause**
  Andrew M. Kaunitz, MD, NCMP; JoAnn V. Pinkerton, MD, NCMP; and JoAnn E. Manson, MD, DrPH, NCMP
  (June 2017)
- **What to do about the problem of non-FDA approved compounded bioidentical hormones**
  Cynthia Stuenkel, MD
  (Audiocast; October 2017)
- **Should risk-reducing gynecologic surgery for *BRCA* mutation carriers include hysterectomy?**
  Andrew M. Kaunitz, MD, NCMP
  (August 2016)

OBG MANAGEMENT

Human trafficking: How ObGyns can—and should—be helping survivors

Erin E. Tracy, MD, MPH

ObGyns are uniquely positioned to help these victimized women, children, and men—of whom there are believed to be more than 20 million worldwide—and thus combat a tragic epidemic, 1 patient at a time

IN THIS ARTICLE

PHOTO: SHUTTERSTOCK

Despite increasing media coverage of human trafficking and the gravity of its many ramifications, I am struck by how often trainees and other clinicians present to me patients for which trafficking is a real potential concern—yet who give me a blank expression when I ask if anyone has screened these patients for being victims of trafficking. I suspect that few of us anticipated, during medical training, that we would be providing care to women who are enslaved.

Dr. Tracy is Attending Physician, Vincent Department of Obstetrics and Gynecology, Massachusetts General Hospital, Boston Massachusetts.

The author reports no financial relationships relevant to this article.

How large is the problem?

It is impossible to comprehend the true scope of human trafficking. Estimates are that 20.9 million men, women, and children globally are forced into work that they are not free to leave.[1]

Although human trafficking is recognized as a global phenomenon, its prevalence in

CONTINUED ON PAGE 25

Balcoltra™
(levonorgestrel and ethinyl estradiol tablets, USP, and ferrous bisglycinate tablets)
0.1mg/0.02mg and 36.5mg

A new choice for balanced control

Balcoltra™ offers a balance of high efficacy and low dose[1]

- **Low-dose levonorgestrel/ethinyl estradiol combination oral contraceptive (COC)[1]**
- **Familiar 21/7 dosing[1]**
- **Cycle control with 4% breakthrough bleeding and 1 unintended pregnancy per 100 woman-years[1]**

Visit balcoltra.com to learn more about how Balcoltra may help your patients.

Patient Savings
$21 for 21*

*Most eligible patients will pay no more than $21 per co-pay. Patients should present this coupon with their prescription to their participating pharmacy. For each Balcoltra prescription, patients pay the first $21 of their out-of-pocket expense and Avion will cover up to $100 of their remaining expense. They could have additional responsibility depending on their insurance plan or remaining expense. This offer is good for 21 uses. Cardholders with questions, please call 1-877-838-3846 (8:30 AM -5:30 PM ET, Monday-Friday).


Not an actual patient.

INDICATIONS AND USAGE

Balcoltra is a progestin/estrogen combination oral contraceptive (COC) indicated for use by females of reproductive potential to prevent pregnancy.

IMPORTANT SAFETY INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg, the most common adverse reactions (incidence ≥ 2%) were headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

DRUG INTERACTIONS

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

Patients should be counseled that COCs do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Please see full Prescribing Information, including BOXED WARNING, for Balcoltra.

References: 1. Balcoltra [package insert]. Alpharetta, GA: Avion Pharmaceuticals LLC; 2018.

Avion PHARMACEUTICALS
1-888-612-8466
Alpharetta, GA 30005

Balcoltra™ (levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets and ferrous bisglycinate 36.5 mg tablets) for oral administration

Brief Summary of Prescribing Information

For additional information, refer to the full Prescribing Information.

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke.

INDICATIONS AND USAGE

Balcoltra is indicated for use by females of reproductive potential to prevent pregnancy.

DOSAGE AND ADMINISTRATION

Patients should take one tablet by mouth at the same time every day in the order directed on the blister pack.

CONTRAINDICATIONS

Balcoltra is contraindicated in individuals with:

- A high risk of arterial or venous thrombotic diseases, including in women who:
  - -Smoke, if over age 35
  - -Have deep vein thrombosis or pulmonary embolism, now or in the past
  - -Have inherited or acquired hypercoagulopathies
  - -Have cerebrovascular disease
  - -Have coronary artery disease
  - -Have thrombogenic valvular or rhythm diseases of the heart
  - -Have uncontrolled hypertension
  - -Have diabetes mellitus with vascular disease
  - -Have headaches with focal neurological symptoms or have migraine headaches with aura
- Women over age 35 with any migraine headaches
- Liver tumors or liver disease
- Undiagnosed abnormal uterine bleeding
- Pregnancy
- Breast cancer or other estrogen- or progestin-sensitive cancer or history of these cancers
- Hypersensitivity of any of the components
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir

WARNINGS AND PRECAUTIONS

Thrombotic Disorders and Other Vascular Problems

Stop Balcoltra if an arterial thrombotic event or venous thromboembolic (VTE) event occurs, or if unexplained visual loss, proptosis, diplopia, papilledema or retinal vascular lesions occur. If possible, stop at least 4 weeks before through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during the following prolonged immobilization. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding.

The use of COCs increases the risk of VTE; however, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke. Use COCs with caution in women with cardiovascular disease risk factors.

Liver Disease

Do not use Balcoltra in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Balcoltra if jaundice develops. Balcoltra is contraindicated in women with benign and malignant liver tumors. Hepatic adenomas are associated with COC use. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Balcoltra prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. Balcoltra can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

High Blood Pressure

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

If used in women with well-controlled hypertension, monitor blood pressure and stop Balcoltra if blood pressure rises significantly.

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

Gallbladder Disease

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

Carbohydrate and Lipid Metabolic Effects

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

Headache

If a woman taking Balcoltra develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Balcoltra if indicated. Consider discontinuation of Balcoltra in the case of increased frequency or severity of migraine during COC use.

Bleeding Irregularities and Amenorrhea

Evaluate irregular bleeding or amenorrhea.

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

Women who use Balcoltra may experience amenorrhea. In the clinical trial, 2.6% of the evaluable cycles were amenorrheic. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was preexistent.

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

FD&C Yellow No. 5 Allergic-type Reaction

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Depression

Carefully observe women with a history of depression and discontinue Balcoltra if depression recurs to a serious degree.

Carcinoma of the Breast and Cervix

Balcoltra is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive.

Effect on Binding Globulins

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

Monitoring

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

Hereditary Angioedema

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

Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Balcoltra.

ADVERSE REACTIONS

In a clinical trial with levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg tablets, a total of 1477 healthy women of child-bearing potential were enrolled and had 7870 cycles of exposure. Of these, 792 subjects had completed 6 cycles of treatment. The women ranged in age from 17 to 49 years and 87% were Caucasian.

Common Adverse Reactions (≥ 2% of women):

Headache (14%), metrorrhagia (8%), dysmenorrhea (7%), nausea (7%), abdominal pain (4%), breast pain (4%), emotional lability (3%), acne (3%), depression (2%), amenorrhea (2%), and vaginal moniliasis (2%).

At the time of the report, 133 (9%) subjects had withdrawn from the study due to adverse events. The most frequent were due to headache and metrorrhagia (1% each). Other adverse events occurring in < 1% of those who discontinued included amenorrhea, depression, emotional lability, hypertension, acne, menorrhagia, nausea, hypercholesterolemia, weight gain, dysmenorrhea, and flatulence. All other reasons for discontinuation were reported by 3 or fewer subjects. These are not all of the possible adverse reactions of Balcoltra.

DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain more information about interactions with hormonal contraceptives. Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors, such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir, nevirapine and efavirenz] or increase [e.g., indinavir, atazanavir/ritonavir and etravirine]).

Combined oral contraceptives containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. Combined oral contraceptives have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

Do not co-administer Balcoltra with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations.

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

USE IN SPECIFIC POPULATIONS

Pregnant Women

Balcoltra is contraindicated in pregnancy because there is no reason to use combined hormonal contraceptives (CHCs) in pregnancy. Discontinue Balcoltra if pregnancy occurs. Based on epidemiologic studies and meta-analyses, there is little or no increased risk of birth defects in the children of females who inadvertently use COCs during early pregnancy.

Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy.

Nursing Mothers

Combined hormonal contraceptives (CHCs) and/or metabolites are present in human milk and in breast-fed infants. CHCs, including Balcoltra, can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Balcoltra and any potential adverse effects on the breast-fed child from Balcoltra or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

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

Hepatic Impairment

The pharmacokinetics of Balcoltra has not been studied in women with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

OVERDOSAGE

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

The FDA-approved product labeling can be found at www.balcoltra.com, or call 1-888-612-8466.

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Avion PHARMACEUTICALS

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the United States is significant enough that it should prompt the health care community to engage in helping identify and assist victims/survivors: From January until June of 2017, the National Human Trafficking Hotline received 13,807 telephone calls, resulting in reporting of 4,460 cases.[2] Indeed, from 2015 to 2016 there was a 35.7% increase in the number of hotline cases reported, for a total of 7,572 (6,340—more than 80%—of which regarded females). California had the most cases reported (1,323), followed by Texas (670) and Florida (550); those 3 states also reported an increase in trafficking crime. Vermont (5), Rhode Island (9), and Alaska (10) reported the fewest calls.[3]

How is trafficking defined?

The United Nations Office on Drugs and Crime defines "trafficking in persons" as:

> … recruitment, transportation, transfer, harbouring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation. Exploitation shall include, at a minimum, the exploitation of the prostitution of others or other forms of sexual exploitation, forced labour or services, slavery or practices similar to slavery, servitude or the removal of organs.[4]

Traffickers prey on potentially vulnerable people. Girls and young women who have experienced poverty, homelessness, childhood sexual abuse, substance abuse, gender nonconformity, mental illness, or developmental delay are at particular risk.[5] Children who have had interactions with Child Protective Services, come from a dysfunctional family, or have lived in a community with high crime, political or social unrest, corruption, or gender bias and discrimination are also at increased risk.[6]

Clues that raise clinical suspicion

A number of potential signs should make providers suspicious about potential human trafficking. Some of those signs are similar to the red flags we see in intimate partner violence, such as:

- having a difficult time talking to the patient alone
- having the accompanying person answer the patient's questions
- body language that suggests fear, anxiety, or distrust (eg, shifting positions, looking away, appearing withdrawn)
- physical examination inconsistent with the history
- physical injury (especially multiple injuries or injuries in various stages of healing)
- refusal of interpreter services.

Trafficked girls or women may appear overly familiar with sex, have unexpected material possessions, or appear to be giving scripted or memorized answers to queries.[7] Traffickers often confiscate their victims' personal identification. They try to prevent victims from knowing their geographic locales: Patients might not have any documentation or awareness of exact surroundings (eg, their home address). Patients may be wearing clothes considered inappropriate for the weather or venue. They may have tattoos that are marks of branding.[8]

CONTINUED ON PAGE 26

TABLE Is this patient a trafficking victim? Screening questions to get at the answer[20]

1.	Can you leave your job or situation if you want?
2.	Can you come and go as you please?
3.	Have you been threatened if you try to leave?
4.	Have you been physically harmed in any way?
5.	What are your working or living conditions like?
6.	Where do you sleep and eat?
7.	Do you sleep in a bed, on a cot, or on the floor?
8.	Have you ever been deprived of food, water, sleep, or medical care?
9.	Do you have to ask permission to eat, sleep, or go to the bathroom?
10.	Are there locks on your doors and windows so you cannot get out?
11.	Has anyone threatened your family?
12.	Has your identification or documentation been taken from you?
13.	Is anyone forcing you to do anything that you do not want to do?

CONTINUED FROM PAGE 25

FIGURE 1 Indicators of human trafficking[21]

Adults at risk for labor trafficking or sex trafficking

May be any age, gender, race/ethnicity, and nationality; may be LGBTQI or of any immigration status

FORCE or FRAUD or COERCION

May be experiencing the following:

1. Is with a person who speaks for them
2. Is unsure of day, date, month, year
3. Moves frequently
4. Not in control of personal identification
5. Doesn't know where they live
6. Story doesn't make sense; seems scripted
7. Not allowed to come and go at will
8. Wears the same clothes over and over
9. Seems afraid to answer questions
10. Works long hours; exhausted; hungry
11. Someone else controls their money
12. Odd living/work space (may include tinted windows, security cameras, barbed wire, people sleeping/living at worksite)
13. Can't move freely; attached to someone
14. Owes a debt to employer

LABOR TRAFFICKING

1. Hired for a different job based on false promises
2. Fearful of employer or supervisor
3. Isolated from family; fears family harm if they quit
4. Lives where they work; can't choose where to live
5. Owes employer money and can't pay it back
6. Abnormal work hours; no breaks or vacations
7. Boss makes them lie about their job duties
8. Multiple people living in a cramped space: housekeeper, sales crew, live-in help

SEX TRAFFICKING

1. Works in the commercial sex industry: escort, exotic dancer, "prostitute," "massage"
2. Signs of having sex with multiple people
3. Has pimp: male, female, boyfriend, husband
4. Tattoos or branding of ownership
5. Uses language of the sex industry
6. Inappropriate clothing for venue or weather
7. Physical abuse, drugs/alcohol, malnourished

SEE SIGNS? Ask your coworker trained to use the Adult Human Trafficking Screening Tool

National Human Trafficking Hotline: 1-888-373-7888, 24/7 (200 languages)

Medical consequences of being trafficked are obvious, numerous, and serious

Many medical sequelae that result from trafficking are obvious, given the nature of work that victims are forced to do. For example, overcrowding can lead to infectious disease, such as tuberculosis.[9] Inadequate access to preventive or basic medical services can result in weight loss, poor dentition, and untreated chronic medical conditions.

If victims are experiencing physical or sexual abuse, they can present with evidence of blunt trauma, ligature marks, skin burns, wounds inflicted by weapons, and vaginal lacerations.[10] A study found that 63% of survivors reported at least 10 somatic symptoms, including headache, fatigue, dizziness, back pain, abdominal or pelvic pain, memory loss, and symptoms of genital infectious disease.[11]

Girls and women being trafficked for sex may experience many of the sequelae of unprotected intercourse: irregular bleeding, unintended pregnancy, unwanted or unsafe pregnancy termination, vaginal trauma, and sexually transmitted infection (STI).[12] In a study of trafficking survivors, 38% were HIV-positive.[13]

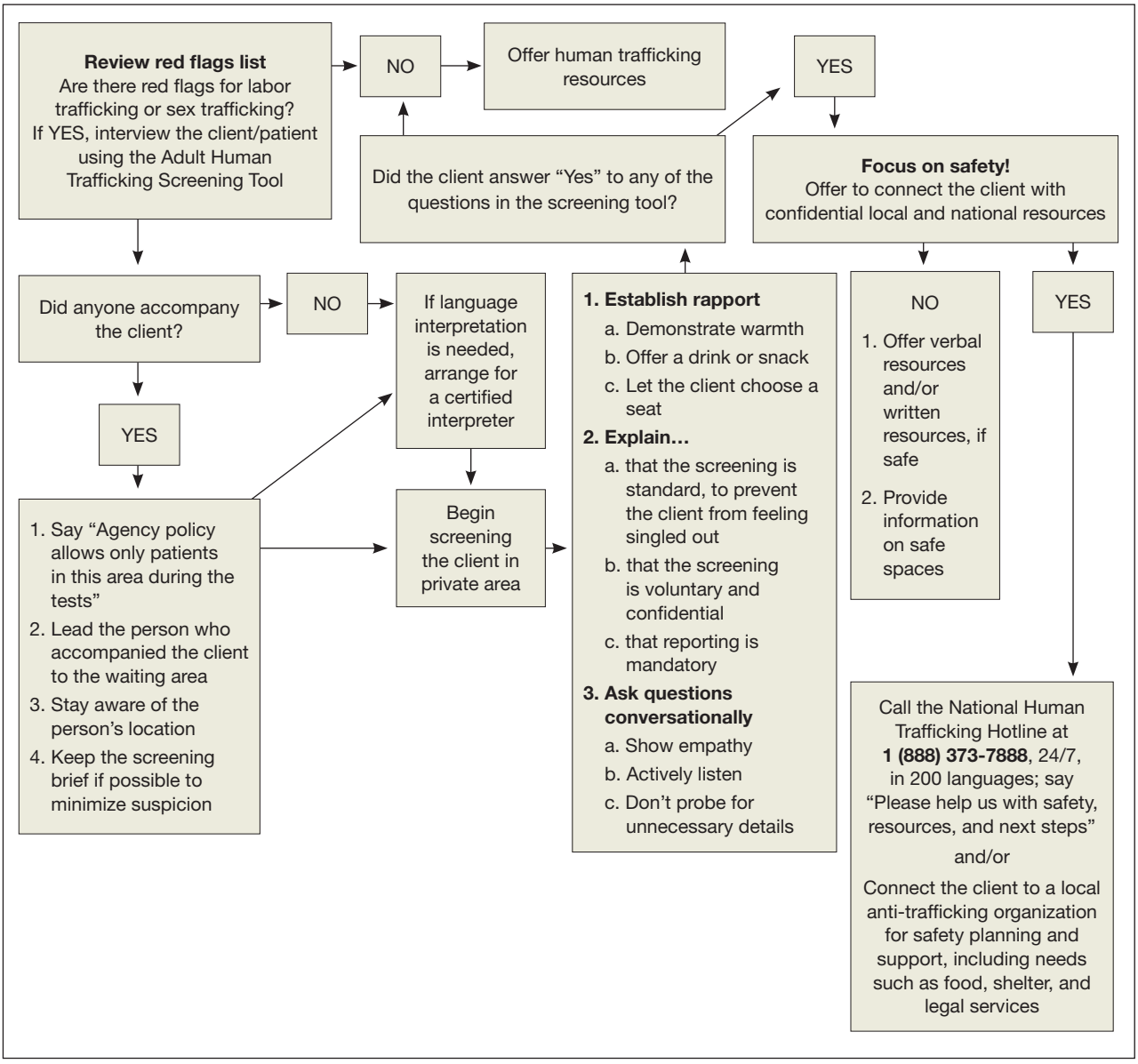
Trafficking survivors can suffer myriad mental health conditions, with high rates of depression, anxiety, posttraumatic stress, and suicidal ideation.[14] A study of 387 survivors found that 12% had attempted to harm themselves or commit suicide the month before they were interviewed.[15]

Substance abuse is also a common problem among trafficking victims.[16] One survivor interviewed in a recent study said:

> It was much more difficult to work sober because I was dealing with emotions or the pain that I was feeling during intercourse, because when you have sex with people 8, 9, 10 times a day, even more than that, it starts to hurt a lot. And being high made it easier to deal with that and also it made it easier for me to get away from my body while it was happening, place my brain somewhere else.[17]

Because of the substantial risk of mental health problems, including substance abuse, among trafficking survivors, the physical exam of a patient should include careful assessment of demeanor and mental health status. Of course, comprehensive inspection for signs of physical or blunt trauma is paramount.

FIGURE 2 Screening flowchart for adults at risk of human trafficking[21]



Patient and staff safety during the visit

Providers should be aware of potential safety concerns, both for the patient and for the staff. Creative strategies should be utilized to screen the patient in private. The use of interpreter services—either in person or over the telephone—should be presented and facilitated as being a routine part of practice. Any person who accompanies the patient should be asked to leave the examining room, either as a statement of practice routine or under the guise of having him (or her) step out to obtain paperwork or provide documentation.

Care of victims

Trauma-informed care should be a guiding principle for trafficking survivors. This involves empowering the patient, who may feel victimized again if asked to undress and undergo multiple physical examinations. Macias-Konstantopoulos noted: "A trauma-informed approach to care acknowledges the

Specialized care is increasingly available[24]

Here is a sampling of the growing number of centers in the United States that provide trauma-centered care for survivors of human trafficking:

- Survivor Clinic at New York Presbyterian Hospital–Weill Cornell Medical College, New York, New York
- EMPOWER Clinic for Survivors of Sex Trafficking and Sexual Violence at NYU Langone Health, New York, New York
- Freedom Clinic at Massachusetts General Hospital, Boston
- The Hope Through Health Clinic, Austin, Texas
- Pacific Survivor Center, Honolulu, Hawaii

FAST TRACK

Nearly 90% of human trafficking victims were seen by a health care provider while in captivity

pervasiveness and effect of trauma across the life span of the individual, recognizes the vulnerabilities and emotional triggers of trauma survivors, minimizes repeated traumatization and fosters physical, psychological, and emotional safety, recovery, health and well-being."[18]

The patient should be counseled that she has control over her body and can guide different aspects of the examination. For example the provider should discuss: 1) the amount of clothing deemed optimal for an examination, 2) the availability of a support person during the exam (for instance, a nurse or a social worker) if the patient requests one, and 3) utilization of whatever strategies the patient deems optimal for her to be most comfortable during the exam (such as leaving the door slightly ajar or having a mutually agreed-on signal to interrupt the exam).

Routine health care maintenance should be offered, including an assessment of overall physical and dental health and screening for STI and mental health. Screening for substances of abuse should be considered. If indicated, emergency contraception, postexposure HIV prophylaxis, immunizations, and empiric antibiotics for STI should be offered.[19]

Screening when indicated by evidence, suspicion, or concern

Unlike the case with intimate partner violence, experts do not recommend universal screening for human trafficking. Clinicians should be comfortable, however, trying to elicit that history when a concern arises, either because of identified risk factors, red flags, or concerns that arise from the findings of the history or physical. Ideally, clinicians should consider becoming comfortable choosing a few screening questions to regularly incorporate into their assessment. The US Department of Health & Human Services (HHS) offers a list of questions that can be utilized (**TABLE**, page 25).[20]

In January 2018, the Office on Trafficking in Persons, a unit of the HHS Administration for Children and Families, released an "Adult Human Trafficking Screening Tool and Guide." The document includes 2 excellent tools[21] that clinicians can utilize to identify patients who should be screened and how to identify and assist survivors (**FIGURE 1**, page 26, and **FIGURE 2**, page 27).

Clinicians, in their encounters with patients, are particularly well-positioned to intersect with, and identify, survivors. Regrettably, such opportunities are often missed—and victims thus remain unidentified and trapped in their circumstances. A study revealed that one-half of survivors who were interviewed reported seeing a physician *while they were being trafficked*.[22] Even more alarming, another study showed that 87.8% of survivors had received health care *during their captivity*.[23] It is dismaying to know that these patients left those health care settings without receiving the assistance they truly need and with their true circumstances remaining unidentified.

Finding assistance and support

Centers in the United States now provide trauma-informed care for trafficking survivors in a confidential setting (see "Specialized care is increasingly available").[24] A physician who works at a center in New York City noted: "Our survivors told us that more than fear or pain, the feelings that sat with them most often were worthlessness and invisibility. We can do better as physicians and as educators to expose this epidemic and care for its victims."[24]

Most clinicians practice in settings that do not have easy access to such subspecialized

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"Hotline" is a valuable resource[25]

Uncertain how you can help a patient who is a victim of human trafficking? For assistance and support, contact the National Human Trafficking Hotline—24 hours a day, 7 days a week, and in 200 languages—in any of 3 ways:

- By telephone: (888) 373-7888
- By text: 233733
- On the web: https://humantraffickinghotline.org[a]

[a]Includes a search field that clinicians can use to look up the nearest resources for additional assistance.

centers, however. For them, the National Human Trafficking Hotline can be an invaluable resource (see "Hotline is a valuable resource").[25] Law enforcement and social services colleagues also can be useful allies.

Let's turn our concern and awareness into results

We, as providers of women's health care, are uniquely positioned to help these most vulnerable of people, many of whom have been stripped of personal documents and denied access to financial resources and community support. As a medical community, we should strive to combat this tragic epidemic, 1 patient at a time. ●

FAST TRACK

Reach out to law enforcement, social services, and the National Human Trafficking Hotline for assistance

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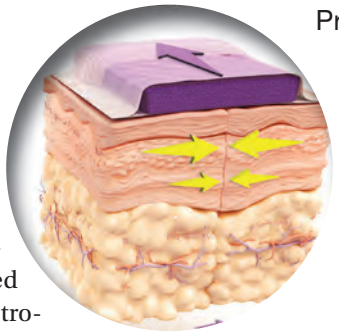
Recent news and expert perspective on therapy for cesarean incision wounds, vaginal cleansing, managing skin abscesses, *C difficile* infection in obstetric patients, and risks of maternal Zika virus infection

In this Update I highlight 5 interesting investigations on infectious diseases. The first addresses the value of applying prophylactically a negative-pressure wound dressing to prevent surgical site infection (SSI) in obese women having cesarean delivery (CD). The second report assesses the effectiveness of a preoperative vaginal wash in reducing the frequency of postcesarean endometritis. The third investigation examines the role of systemic antibiotics, combined with surgical drainage, for patients who have subcutaneous abscesses ranging in size up to 5 cm. The fourth study presents new information about the major risk factors for *Clostridium difficile* infections in obstetric patients. The final study presents valuable sobering new data about the risks of congenital Zika virus infection.

IN THIS ARTICLE

Negative-pressure wound therapy after CD shows some benefit in preventing SSI



Yu L, Kronen RJ, Simon LE, Stoll CR, Colditz GA, Tuuli MG. Prophylactic negative-pressure wound therapy after cesarean is associated with reduced risk of surgical site infection: a systematic review and meta-analysis. Am J Obstet Gynecol. 2018;218(2):200–210.e1.

Yu and colleagues sought to determine if the prophylactic use of negative-pressure devices, compared with standard wound dressing, was effective in reducing the frequency of SSI after CD.

The authors searched multiple databases and initially identified 161 randomized controlled trials and cohort studies for further assessment. After applying rigorous exclusion criteria, they ultimately selected 9 studies for systematic review and meta-analysis. Six studies were randomized controlled trials (RCTs), 2 were retrospective cohort studies, and 1 was a prospective cohort study. Five studies were considered high quality; 4 were of low quality.

Details of the study

Several types of negative-pressure devices were used, but the 2 most common were the Prevena incision management system (KCI, San Antonio, Texas) and PICO negative-pressure wound therapy (Smith & Nephew, St. Petersburg, Florida). The majority of patients in all groups were at high risk for wound complications because of obesity.

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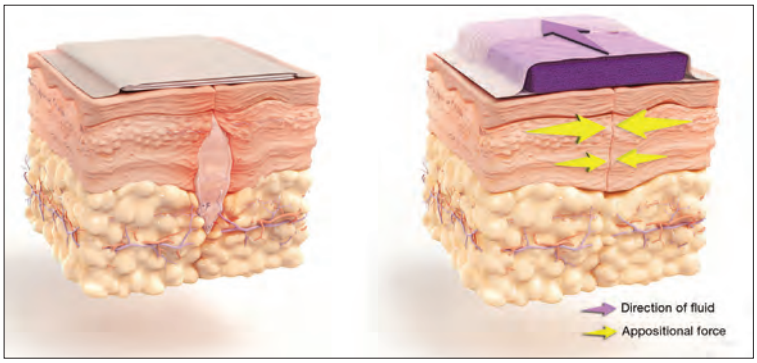


Passive wound closure (left) compared with negative-pressure wound therapy with the Prevena incision management system (right).

The primary outcome of interest was the frequency of SSI. Secondary outcomes included dehiscence, seroma, endometritis, a composite measure for all wound complications, and hospital readmission.

The absolute risk of SSI in the intervention group was 5% (95% confidence interval [CI], 2.0%–7.0%) compared with 11% (95% CI, 7.0%–16.0%) in the standard dressing group. The pooled risk ratio was 0.45 (95% CI, 0.31–0.66). The absolute risk reduction was 6% (95% CI, -10.0% to -3.0%), and the number needed to treat was 17.

There were no significant differences in the rate of any of the secondary outcomes other than the composite of all wound complications. This difference was largely accounted for by the difference in the rate of SSI.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Results of the systematic review and meta-analysis by Yu and colleagues suggest that prophylactic negative-pressure wound therapy in high-risk mostly obese women after CD reduces SSI and overall wound complications. The study's limitations, however, must be kept in mind, and more data are needed. It would be most helpful if a large, well-designed RCT was conducted and included 2 groups with comparable multiple major risk factors for wound complications, and in which all women received the following important interventions[2–4]:

- removal of hair in the surgical site with a clipper, not a razor
- cleansing of the skin with a chlorhexidine rather than an iodophor solution
- closure of the deep subcutaneous tissue if the total subcutaneous layer exceeds 2 cm in depth
- closure of the skin with suture rather than staples
- administration of antibiotic prophylaxis, ideally with a combination of cefazolin plus azithromycin, prior to the surgical incision.

How negative-pressure devices aid wound healing

Yu and colleagues explained that negative-pressure devices exert their beneficial effects in various ways, including:

- shrinking the wound
- inducing cellular stretch
- removing extracellular fluids
- creating a favorable environment for healing
- promoting angiogenesis and neurogenesis.

Multiple studies in nonobstetric patients have shown that prophylactic use of negative-pressure devices is beneficial in reducing the rate of SSI.[1] Yu and colleagues' systematic review and meta-analysis confirms those findings in a high-risk population of women having CD.

Study limitations

Before routinely adopting the use of negative-pressure devices for all women having CD, however, obstetricians should consider the following caveats:

- The investigations included in the study by Yu and colleagues did not consistently distinguish between scheduled versus unscheduled CDs.
- The reports did not systematically consider other major risk factors for wound complications besides obesity, and they did not control for these confounders in the statistical analyses.
- The studies included in the meta-analysis did not provide full descriptions of other measures that might influence the rate of SSIs, such as timing and selection of prophylactic antibiotics, selection of suture material, preoperative skin preparation, and closure techniques for the deep subcutaneous tissue and skin.
- None of the included studies systematically considered the cost-effectiveness of the negative-pressure devices. This is an important consideration given that the acquisition cost of these devices ranges from $200 to $500.

Vaginal cleansing before CD lowers risk of postop endometritis

Caissutti C, Saccone G, Zullo F, et al. Vaginal cleansing before cesarean delivery: a systematic review and meta-analysis. Obstet Gynecol. 2017;130(3):527–538.

Caissutti and colleagues aimed to determine if cleansing the vagina with an antiseptic solution prior to surgery reduced the frequency of postcesarean endometritis. They included 16 RCTs (4,837 patients) in their systematic review and meta-analysis. The primary outcome was the frequency of postoperative endometritis.

Details of the study

The studies were conducted in several countries and included patients of various socioeconomic classes. Six trials included only patients having a scheduled CD; 9 included both scheduled and unscheduled cesareans; and 1 included only unscheduled cesareans. In 11 studies, povidone-iodine was the antiseptic solution used. Two trials used chlorhexidine diacetate 0.2%, and 1 used chlorhexidine diacetate 0.4%. One trial used metronidazole 0.5% gel, and another used the antiseptic cetrimide, which is a mixture of different quaternary ammonium salts, including cetrimonium bromide.

In all trials, patients received prophylactic antibiotics. The antibiotics were administered prior to the surgical incision in 6 trials; they were given after the umbilical cord was clamped in 6 trials. In 2 trials, the antibiotics were given at varying times, and in the final 2 trials, the timing of antibiotic administration was not reported. Of note, no trials described the method of placenta removal, a factor of considerable significance in influencing the rate of postoperative endometritis.[5,6]

Endometritis frequency reduced with vaginal cleansing; benefit greater in certain groups. Overall, in the 15 trials in which vaginal cleansing was compared with placebo or with no treatment, women in the treatment group had a significantly lower rate of endometritis (4.5% compared with 8.8%; relative risk [RR], 0.52; 95% CI, 0.37–0.72). When only women in labor were considered, the frequency of endometritis was 8.1% in the intervention group compared with 13.8% in the control group (RR, 0.52; 95% CI, 0.28–0.97). In the women who were not in labor, the difference in the incidence of endometritis was not statistically significant (3.5% vs 6.6%; RR, 0.62; 95% CI, 0.34–1.15).

In the subgroup analysis of women with ruptured membranes at the time of surgery, the incidence of endometritis was 4.3% in the treatment group compared with 20.1% in the control group (RR, 0.23; 95% CI, 0.10–0.52). In women with intact membranes at the time of surgery, the incidence of endometritis was not significantly reduced in the treatment group.

Interestingly, in the subgroup analysis of the 10 trials that used povidone-iodine, the reduction in the frequency of postcesarean endometritis was statistically significant (2.8% vs 6.3%; RR, 0.42; 95% CI, 0.25–0.71). However, this same protective effect was not observed in the women treated with chlorhexidine. In the 1 trial that directly compared povidone-iodine with chlorhexidine, there was no statistically significant difference in outcome.

Simple intervention, solid benefit

Endometritis is the most common complication following CD. The infection is polymicrobial, with mixed aerobic and anaerobic organisms. The principal risk factors for postcesarean endometritis are low socioeconomic status, extended duration of labor and ruptured membranes, multiple vaginal

FAST TRACK

Women treated with vaginal cleansing before cesarean had a significantly lower rate of endometritis compared with those who received placebo or no treatment—4.5% vs 8.8% (RR, 0.52; 95% CI, 0.37–0.72)

PHOTO: SHUTTERSTOCK

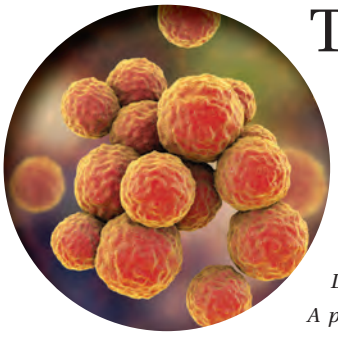
WHAT THIS EVIDENCE MEANS FOR PRACTICE

From my perspective, the interesting unanswered question is why a chlorhexidine solution with low alcohol content was not more effective than povidone-iodine, given that a chlorhexidine abdominal wash is superior to povidone-iodine in preventing wound infection after cesarean delivery.[7] Until additional studies confirm the effectiveness of vaginal cleansing with chlorhexidine, I recommend the routine use of the povidone-iodine solution in all women having CD.

examinations, internal fetal monitoring, and pre-existing vaginal infections (principally, bacterial vaginosis and group B streptococcal colonization).

Two interventions are clearly of value in reducing the incidence of endometritis: administration of prophylactic antibiotics prior to the surgical incision and removal of the placenta by traction on the cord as opposed to manual extraction.[5,6]

The assessment by Caissutti and colleagues confirms that a third measure—preoperative vaginal cleansing—also helps reduce the incidence of postcesarean endometritis. The principal benefit is seen in women who have been in labor with ruptured membranes, although certainly it is not harmful in lower-risk patients. The intervention is simple and straightforward: a 30-second vaginal wash with a povidone-iodine solution just prior to surgery.



Treat smaller skin abscesses with antibiotics after surgical drainage? Yes.

Daum RS, Miller LG, Immergluck L, et al; for the DMID 07-0051 Team. A placebo-controlled trial of antibiotics for smaller skin abscesses. N Engl J Med. 2017;376(26):2545–2555.

For treatment of subcutaneous abscesses that were 5 cm or smaller in diameter, investigators sought to determine if surgical drainage alone was equivalent to surgical drainage plus systemic antibiotics. After their abscess was drained, patients were randomly assigned to receive either clindamycin (300 mg 3 times daily) or trimethoprim-sulfamethoxazole (80 mg/400 mg twice daily) or placebo for 10 days. The primary outcome was clinical cure 7 to 10 days after treatment.

Details of the study

Daum and colleagues enrolled 786 participants (505 adults, 281 children) in the prospective double-blind study. *Staphylococcus aureus* was isolated from 527 patients (67.0%); methicillin-resistant *S aureus* (MRSA) was isolated from 388 (49.4%). The cure rate was similar in patients in the clindamycin group (83.1%) and the trimethoprim-sulfamethoxazole group (81.7%), and the cure rate in each antibiotic group was significantly higher than that in the placebo group (68.9%; $P<.001$ for both comparisons). The difference in treatment effect was specifically limited to patients who had *S aureus* isolated from their lesions.

Findings at follow-up. At 1 month of follow-up, new infections were less common in the clindamycin group (6.8%) than in the trimethoprim-sulfamethoxazole group (13.5%; $P = .03$) or the placebo group (12.4%; $P = .06$). However, the highest frequency of adverse effects occurred in the patients who received clindamycin (21.9% vs 11.1% vs 12.5%). No adverse effects were judged to be serious, and all resolved without sequela.

Controversy remains on antibiotic use after drainage

This study is important for 2 major reasons. First, soft tissue infections are quite common

PHOTO: SHUTTERSTOCK

CONTINUED ON PAGE 36

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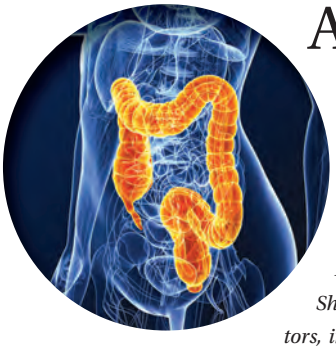
CONTINUED FROM PAGE 34

WHAT THIS EVIDENCE MEANS FOR PRACTICE

In my opinion, this investigation by Daum and colleagues supports a role for consistent use of systemic antibiotics following surgical drainage of clinically significant subcutaneous abscesses that have a 5 cm or smaller diameter. Several oral antibiotics are effective against *S aureus*, including MRSA.[10] These drugs include trimethoprim-sulfamethoxazole (1 double-strength tablet orally twice daily), clindamycin (300–450 mg 3 times daily), doxycycline (100 mg twice daily), and minocycline (200 mg initially, then 100 mg every 12 hours).

Of these drugs, I prefer trimethoprim-sulfamethoxazole, provided that the patient does not have an allergy to sulfonamides. Trimethoprim-sulfamethoxazole is significantly less expensive than the other 3 drugs and usually is better tolerated. In particular, compared with clindamycin, trimethoprim-sulfamethoxazole is less likely to cause antibiotic-associated diarrhea, including *Clostridium difficile* infection. Trimethoprim-sulfamethoxazole should not be used in the first trimester of pregnancy because of concerns about fetal teratogenicity.

and can evolve into serious problems, especially when the offending pathogen is MRSA. Second, controversy exists about whether systemic antibiotics are indicated if the subcutaneous abscess is relatively small and is adequately drained. For example, Talan and colleagues demonstrated that, in settings with a high prevalence of MRSA, surgical drainage combined with trimethoprim-sulfamethoxazole (1 double-strength tablet orally twice daily) was superior to drainage plus placebo.[8] However, Daum and Gold recently debated the issue of drainage plus antibiotics in a case vignette and reached opposite conclusions.[9]



Antibiotic use, common in the obstetric population, raises risk for *C difficile* infection

Ruiter-Ligeti J, Vincent S, Czuzoj-Shulman N, Abenhaim HA. Risk factors, incidence, and morbidity associated with obstetric Clostridium difficile infection. Obstet Gynecol. 2018;131(2):387–391.

The objective of this investigation was to identify risk factors for *Clostridium difficile* infection (previously termed pseudomembranous enterocolitis) in obstetric patients. The authors performed a retrospective cohort study using information from a large database maintained by the Agency for Healthcare Research and Quality. This database provides information about inpatient hospital stays in the United States, and it is the largest repository of its kind. It includes data from a sample of 1,000 US hospitals.

Details of the study

Ruiter-Ligeti and colleagues reviewed 13,881,592 births during 1999–2013 and identified 2,757 (0.02%) admissions for delivery complicated by *C difficile* infection, a rate of 20 admissions per 100,000 deliveries per year (95% CI, 19.13–20.62). The rate of admissions with this diagnosis doubled from 1999 (15 per 100,000) to 2013 (30 per 100,000, $P<.001$).

Among these obstetric patients, the principal risk factors for *C difficile* infection were older age, multiple gestation, long-term antibiotic use (not precisely defined), and concurrent diagnosis of inflammatory bowel disease. In addition, patients with pyelonephritis, perineal or cesarean wound infections, or pneumonia also were at increased risk, presumably because those patients required longer courses of broad-spectrum antibiotics.

Of additional note, when compared with women who did not have *C difficile* infection,

CONTINUED ON PAGE 37

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Tommaso Falcone, MD
Cleveland Clinic

Mickey M. Karram, MD
The Christ Hospital

SPECIAL KEYNOTE SPEAKER

Sawsan As-Sanie, MD, MPH
University of Michigan Hospitals and Health Centers

Faculty

Michael S. Baggish, MD
St. Helena Hospital

Linda D. Bradley, MD
Cleveland Clinic

Andrew I. Brill, MD
California Pacific Medical Center

Amanda Nickles Fader, MD
Johns Hopkins Hospital

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- Incontinence and Prolapse Surgery
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- Medical Legal Cases
- Fibroid Management
- Safe Use of Energy Devices in Gynecologic Surgery
- Surgical Tips for Successful Pelvic Surgery Video Session

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

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

PAGS AGENDA

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

TUESDAY, DECEMBER 4, 2018

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

WEDNESDAY, DECEMBER 5, 2018

Optional Hands-On Workshops

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

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

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

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

THURSDAY, DECEMBER 6, 2018

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

7:10 AM **Breakfast Symposium**

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

PELVIC ANATOMY

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

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

INCONTINENCE AND PROLAPSE SURGERY

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

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

10:25 AM **Break/Exhibits**

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

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

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

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

1:10 PM **Luncheon Symposium**

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

THURSDAY'S KEYNOTE LECTURE

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

FIBROID MANAGEMENT & PRINCIPLES OF ELECTROSURGERY

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

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

4:25 PM **Break/Exhibits**

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

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

FRIDAY, DECEMBER 7, 2018

7:00 AM **Breakfast/Exhibits**

7:10 AM **Breakfast Symposium**

HYSTERECTOMY - TECHNIQUE

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

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

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

10:00 AM **Break /Exhibits**

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

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

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

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

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

1:00 PM **Luncheon Symposium**

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

FRIDAY'S KEYNOTE LECTURE

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

ONCOLOGY FOR THE GENERALIST

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

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

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

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

SATURDAY, DECEMBER 8, 2018

6:30 AM **Breakfast**

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

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

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

10:30 AM **Break**

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

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

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

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

Open to Non-Attendees—So bring your staff!

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

Make Your Practice More Profitable, Efficient, and Productive!

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

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

SATURDAY, DECEMBER 8, 2018

2:00 PM **Course Overview**

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

3:30 PM **Break**

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

5:00 PM **Q and A**

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

PAGS Scientific Faculty

Course Chairs

Tommaso Falcone, MD
Professor of Surgery
Cleveland Clinic Lerner College of Medicine
Chairman
Obstetrics, Gynecology and Women's Health Institute
Cleveland Clinic
Cleveland, Ohio

Mickey M. Karram, MD
Director of Fellowship Program
Female Pelvic Medicine & Reconstructive Surgery
The Christ Hospital
Professor of OB/GYN & Urology
University of Cincinnati
Cincinnati, Ohio

Special Keynote Speaker

Sawsan As-Sanie, MD, MPH
Associate Professor
University of Michigan
Michigan Medical
Von Voigtlander Women's Hospital
Ann Arbor, Michigan

Faculty

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Vice Chair
Obstetrics, Gynecology, and Women's Health Institute
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Mayo Clinic
Phoenix, Arizona

Beri Ridgeway, MD
Obstetrics and Gynecology
Cleveland Clinic
Cleveland, Ohio

Optional Workshops

For complete information please see PAGS-CME.org.

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

Optional Opioid REMS Course

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

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

Optional Hands-on Workshops

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

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

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

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

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

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

Who Should Attend?

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

ACCREDITATION

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

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3.25 CME Credits Available
December 8, 2018

About Our Venue Encore at Wynn Las Vegas

The 2018 Pelvic Anatomy and Gynecologic Surgery Symposium (PAGS) will take place at the Encore Wynn Las Vegas where we have arranged for a discount room rate of just $189* a night for PAGS participants. To make your reservation, please call (866) 770-7555. You must identify yourself as a Pelvic Anatomy and Gynecologic Surgery Symposium 2018 attendee or reference the block code: 6PAG1218 to receive the discounted rate.

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

*Plus $25 amenity fee

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

Highlights Include

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

SPECIAL KEYNOTES:

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

How to Register for PAGS

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■ **Laparoscopic Suturing** Morning Workshop	$225	$245	$275	$345
■ **Tissue Extraction Techniques** Morning Workshop	$225	$245	$275	$345
■ **Vaginal Hysterectomy & Cystourethroscopy** Afternoon Workshop	$245	$275	$325	$395
■ **Opioid REMS Course** *Pre-registration required*	Free	Free	Free	Free

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CONTINUED FROM PAGE 36

patients with infection were more likely to develop a thromboembolic event (38.4 per 1,000), paralytic ileus (58.0 per 1,000), sepsis (46.4 per 1,000), and death (8.0 per 1,000).

Be on guard for *C difficile* infection in antibiotic-treated obstetric patients

C difficile infection is an uncommon but potentially very serious complication of antibiotic therapy. Given that approximately half of all women admitted for delivery are exposed to antibiotics because of prophylaxis for group B streptococcus infection, prophylaxis for CD, and treatment of chorioamnionitis and puerperal endometritis, clinicians constantly need to be vigilant for this complication.[11]

Affected patients typically present with frequent loose, watery stools and lower abdominal cramping. In severe cases, blood may be present in the stool, and signs of intestinal distention and even acute peritonitis may be evident. The diagnosis can be established by documenting a positive culture or polymerase chain reaction (PCR) assay for *C difficile* and a positive cytotoxin assay for toxins A and/or B. In addition, if endoscopy is performed, the characteristic gray membranous plaques can be visualized on the rectal and colonic mucosa.[11]

Discontinue antibiotic therapy. The first step in managing affected patients is to stop all antibiotics, if possible, or at least the one most likely to be the causative agent of *C difficile* infection. Patients with relatively mild clinical findings should be treated with oral metronidazole, 500 mg every 8 hours for 10 to 14 days. Patients with severe findings should be treated with oral vancomycin, 500 mg every 6 hours, plus IV metronidazole, 500 mg every 8 hours. The more seriously ill patient must be observed carefully for signs of bowel obstruction, intestinal perforation, peritonitis, and sepsis.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Clearly, clinicians should make every effort to prevent *C difficile* infection in the first place. The following preventive measures are essential:

- Avoid the use of extremely broad-spectrum antibiotics for prophylaxis for CD.
- When using therapeutic antibiotics, keep the spectrum as narrow as possible, consistent with adequately treating the pathogens causing the infection.
- Administer antibiotics for the shortest time possible, consistent with achieving a clinical cure or providing appropriate prophylaxis for surgical procedures (usually, a maximum of 3 doses).
- If a patient receiving antibiotics experiences more than 3 loose stools in 24 hours, either discontinue all antibiotics or substitute another drug for the most likely offending agent, depending on the clinical situation.
- If, after stopping or changing antibiotics, the clinical findings do not resolve promptly, perform a culture or PCR assay for *C difficile* and assays for the *C difficile* toxin. Treat as outlined above if these tests are positive.

Danger for birth defects with maternal Zika infection present in all trimesters, but greatest in first

PHOTO: SHUTTERSTOCK

Hoen B, Schaub B, Funk AL, et al. Pregnancy outcomes after ZIKV infection in French territories in the Americas. N Engl J Med. 2018;378(11):985–994.

To estimate the risk of congenital neurologic defects associated with Zika virus infection, Hoen and colleagues conducted a prospective

cohort study of pregnant women with symptomatic Zika virus infection who were enrolled during March through November 2016 in French Guiana, Guadeloupe, and Martinique. All women had Zika virus infection confirmed by PCR assay.

Details of the study

The investigators reviewed 546 pregnancies, which resulted in the birth of 555 fetuses and infants. Thirty-nine fetuses and neonates (7%; 95% CI, 5.0–9.5) had neurologic and ocular findings known to be associated with Zika virus infection. Of these, 10 pregnancies were terminated, 1 fetus was stillborn, and 28 were live-born.

Microcephaly (defined as head circumference more than 2 SD below the mean) was present in 32 fetuses and infants (5.8%); 9 had severe microcephaly, defined as head circumference more than 3 SD below the mean. Neurologic and ocular abnormalities were more common when maternal infection occurred during the first trimester (24 of 189 fetuses and infants, 12.7%) compared with infection during the second trimester (9 of 252, 3.6%) or third trimester (6 of 114, 5.3%) ($P = .001$).

FAST TRACK

The Zika virus is quite pathogenic and can cause debilitating injury to the developing fetus at any stage of gestation

Studies report similar rates of fetal injury

Zika virus infection primarily is caused by a bite from the *Aedes aegypti* mosquito. The infection also can be transmitted by sexual contact, laboratory accident, and blood transfusion. Eighty percent of infected persons are asymptomatic. In symptomatic patients, the most common clinical manifestations are low-grade fever, a disseminated maculopapular rash, arthralgias, swelling of the hands and feet, and nonpurulent conjunctivitis.

The most ominous manifestation of congenital Zika virus infection is microcephaly. Other important manifestations include lissencephaly, pachygyria, cortical atrophy, ventriculomegaly, subcortical calcifications, ocular abnormalities, and arthrogryposis. Although most of these abnormalities are immediately visible in the neonate, some may not appear until the child is older.

The present study is an excellent complement to 2 recent reports that defined the risk of Zika virus–related fetal injury in patients in the United States and its territories. Based on an analysis of data from the US Zika Pregnancy Registry, Honein and colleagues reported an overall rate of congenital infection of 6%.[12] The rate of fetal injury was 11% when the mother was infected in the first trimester and 0% when the infection occurred in the second or third trimester. The overall rate of infection and the first trimester rate of infection were similar to those reported by Hoen and colleagues.

Conversely, Shapiro-Mendoza and colleagues evaluated rates of infection in US territories (American Samoa, Puerto Rico, and the US Virgin Islands) and observed cases of fetal injury associated with second- and third-trimester maternal infection.[13] These authors reported an overall rate of infection of 5% and an 8% rate of infection with first-trimester maternal infection. When maternal infection occurred in the second and third trimesters, the rates of fetal injury were 5% and 4%, respectively, figures almost identical to those reported by Hoen and colleagues. Of note, the investigations by Honein and Shapiro-Mendoza included women with both symptomatic and asymptomatic infection. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Taken together, the studies discussed provide 2 clear take-home messages:

- Both symptomatic and asymptomatic maternal infection pose a significant risk of injury to the fetus and neonate.
- Although the risk of fetal injury is greatest when maternal infection occurs in the first trimester, exposure in the second and third trimesters is still dangerous. The Zika virus is quite pathogenic and can cause debilitating injury to the developing fetus at any stage of gestation.

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How to differentiate maternal from fetal heart rate patterns on electronic fetal monitoring

Three cases illustrate how maternal heart rate may masquerade as a fetal heart rate pattern and obscure the interpretation of EFM recordings

Michael G. Ross, MD, MPH

IN THIS ARTICLE

Continuous electronic fetal heart rate monitoring (EFM) is used in the vast majority of all labors in the United States. With the use of EFM categories and definitions from the American College of Obstetricians and Gynecologists, the National Institutes of Health, and the Society for Maternal-Fetal Medicine, clinicians can now better define and communicate tracing assessments. Except for reducing neonatal seizure activity, however, EFM use during labor has not been demonstrated to significantly improve fetal and neonatal outcomes, yet EFM is associated with an increase in cesarean deliveries and instrument-assisted vaginal births.[1]

The negative predictive value of EFM for fetal hypoxia/acidosis is high, but its positive predictive value is only 30%, and the false-positive rate is as high as 60%.[2] Although a false-positive assessment may result in a potentially unnecessary operative vaginal or cesarean delivery, a falsely reassuring strip may produce devastating consequences in the newborn and, not infrequently, medical malpractice liability. One etiology associated with falsely reassuring assessments is that of EFM monitoring of the maternal heart rate and the failure to recognize the tracing as maternal.

In this article, I discuss the mechanisms and periods of labor that often are associated with the maternal heart rate masquerading as the fetal heart rate. I review common EFM patterns associated with the maternal heart rate so as to aid in recognizing the maternal heart rate. In addition, I provide 3 case scenarios that illustrate the simple yet critical steps that clinicians can take to remedy the situation. Being aware of the potential for a maternal heart rate recording, investigating the EFM signals, and correcting the monitoring can help prevent significant morbidity.

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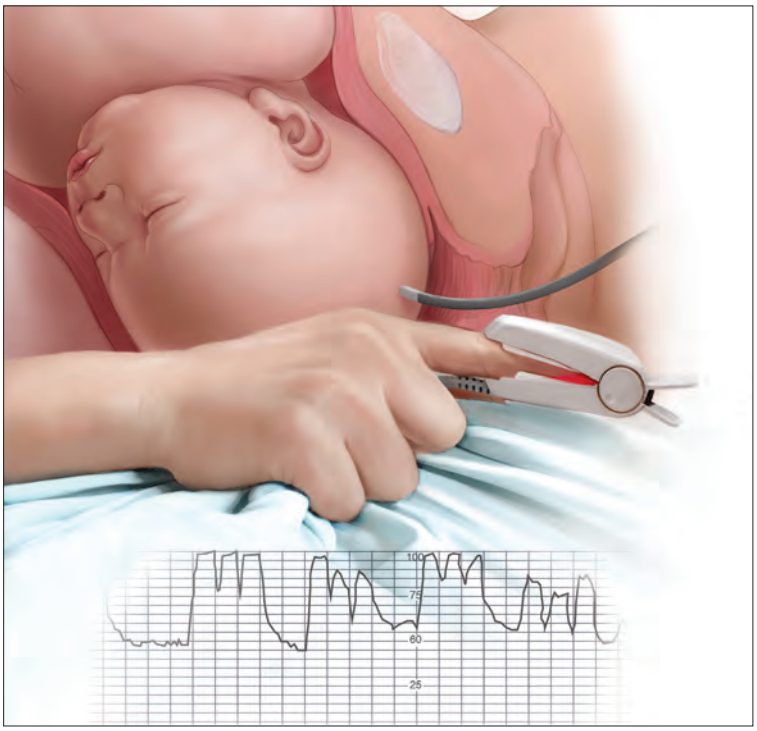
The author reports no financial relationships relevant to this article.

CASE 1 EFM shows seesaw decelerations and returns to baseline rate

A 29-year-old woman (G3P2) at 39 weeks' gestation was admitted to the hospital with spontaneous labor. Continuous EFM external monitoring was initiated. After membranes spontaneously ruptured at 4 cm dilation, an epidural was placed. Throughout the active phase of labor, the fetus demonstrated intermittent mild variable decelerations, and the fetal heart rate baseline increased to 180 beats per minute (BPM). With complete dilation, the patient

initiated pushing. During the first several pushes, the EFM demonstrated an initial heart rate deceleration, and a loss of signal, but the heart rate returned to a baseline rate of 150 BPM. With the patient's continued pushing efforts, the EFM baseline increased to 180 BPM, with evidence of variable decelerations to a nadir of 120 BPM, although with some signal gaps (**FIGURE 1,** red arrow). The tracing then appeared to have a baseline of 120 BPM with variability or accelerations (**FIGURE 1**, green arrow) before shifting again to 170 to 180 BPM.

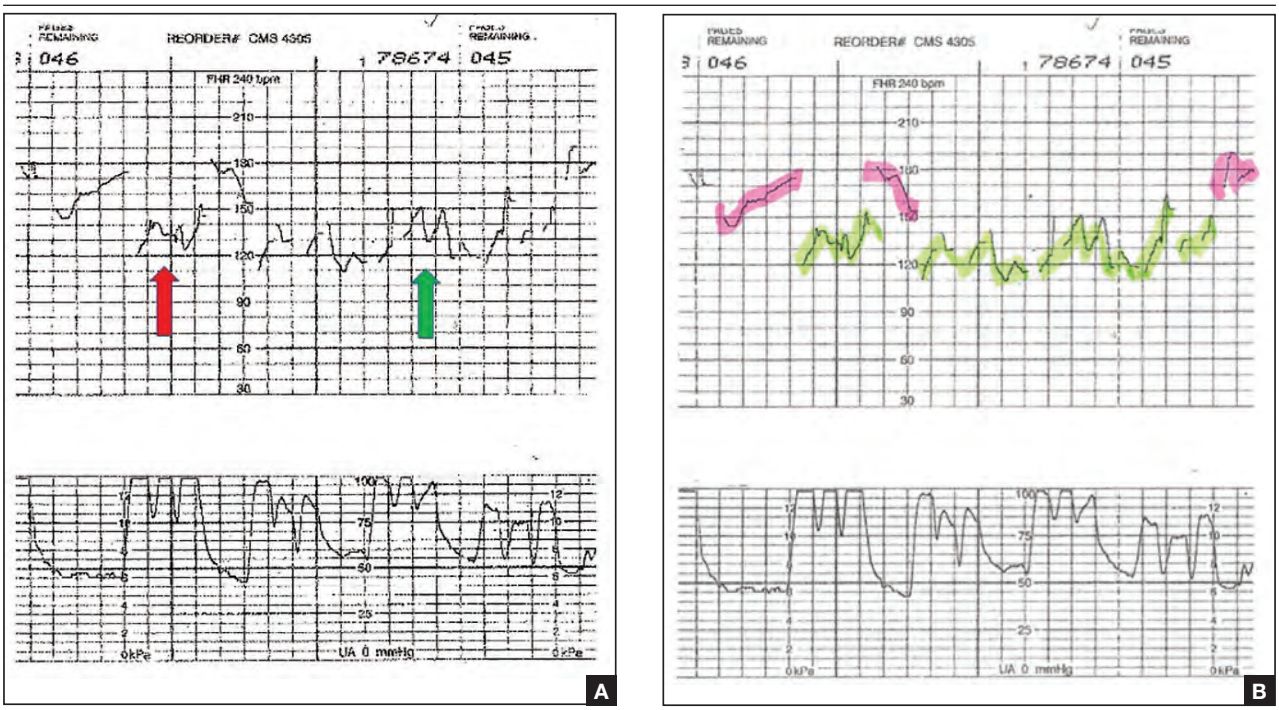
What was happening?



Why does the EFM record the maternal heart rate?

Most commonly, EFM recording of the maternal heart rate occurs during the second stage of labor. Early in labor, the normal fetal heart rate (110–160 BPM) typically exceeds the basal maternal heart rate. However, in

FIGURE 1 Variable decelerations



This EFM recording during the second stage of labor demonstrates pushing efforts every 1 minute (**panel A**). The red arrow indicates signal gaps; the green arrow shows variability or accelerations. In **panel B**, with the maternal heart rate highlighted in green and the fetal heart rate in pink, the patterns are now visible.

Abbreviation: EFM, electronic fetal heart rate monitoring.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

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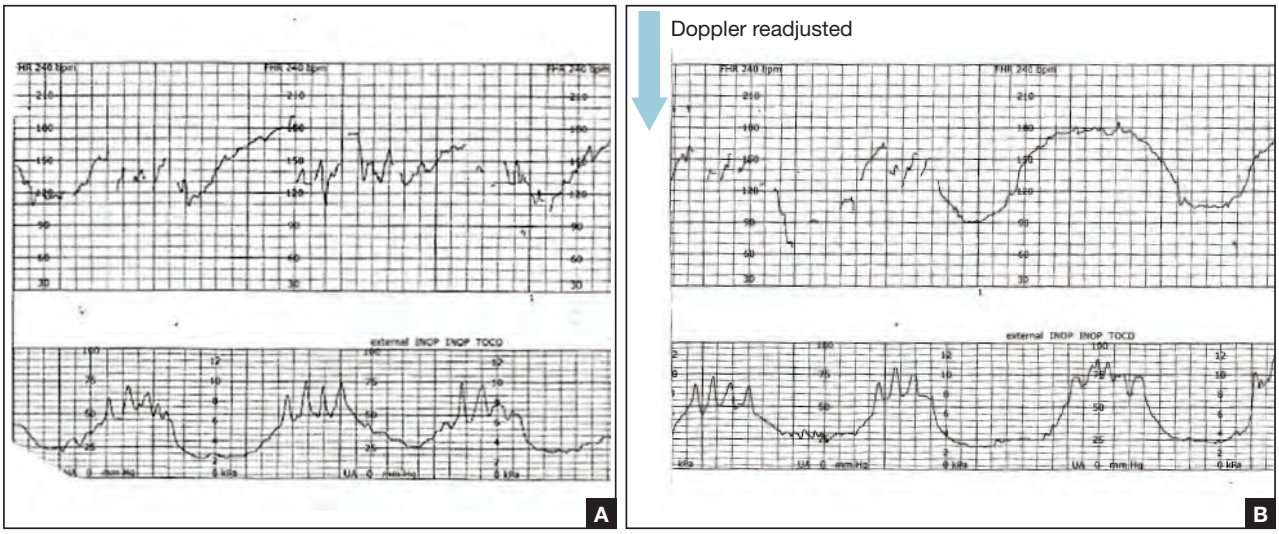
FIGURE 2 Breaks in the tracing



This EFM recording during the second stage of labor shows pushing efforts every 2 minutes (**panel A**). With adjustment of the Doppler monitor, the pattern of late decelerations is visible (**panel B**).

Abbreviation: EFM, electronic fetal heart rate monitoring.

FAST TRACK

The external Doppler fetal monitor may lose focus on the fetal heart as a result of descent of the baby, the abdominal shape-altering effect of uterine contractions, and the patient's pushing

the presence of chorioamnionitis and maternal fever or with the stress of maternal pushing, the maternal heart rate frequently approaches or exceeds that of the fetal heart rate. The maximum maternal heart rate can be estimated as 220 BPM minus the maternal age. Thus, the heart rate in a 20-year-old gravida may reach rates of 160 to 180 BPM, equivalent to 80% to 90% of her maximum heart rate during second-stage pushing.

The external Doppler fetal monitor, having a somewhat narrow acoustic window, may lose the focus on the fetal heart as a result of descent of the baby, the abdominal shape-altering effect of uterine contractions, and the patient's pushing. During the second stage, the EFM may record the maternal heart rate from the uterine arteries. Although some clinicians claim to differentiate the maternal from the fetal heart rate by the "whooshing" maternal uterine artery signal as compared with the "thumping" fetal heart rate signal, this auditory assessment is unproven and likely unreliable.

CASE 1 Problem recognized and addressed

In this case, the obstetrician recognized that "slipping" from the fetal to the maternal heart rate recording occurred with the onset of maternal pushing. After the pushing ceased, the maternal heart rate slipped back to the fetal heart rate. With the next several contractions, only the maternal heart rate was recorded. A fetal scalp electrode was then placed, and fetal variable decelerations were recognized. In view of the category II EFM recording, a vacuum procedure was performed from +3 station and a female infant was delivered. She had Apgar scores of 6 and 8 at 1 and 5 minutes, respectively, and she did well in the nursery.

CASE 2 EFM tracings belie the clinical situation

A 20-year-old woman (G1P0) presented for induction of labor at 41 weeks' gestation. Continuous EFM recording was initiated, and the patient was given dinoprostone and, subsequently, oxytocin. Rupture of membranes at 3 cm demonstrated a small amount of fluid with thick meconium. The patient progressed to complete dilation and developed a temperature of 38.5°C; the EFM baseline increased to 180 BPM. Throughout the first hour of the second stage of labor, the EFM demonstrated breaks in the tracing and a heart rate of 130 to 150 BPM with each pushing effort (**FIGURE 2A**). The Doppler monitor was subsequently adjusted to focus on the fetal heart and repetitive late decelerations were

observed (**FIGURE 2B**). An emergent cesarean delivery was performed. A depressed newborn male was delivered, with Apgar scores of 2 and 4 at 1 and 5 minutes, respectively, and significant metabolic acidosis.

What happened?

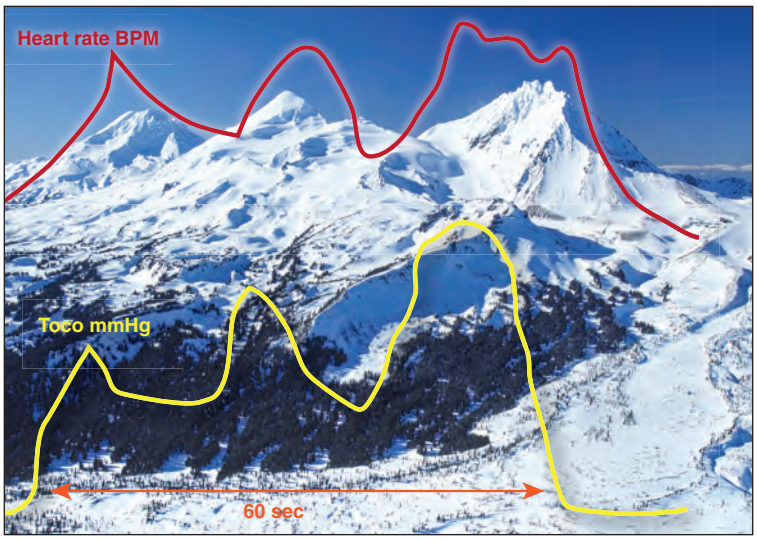
Fetal versus maternal responses to pushing

The fetal variable deceleration pattern is well recognized by clinicians. As a result of umbilical cord occlusion (due to compression, stretching, or twisting of the cord), fetal variable decelerations have a typical pattern. An initial acceleration shoulder resulting from umbilical vein occlusion (due to reduced venous return) is followed by an umbilical artery occlusion–induced sharp deceleration. The relief of the occlusion allows the sharp return toward baseline with the secondary shoulder overshoot.

In some cases, partial umbilical cord occlusion that affects only the fetal umbilical vein may result in an acceleration, although these usually resolve or evolve into variable decelerations within 30 minutes. By contrast, the maternal heart rate typically increases with contractions and with maternal pushing efforts. Thus, a repetitive pattern of *heart rate accelerations with each contraction* should warn of a possible maternal heart rate recording.

How maternal heart rate responds to pushing. Maternal pushing is a Valsalva maneuver. Although there are 4 classic cardiovascular phases of Valsalva responses, the typical maternal pushing effort results in an increase in the maternal heart rate. With the common sequence of three 10-second pushes during each contraction, the maternal heart rate often exhibits 3 acceleration and deceleration responses. The maternal heart rate tracing looks similar to the shape of the Three Sisters mountain peaks in Oregon (**FIGURE 3**). Due to Valsalva physiology, the 3 peaks of the Sisters mirror the 3 uterine wave form peaks, although with a 5- to 10-second delay in the heart rate responses (mountain peaks) from the pushing efforts.

FIGURE 3 Pattern of maternal heart rate



The shape of the Three Sisters mountain peaks is similar to the pattern of maternal heart rate (red line) in response to 3 maternal pushing efforts during a single uterine contraction (yellow line).

Pre- and postcontraction changes offer clues. Several classic findings aid in differentiating the maternal from the fetal heart rate. If the tracing is maternal, typically the heart rate gradually *decreases* following the end of the contraction/pushing and continues to decrease until the start of the next contraction/pushing, at which time it increases. During the push, the Three Sisters wave form, with the 5- to 10-second offset, should alert the clinician to possible maternal heart rate recordings. By contrast, the fetal heart rate variable deceleration typically *increases* following the end of the maternal contraction/pushing and is either stable or increases further (variable with slow recovery) prior to the next uterine contraction/pushing effort. These differences in the patterns of precontraction and postcontraction changes can be very valuable in differentiating periods of maternal versus fetal heart rate recordings.

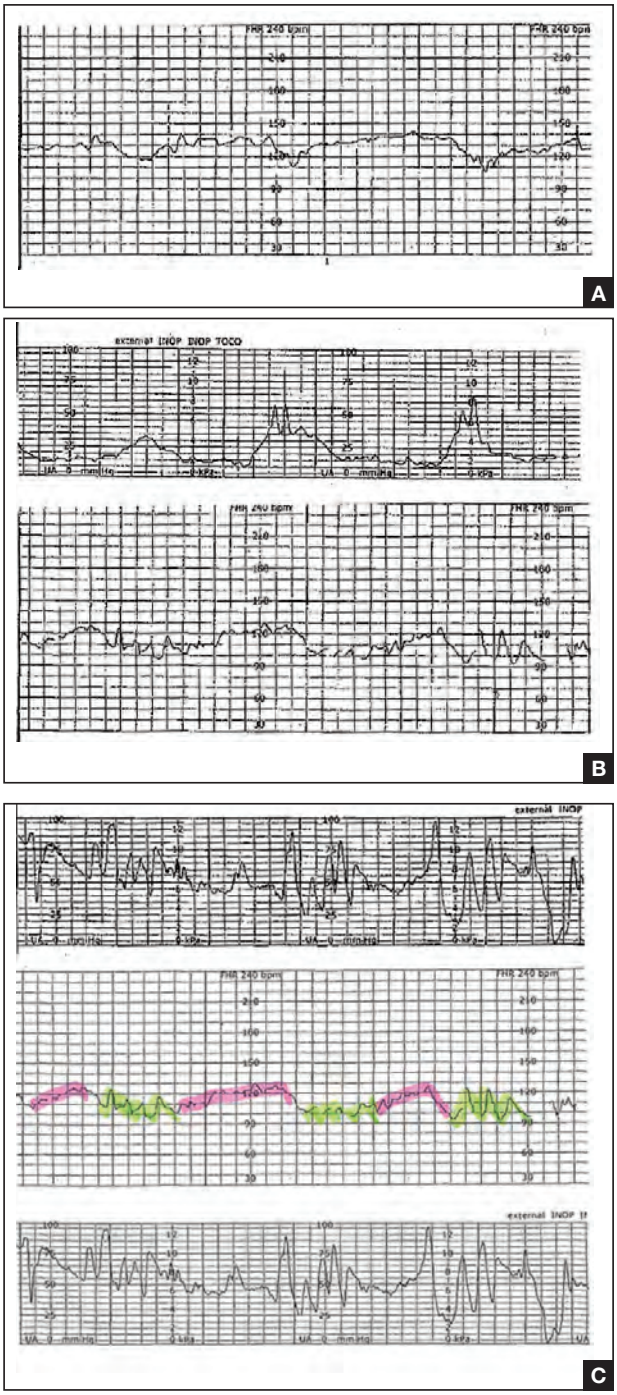
With "slipping" between fetal and maternal recording, it is not uncommon to record fetal heart rate between contractions, slip to the maternal heart rate during the pushing effort, and return again to the fetal heart rate with the end of the contraction. When confounded with the potential for other EFM

FAST TRACK

A repetitive pattern of heart rate accelerations with each contraction should warn of a possible maternal heart rate recording

PHOTO: SHUTTERSTOCK

FIGURE 4 Fetal to maternal heart rate recording



EFM recording during the active phase of labor (**panel A**). Note the small decelerations with each contraction. Maternal pulse was recorded as 71 BPM during this period, confirming this is the fetal heart rate. In the second stage, the tracing appears similar (**panel B**). However, as shown in **panel C**, the EFM is now recording the maternal heart rate (highlighted in green) during each contraction and the fetal heart rate (highlighted in pink) between contractions.

Abbreviations: BPM, beats per minute; EFM, electronic fetal heart rate monitoring.

artifacts, including doubling of a low maternal or fetal heart rate, or halving of a tachycardic signal, it is not surprising that it is challenging to recognize an EFM maternal heart rate recording.

CASE 2 Check the monitor for accurate focus

A retrospective analysis of this case revealed that the maternal heart rate was recorded with each contraction throughout the second stage. The actual fetal heart rate pattern of decelerations was revealed with the refocusing of the Doppler monitor.

CASE 3 Low fetal heart rate and variability during contractions

A 22-year-old woman (G2P1) in spontaneous labor at term progressed to complete dilation. Fetal heart rate accelerations occurred for approximately 30 minutes. With the advent of pushing, the fetal heart rate showed a rate of 130 to 140 BPM and mild decelerations with each contraction (**FIGURE 4A**). As the second stage progressed, the tracing demonstrated an undulating baseline heart rate between 100 and 130 BPM with possible variability during contractions (**FIGURE 4B**). This pattern continued for an additional 60 minutes. At vaginal delivery, the ObGyn was surprised to deliver a depressed newborn with Apgar scores of 1 and 3 at 1 and 5 minutes, respectively.

Slipping from the fetal to the maternal heart rate may be imperceptible

In contrast to the breaks in the tracings seen in Case 1 and Case 2, the EFM tracing in Case 3 appears continuous. Yet, slipping from the fetal to the maternal recording was occurring.

As seen in **FIGURE 4C**, the maternal heart rate with variability was recorded during pushing efforts, and the fetal heart rate was seen rising back toward a baseline between contractions. Note that the fetal heart rate did not reach a level baseline, but rather decelerated with the next contraction. The slipping to the maternal heart rate occurred without

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a perceptible break in the recording, making this tracing extremely difficult to interpret.

CASE 3 Be ever vigilant

The lack of recognition that the EFM recording had slipped to the maternal heart rate resulted in fetal and newborn hypoxia and acidosis, accounting for the infant's low Apgar scores.

Follow 3 steps to discern fetal vs maternal heart rate

These cases illustrate the difficulties in recognizing maternal heart rate patterns on the fetal monitor tracing. The 3 simple steps described below can aid in differentiating maternal from fetal heart rate patterns.

1 Be aware and alert

Recognize that EFM monitoring of the maternal heart rate may occur during periods of monitoring, particularly in second-stage labor. Often, the recorded tracing is a mix of fetal and maternal patterns. Remember that the maternal heart rate may increase markedly during the second stage and rise even higher during pushing efforts. When presented with a tracing that ostensibly represents the fetus, it may be challenging for the clinician to question that assumption. Thus, be aware that tracings may not represent what they seem to be.

Often, clinicians view only the 10-minute portion of the tracing displayed on the monitor screen. I recommend, however, that clinicians review the tracing over the past 30 to 60 minutes, or since their last EFM assessment, for an understanding of the recent fetal baseline heart rate and decelerations.

2 Investigate

Although it is sometimes challenging to recognize EFM maternal heart rate recordings, this is relatively easy to investigate. Even without a pulse oximeter in place, carefully examine the EFM recording for maternal signs to determine if the maternal heart rate is within the range of the recording. You can confirm that the recording is *maternal* through 1 of 3 easy measures:

- First, check the maternal radial pulse and correlate it with the heart rate baseline.
- Second, place a maternal electrocardiographic (EKG) heart rate monitor.
- Last, and often the simplest approach for continuous tracings, place a finger pulse oximeter to provide a continuous maternal pulse reading. Should the maternal heart rate superimpose on the EFM recording, maternal patterns are likely being detected. However, since the pulse oximeter and EFM Doppler devices use different technologies, they will provide similar—but not precisely identical—heart rate numerical readings if both are assessing the maternal heart rate. In that case, take steps to assure that the EFM truly is recording the fetal heart rate.

3 Treat and correct

If the EFM is recording a maternal signal or if a significant question remains, place a fetal scalp electrode (unless contraindicated), as this may likely occur during the second stage. Alternatively, place a maternal surface fetal EKG monitor, or use ultrasonography to visually assess the fetal heart rate in real time.

Key point summary

The use of a maternal finger pulse oximeter, combined with a careful assessment of the EFM tracing, and/or a fetal scalp electrode are appropriate measures for confirming a fetal heart rate recording.

The 3 steps described (be aware and alert, investigate, treat and correct) can help you effectively monitor the fetal heart rate and avoid the potentially dangerous outcomes that might occur when the maternal heart rate masquerades as the fetal heart rate. ●

FAST TRACK

To confirm that a recording is maternal, check the maternal radial pulse and correlate it with baseline heart rate, place a maternal EKG, or place a finger pulse oximeter to provide a continuous maternal pulse reading

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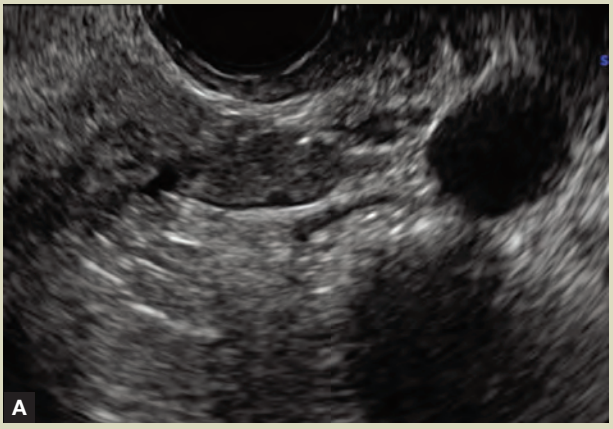
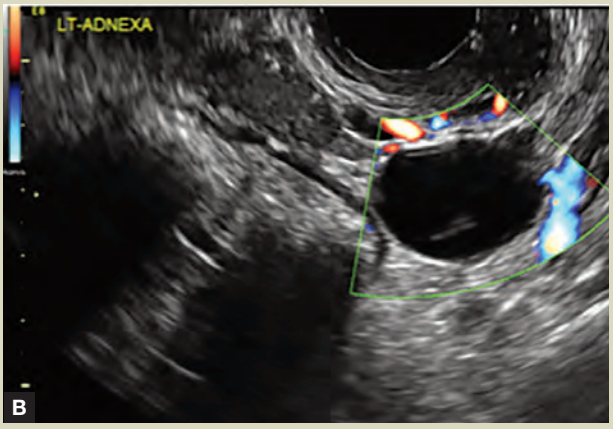
32-year-old woman with pelvic pain and irregular menstrual periods

Devaraju Kanmaniraja, MD, and Andrew M. Kaunitz, MD

CASE

A 32-year-old woman presents to her gynecologist's office reporting pelvic pain and irregular menstrual periods. Results of a urine pregnancy test are negative. Pelvic ultrasonography is performed, with gray scale (**A**) and color Doppler (**B**) images of the left adnexa obtained.





What is the diagnosis based on sonographic findings?

- Paratubal cyst
- Hydrosalpinx
- Peritoneal inclusion cyst
- Dilated pelvic veins

Turn the page to see if you are correct.

CONTINUED ON PAGE 48

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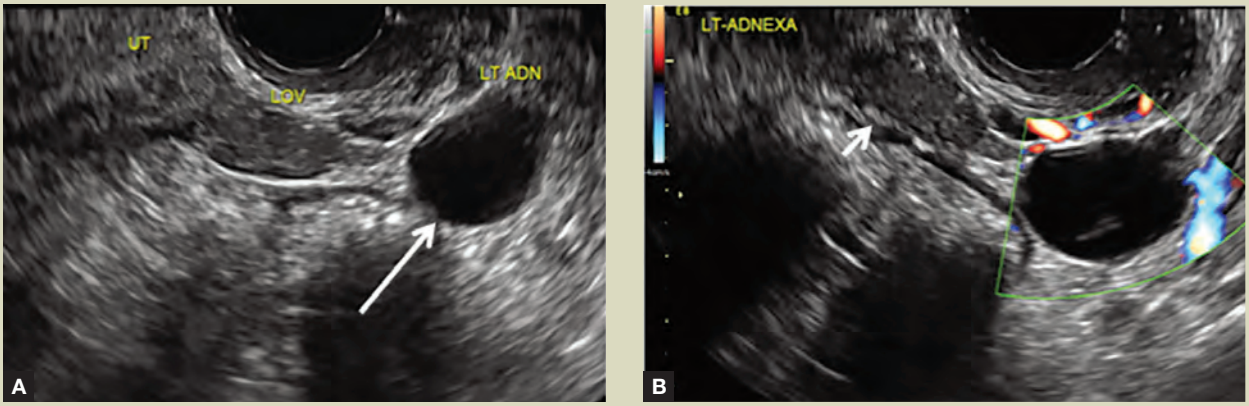
CORRECT

Paratubal cyst

Paratubal, or paraovarian, cysts typically are round or oval avascular hypoechoic cysts separate from the adjacent ovary. Since they are congenital remnants of the Wolffian duct, they arise from the mesosalpinx, specifically the broad ligament or fallopian tube.[1,2] They usually are seen in close proximity to but separate from the ovary without distorting the ovary's architecture.[1,2]

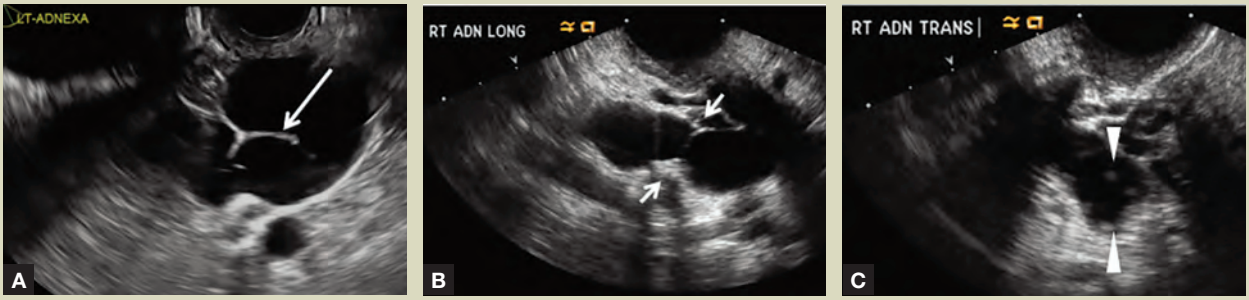


Paratubal cyst. (**A**) Transvaginal pelvic ultrasound of the left adnexa demonstrates an oval hypoechoic cyst (long arrow) separate from the adjacent ovary (short arrow). (**B**) The paratubal cyst is avascular on color Doppler.

INCORRECT

Hydrosalpinx

A hydrosalpinx appears as an elongated C- or S-shaped, thin-walled tubular serpiginous cystic lesion separate from the ovary. It often has incomplete septations that are infolding of the tube on itself.[3] Other findings include diametrically opposed indentations of the wall (Waist sign) and short linear mucosal or submucosal folds that when viewed in cross section appear similar to the spokes of a cogwheel (Cogwheel sign).[1–3] Prior tubal infection or gynecologic surgery represent risk factors for hydrosalpinx.

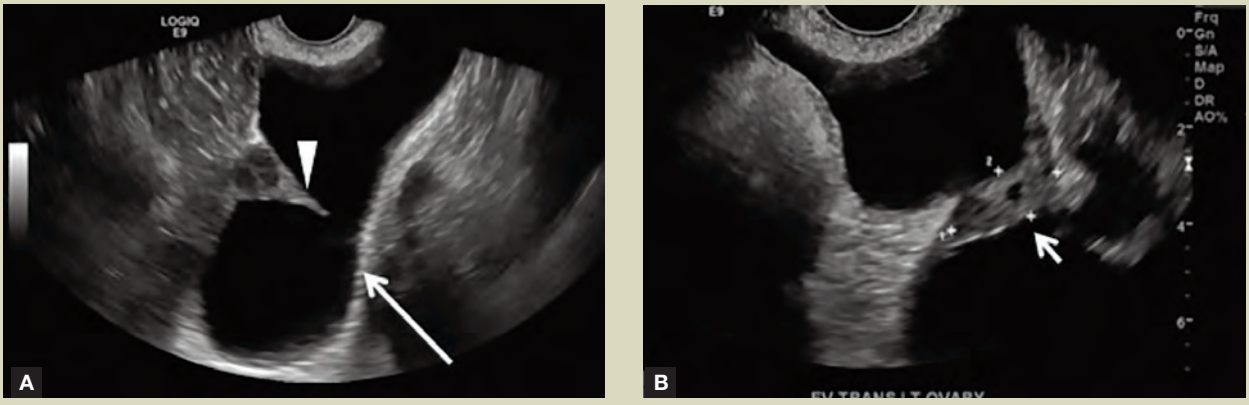


Hydrosalpinx. (**A**) Transvaginal pelvic ultrasound of the left adnexa demonstrates an elongated C- or S-shaped, thin-walled tubular serpiginous cystic lesion with incomplete septations (long arrow). (**B**) Longitudinal image of the right adnexa shows the dilated fallopian tube with diametrically opposed indentations of the wall consistent with the Waist sign (short arrows). (**C**) Transverse image of the dilated fallopian tube viewed in cross section has the appearance of several short mural nodules similar to the spokes of a cogwheel (arrowheads).

INCORRECT

Peritoneal inclusion cyst

A peritoneal inclusion cyst appears as an anechoic cystic mass that conforms passively to the shape of the peritoneal cavity/pelvic sidewall and may contain entrapped ovaries within or along the periphery of the fluid collection.[1,2] Septations within it are likely from peritoneal adhesions and may show vascularity.[2] Prior (often multiple) gynecologic surgeries represent a risk factor for peritoneal inclusion cysts.

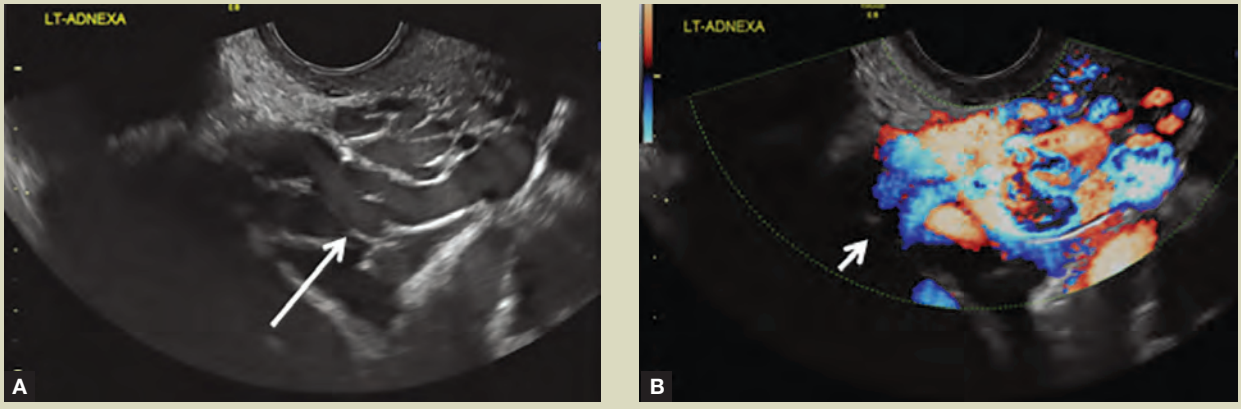


Peritoneal inclusion cyst. (**A**) Longitudinal transvaginal pelvic ultrasound of the left adnexa demonstrating an anechoic cystic lesion that conforms passively to the shape of the peritoneal cavity/pelvic sidewall (long arrow) with a thick septation (arrowhead). (**B**) Transverse image demonstrates the left ovary entrapped within the fluid collection (short arrow).

INCORRECT

Dilated pelvic veins

Dilated pelvic veins appear on sonography as a cluster of elongated and tubular cystic lesions in the adnexa along the broad ligament and demonstrate low level echoes due to sluggish flow and visible red blood cell rouleaux formation. This can be confirmed on color Doppler images and help differentiate it from hydrosalpinx.



Dilated pelvic veins. (**A**) Transvaginal pelvic ultrasound of the left adnexa reveals a cluster of elongated and tubular cystic lesions that demonstrate low level echoes due to sluggish flow (long arrow). (**B**) Color Doppler ultrasound confirms vascularity within these dilated pelvic veins (short arrow). ●

References

1. Laing FC, Allison SF. US of the ovary and adnexa: to worry or not to worry? Radiographics. 2012:32(6):1621–1639.
2. Moyle PL, Kataoka MY, Nakai A, Takahata A, Reinhold C, Sala E. Nonovarian cystic lesions of the pelvis. Radiographics. 2010;30(4):921–938.
3. Rezvani M, Shaaban AM. Fallopian tube disease in the nonpregnant patient. Radiographics. 2011;31(2):527–548.

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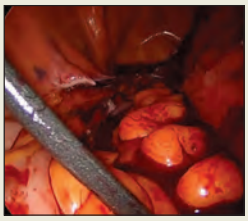
OBG MANAGEMENT

Size can matter: Laparoscopic hysterectomy for the very large uterus

DEIRDRE LUM, MD



In this video, the author describes surgical approaches to laparoscopic hysterectomy of a very large uterus (>2.5 kg). Preoperative strategies include the use of radial artery–uterine artery embolization, magnetic resonance imaging, and a gonadotropin-releasing hormone agonist. Intraoperative techniques include use of ureteral stents, securing the uterine artery at its origin, and maximizing port placement to allow for visualization and tissue extraction.

◀ Use this QR code* to view the video at **mdedge.com/obgmanagement**

*Free QR readers are available for smartphones at the iPhone App Store, Android Market, and BlackBerry App World.

INDEX OF ADVERTISERS

When did the bowel injury occur?

ONE DAY AFTER UNDERGOING a hysterectomy, a woman went to the emergency department (ED) because she was feeling ill. She received a diagnosis of a pulmonary embolism for which she was given anticoagulant medications. The patient's symptoms persisted. Computed tomography (CT) imaging showed a bowel injury, and, 17 days after the initial surgery, an emergency laparotomy was performed.

PATIENT'S CLAIM: The patient sued the surgeon and the hospital. The hospital settled before the trial and the case continued against the surgeon.

The patient's early symptoms after surgery were evidence of a bowel injury, but imaging was not undertaken for several days. If the imaging had been undertaken earlier, the bowel injury would have been detected before it caused a rectovaginal fistula. An expert pathologist testified that the microscopic findings he detected postlaparotomy could only exist if a bowel perforation had been there for a significant period of time before the fistula developed. The patient's experts argued that the injury was not a "free perforation," but had been contained by her body, preventing the spread of the infection.

DEFENDANT'S DEFENSE: The surgeon maintained that the injury did not occur during the hysterectomy but developed in the days just before it was discovered. Over time, a collection of infected fluid at the vaginal cuff eroded into the bowel above it, creating an entryway for stool to pass through. Continuous leakage from the bowel for 17 days (the length of time between development of symptoms and discovery of the bowel injury) would have likely resulted in the patient's death.

VERDICT: A Missouri defense verdict was returned.

Did unsafe oxytocin dose cause uterine rupture? $3.5M settlement

WHEN A MOTHER PRESENTED to the hospital in labor, the on-call ObGyn ordered oxytocin with the dosage to be increased by 2 mU/min until she was receiving 30 mU/min or until an adequate contraction pattern was achieved and maintained. Over the next few hours, the labor and delivery nurse increased the dosage of the infusion several times.

As the patient began to push, a trickle of bright red blood was seen coming from her vagina and the baby's heart tones were temporarily lost. When the fetal heart tones were restored, his heart rate was approximately 50 bpm. After vaginal delivery was attempted using vacuum extraction and forceps, an emergency cesarean delivery was performed, leading to the finding that the mother's uterus had ruptured.

The baby suffered a permanent brain injury due to hypoxic-ischemic encephalopathy.

PATIENT'S CLAIM: The mother sued the hospital and on-call ObGyn. She alleged that the health care providers breached the standard of care by negligently increasing and maintaining the oxytocin at unsafe levels, which caused the mother's uterus to be overworked and eventually rupture. The rupture led to the child's hypoxia. An expert ObGyn noted that the patient's contractions were adequate by the time the oxytocin dose reached 14 mU/min, but the dosage continued to be increased.

DEFENDANTS' DEFENSE: The case was settled during the trial.

VERDICT: A $3.5 million Kansas settlement was reached.

Nuchal cord: Undisclosed settlement

DURING DELIVERY, the labor and delivery nurses lost the fetal heart-rate (FHR) monitor tracing, resulting in their being unaware of increasing signs of fetal intolerance to labor. The nurses continued to administer oxytocin to induce labor.

At birth, a nuchal cord was identified. The baby was born without signs of life but was successfully resuscitated by hospital staff.

The baby was found to have sustained severe brain damage as a result of profound fetal hypoxia. The child will require 24-hour nursing and supportive care for as long as she lives.

PARENT'S CLAIM: The nurses and ObGyn breached the standard of care resulting in her child's severe brain damage. The hospital nurses failed to continuously monitor the FHR. Profound brain damage was preventable in this case.

DEFENDANTS' DEFENSE: The nurses continuously monitored by listening to sounds coming out of the bedside monitor even though no taping of FHR was occurring on the central monitors or FHR monitor strip. A nuchal cord is an unforeseeable medical emergency; nothing different could have been done to change the outcome.

VERDICT: An undisclosed Texas settlement was reached. ●

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

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]

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.

References: 1. Kaneshiro B, Aeby T. Long-term safety, efficacy, and patient acceptability of the intrauterine Copper T-380A contraceptive device. *Int J Womens Health*. 2010;2:211-220. **2.** Diedrich JT, Desai S, Zhao Q, Secura G, Madden T, Peipert JF. Association of short-term bleeding and cramping patterns with long-acting reversible contraceptive method satisfaction. *Am J Obstet Gynecol*. 2015;212(1):50.e1- 50.e8. **3.** Data on File. CooperSurgical, Inc., September 2017.

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

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