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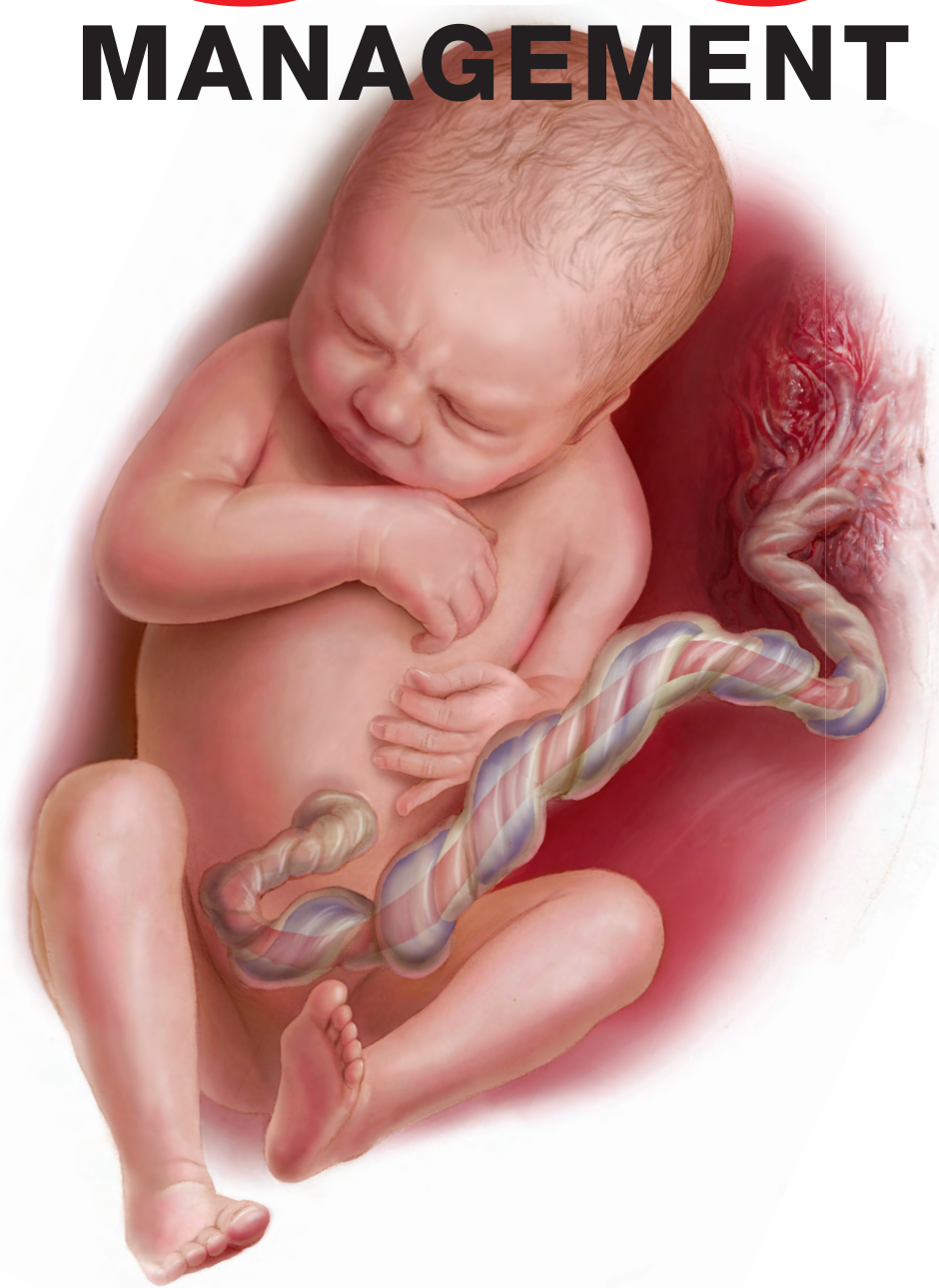

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She wanted to labor on her hands and knees: $16M verdict

References: 1. The North American Menopause Society. Management of symptomatic vulvovaginal atrophy: 2013 position statement of The North American Menopause Society. *Menopause.* 2013;20(9):888-902. **2**. Wysocki S, Kingsberg S, Krychman M. Management of vaginal atrophy: implications from the REVIVE survey. *Clin Med Insights Reprod Health.* 2014;8:23-30. **3.** Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. *Mayo Clin Proc*. 2010;85(1):87-94. **4**. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause.* 2014;21(10):1063-1068. **5**. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (REal Women's VIews of Treatment Options for Menopausal Vaginal ChangEs) survey. *J Sex Med*. 2013;10(7):1790-1799.

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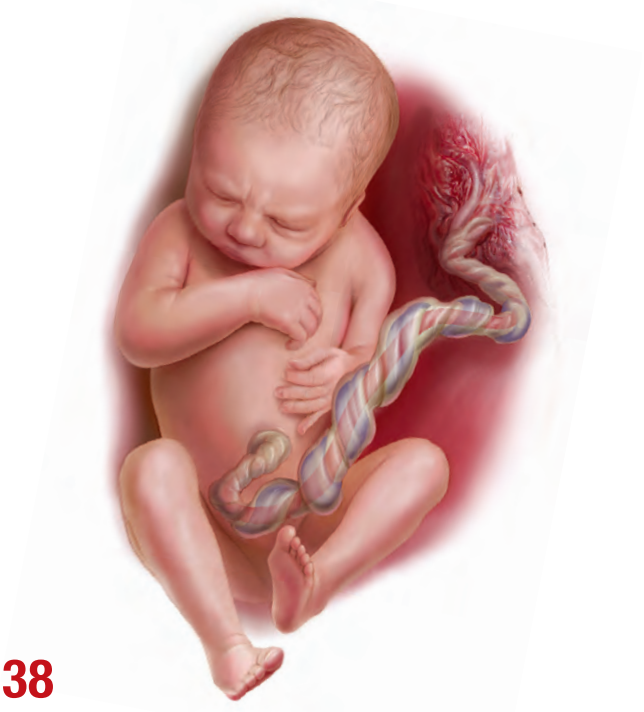

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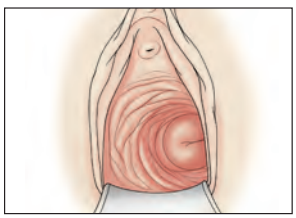

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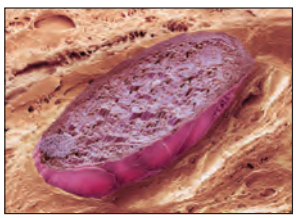

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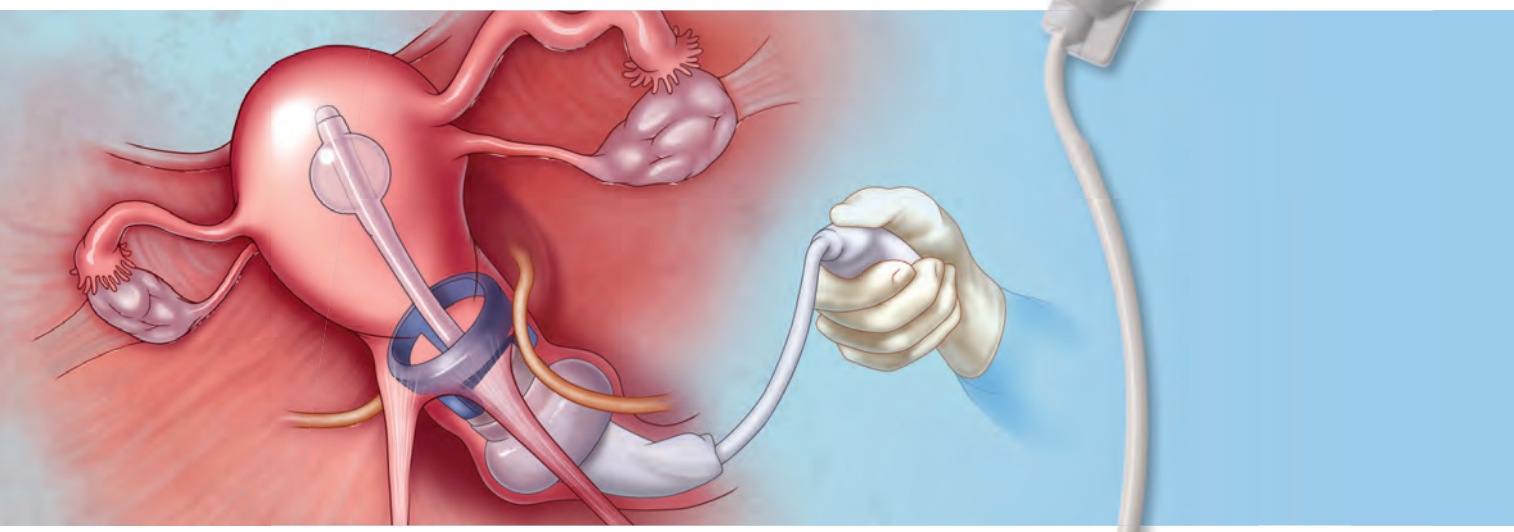

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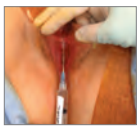

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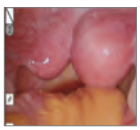

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Why are there delays in the diagnosis of endometriosis?

As leaders in women's health care, we can do much more to improve the timely diagnosis of endometriosis in women with pelvic pain

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

Endometriosis is a common gynecologic problem in adolescents and women. It often presents with pelvic pain, an ovarian endometrioma, and/or subfertility. In a prospective study of 116,678 nurses, the incidence of a new surgical diagnosis of endometriosis was greatest among women aged 25 to 29 years and lowest among women older than age 44.[1] Using the incidence data from this study, the calculated prevalence of endometriosis in this large cohort of women of reproductive age was approximately 8%.

Instant Poll

Our readers want to know: What are your clinical pearls for the timely diagnosis of endometriosis?

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

Although endometriosis is known to be a very common gynecologic problem, many studies report that there can be long delays between onset of pelvic pain symptoms and the diagnosis of endometriosis (**FIGURE 1,** page 10).[2–6] Combining the results from 5 studies, involving 1,187 women, the mean age of onset of pelvic pain symptoms was 22.1 years, and the mean age at the diagnosis of endometriosis was 30.7 years. This is a difference of 8.6 years between the age of symptom onset and age at diagnosis.[2–6]

What factors contribute to the diagnosis delay?

Both patient and physician factors contribute to the reported lengthy delay between symptom onset and endometriosis diagnosis.[7,8] Differentiating dysmenorrhea due to primary and secondary causes is difficult for both patients and physicians. Women may conceal the severity of menstrual pain to avoid both the embarrassment of drawing attention to themselves and being stigmatized as unable to cope. Most disappointing is that many women with endometriosis reported that they asked their clinician if endometriosis could be the cause of their severe dysmenorrhea and were told, "No."[7,8]

Of interest, the reported delay in the diagnosis of endometriosis is much shorter for women who present with infertility than for women who present with pelvic pain. In one study from the United States, the delay to diagnosis was 3.13 years for women who presented with infertility and 6.35 years for women who presented with severe pelvic pain.[3] This suggests that clinicians and patients more rapidly pursue the diagnosis of endometriosis in women with infertility, but not pelvic pain.

Initial treatment of pelvic pain with NSAIDs and estrogen—progestin contraceptives

Many women with undiagnosed endometriosis present with pelvic pain symptoms including moderate to severe dysmenorrhea. These women are often empirically treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and combination estrogen–progestin contraceptives in either a cyclic or continuous manner.[9,10] Since many women with endometriosis

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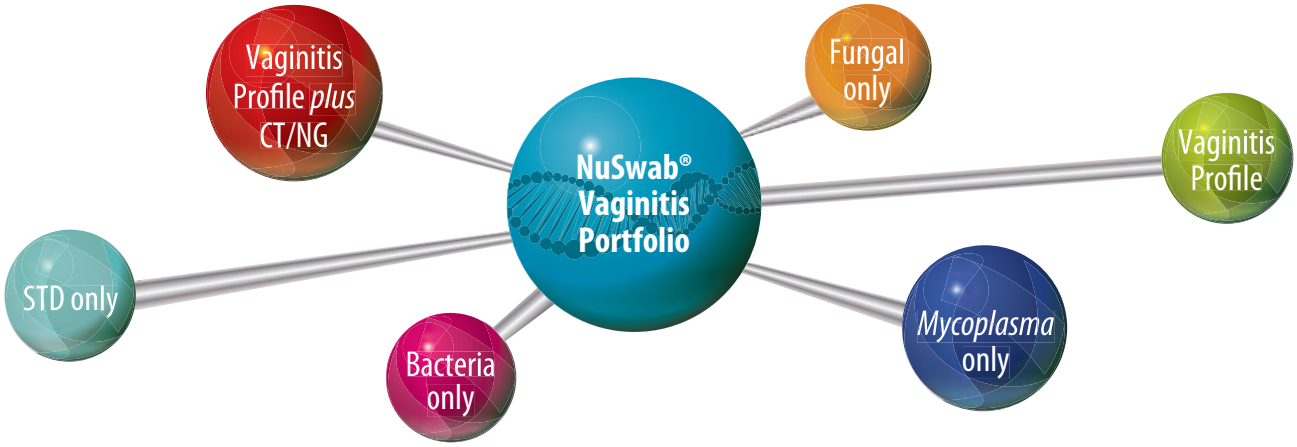

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1. Willett LL, Centor RM. Evaluating vaginitis. The importance of patient factors. *J Gen Intern Med.* 2005 Sept;20(9): 871.
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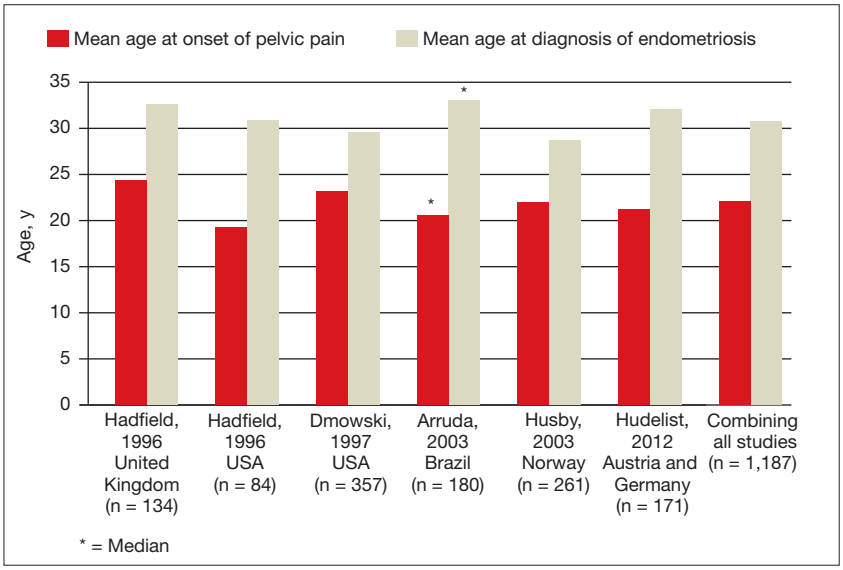
FIGURE 1 Women with pelvic pain and endometriosis report lengthy delays between the onset of symptoms of pelvic pain and the diagnosis of endometriosis[2–6]



will have a reduction in their pelvic pain with NSAID and contraceptive treatment, diagnosis of their endometriosis may be delayed until their disease progresses years after their initial presentation. It is important to gently alert these women to the possibility that they have undiagnosed endometriosis as the cause of their pain symptoms and encourage them to report any worsening pain symptoms in a timely manner.

Sometimes women with pelvic pain are treated with NSAIDs and contraceptives but no significant reduction in pain symptoms occurs. For these women, speedy consideration should be given to offering a laparoscopy to determine the cause of their pain.

Diagnosing endometriosis relies on identifying flags in the patient's history

The gold standard for endometriosis diagnosis is surgical visualization of endometriosis lesions, most often with laparoscopy, plus histologic confirmation of endometriosis on a tissue biopsy.[9,10] A key to reducing the time between onset of symptoms and diagnosis of endometriosis is identifying adolescents and women who are at high risk for having the disease. These women should be offered a laparoscopy procedure. In women with moderate to severe pelvic pain of at least 6 months duration, medical history, physical examination, and imaging studies can be helpful in identifying those at increased risk for endometriosis.

Items from the patient history that might raise the likelihood of endometriosis include:

- abdominopelvic pain, dysmenorrhea, menorrhagia, subfertility, dyspareunia and/or postcoital bleeding[11]
- symptoms of dysmenorrhea and/or dyspareunia that are not responsive to NSAIDs or estrogen–progestin contraceptives[12]
- symptoms of dysmenorrhea and/or dyspareunia associated with absenteeism from school or work[13]
- multiple visits to the emergency department for severe dysmenorrhea
- endometriosis in the patient's mother or sister
- subfertility with regular ovulation, patent fallopian tubes, and a partner with a normal semen analysis
- urinary frequency, urgency, and/or pain on urination
- diarrhea, constipation, nausea, dyschezia, bowel cramping, abdominal distention, and early satiety.

A daunting clinical challenge is that symptoms of endometriosis overlap with other gynecologic and nongynecologic problems including pelvic infection, adhesions, ovarian cysts, fibroids, irritable bowel syndrome, inflammatory bowel disease, interstitial cystitis, myofascial pain, depression, and history of sexual abuse.

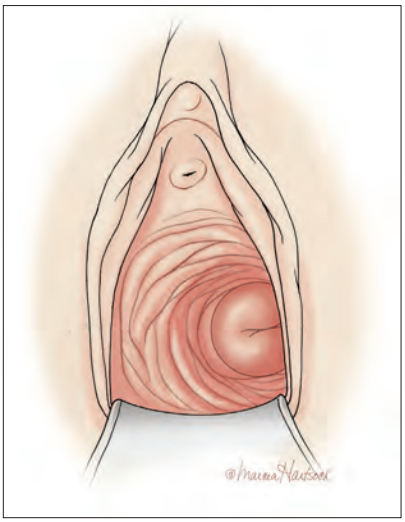
Diagnosing endometriosis relies on identifying flags on physical exam

Physical examination findings that raise the likelihood that the patient has endometriosis include:

- fixed and retroverted uterus
- adnexal mass
- lesions of the cervix or posterior fornix that visually appear to be endometriosis
- uterosacral ligament abnormalities, including tenderness, thickening, and/or nodularity[14,15]
- lateral displacement of the cervix (**FIGURE 2**)[16,17]
- severe cervical stenosis.

In one study of 57 women with a surgical diagnosis of endometriosis, uterosacral ligament abnormalities, lateral displacement of the cervix, and cervical stenosis were observed in 47%, 28%, and 19% of the women, respectively.[17] In this same study 22 women had none of these findings, but 8 had a complex ovarian

FIGURE 2 Lateral displacement of the cervix



Lateral displacement of the cervix, which can be documented by visual examination of the cervix on speculum examination or by digital examination, is probably caused by the asymmetric involvement of one uterosacral ligament by endometriosis, causing one ligament to shorten and pull the cervix to that side of the body.

mass consistent with endometriosis.

The possibility of endometriosis increases as the number of history and physical examination findings suggestive of endometriosis increase.

When transvaginal ultrasound can aid diagnosis

Most women with endometriosis have normal transvaginal ultrasonography (TVUS) results because ultrasound cannot detect small isolated peritoneal lesions of endometriosis present in Stage I disease, the most common stage of endometriosis. However, ultrasound is useful in detecting both ovarian endometriomas and nodules of deep infiltrating endometriosis (DIE).[18] TVUS has excellent sensitivity (>90%) and specificity (>90%) for the detection of ovarian endometriomas because these cysts have characteristic, homogenous, low-level internal echoes.[19,20] For the diagnosis of DIE of the uterosacral ligaments and rectovaginal septum, TVUS has fair sensitivity (>50%) and excellent specificity (>90%).[21] In most studies, magnetic resonance imaging performs no better than TVUS for imaging ovarian endometriomas and DIE. Hence, TVUS is the preferred imaging modality for detecting endometriosis.[22]

Key points for primary care physicians and patients

- Endometriosis is a common gynecologic disease. Approximately 8% of women of reproductive age have the condition.
- Many patients report lengthy delays between the onset of symptoms of pelvic pain and the diagnosis of endometriosis.
- Both patients and clinicians contribute to the delay in the diagnosis of endometriosis: Women are often reluctant to report the severity of their pelvic pain symptoms, and clinicians often under-respond to a patient's report of severe pelvic pain symptoms.
- First-line therapy for the treatment of moderate to severe dysmenorrhea is nonsteroidal anti-inflammatory drugs and estrogen–progestin contraceptives.
- Increasing vigilance for endometriosis will shorten the time between onset of symptoms and definitive diagnosis.
- Reducing the time between the onset of symptoms and diagnosis of endometriosis will improve the quality of life of women with the disease because they will receive timely treatment.

This is a practice gap we can close

Clinicians take great pride in accurately solving patient problems in a timely and efficient manner. Substantial research indicates that we can improve the timeliness of our diagnosis of endometriosis. By acknowledging patients' pain symptoms and recognizing the myriad symptoms and physical examination and imaging findings that are associated with endometriosis, we will close the gap and make this diagnosis with greater speed.

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

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All health care providers performing insertions and/or removals of NEXPLANON should receive instructions and training prior to inserting or removing the implant.

SELECTED SAFETY INFORMATION (*continued*)

- 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.
- 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.

Before prescribing NEXPLANON, 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 infection from HIV infection (AIDS) or other sexually transmitted diseases.

INDICATION AND USAGE

NEXPLANON is indicated for use by women for the prevention of 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), 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.

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®) (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.

DRUG INTERACTIONS

Changes in Contraceptive Effectiveness Associated With Coadministration of Other Products

Drugs or herbal products that induce enzymes, including CYP3A4, that metabolize progestins may decrease the plasma concentrations of progestins, and may decrease the effectiveness of NEXPLANON. In women on long-term treatment with hepatic enzyme inducing drugs, it is recommended to remove the implant and to advise a contraceptive method that is unaffected by the interacting drug.

Some of these drugs or herbal products that induce enzymes, including CYP3A4, include:

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

HIV Antiretrovirals

Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of co-administration with HIV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors. Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Increase in Plasma Concentrations of Etonogestrel Associated with Coadministered Drugs

CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma concentrations of etonogestrel.

Changes in Plasma Concentrations of Coadministered Drugs

Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporin) 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**
NEXPLANON is not indicated for use during pregnancy *[see Contraindications]*.

   Teratology studies have been performed in rats and rabbits using oral administration up to 390 and 790 times the human etonogestrel dose (based upon body surface), respectively, and revealed no evidence of fetal harm due to etonogestrel exposure. Studies have revealed no increased risk of birth defects in women who have used combination oral contraceptives before pregnancy or during early pregnancy. There is no evidence that the risk associated with etonogestrel is different from that of combination oral contraceptives. NEXPLANON should be removed if maintaining a pregnancy.
2. **Nursing Mothers**
Based on limited clinical data, NEXPLANON may be used during breastfeeding after the fourth postpartum week. Use of NEXPLANON before the fourth postpartum week has not been studied. Small amounts of etonogestrel are excreted in breast milk. During the first months after insertion of NEXPLANON, when maternal blood levels of etonogestrel are highest, about 100 ng of etonogestrel may be ingested by the child per day based on an average daily milk ingestion of 658 mL. Based on daily milk ingestion of 150 mL/kg, the mean daily infant etonogestrel dose one month after insertion of the non-radiopaque etonogestrel implant (IMPLANON) is about 2.2% of the weight-adjusted maternal daily dose, or about 0.2% of the estimated absolute maternal daily dose. The health of breastfed infants whose mothers began using the non-radiopaque etonogestrel implant during the fourth to eighth week postpartum (n=38) was evaluated in a comparative study with infants of mothers using a non-hormonal IUD (n=33). They were breastfed for a mean duration of 14 months and followed up to 36 months of age. No significant effects and no differences between the groups were observed on the physical and psychomotor development of these infants. No differences between groups in the production or quality of breast milk were detected. Healthcare providers should discuss both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients.
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. **Renal Impairment**
No studies were conducted to evaluate the effect of renal disease on the disposition of NEXPLANON.
7. **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.

Revised: 03/2016
uspi-mk8415-iptx-1603r017
WOMN-1185102-0000 08/16

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Commentary

›› Barbara S. Levy, MD

It is time for HPV vaccination to be considered part of routine preventive health care

The ACIP now recommends a 2-dose HPV vaccine schedule for girls and boys younger than age 15. We are a step closer to higher vaccination rates.

The recognition that human papillomavirus (HPV) oncogenic viruses cause cervical carcinoma remains one of the most game-changing medical discoveries of the last century. Improvements in screening options for detecting cervical cancer precursors followed. We now have the ability to detect high-risk HPV subtypes in routine specimens. Finally, a highly effective vaccine was developed that targets HPV types 16 and 18, which are responsible for causing approximately 70% of all cases of cervical carcinoma.

In one of the original vaccines HPV types 6 and 11, responsible for 90% of all genital warts, were also targeted. In 2014, a 9-valent vaccine incorporating an additional 5 HPV strains (31, 33, 45, 52, and 58) was approved and is set to replace all previous vaccine versions. Together, these 7 oncogenic HPV types are responsible for approximately 90% of HPV-related cancers, including cervical, anal, oropharyngeal, vaginal, and vulvar cancer.

By vaccinating boys and girls between ages 9 and 21 (for males) and 9 and 26 (for females), we could effectively eliminate 90% of genital warts and 90% of all HPV-related cancers. So why have we not capitalized on this extraordinary discovery? In 2016, why were only 40% of teenage girls and less than 25% of teenage boys vaccinated against HPV when we are immunizing 80% to 90% of these populations with tetanus, diphtheria, and acellular pertusis (Tdap) and meningococcal vaccines?

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The author reports no financial relationships relevant to this article.

Barriers to HPV vaccination

When the first HPV vaccine was approved in 2006, cost was a significant factor. Many health insurance plans did not cover this "discretionary" vaccine, which was viewed as a prevention for sexually transmitted infections rather than as a valuable intervention for the prevention of cervical and other cancers. At well over $125 per dose with 3 doses required for a full series, ObGyns were reluctant to stock and provide these expensive vaccines without assurance of reimbursement. The logistics of recalling patients for their subsequent vaccine doses were challenging for offices that were not accustomed to seeing patients for preventive care activities more than once a year. In addition, the office infrastructure required to maintain the vaccine stock and manage the necessary paperwork could be daunting. Finally, the requirement that patients be observed for 15 to 30 minutes in the office after vaccine administration created efficiency and rooming problems in busy, active practices.

Over time, almost all payers covered the HPV vaccines, but the logistical issues in ObGyn practices remain. Pediatric practices, on the other hand, are ideally suited for vaccine administration. Unfortunately, our colleagues delivering preventive care to young teens have persisted in considering the HPV vaccine as an optional adjunct to routine vaccination despite the advice of the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), which for many years has recommended the HPV vaccine for girls. In 2011, the ACIP extended the HPV vaccine recommendation to include boys beginning at ages 11 to 12.

New 2-dose HPV vaccine schedule for children <15 years

In October 2016, 10 years after the first HPV vaccine approval, the ACIP and

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the CDC approved a reduced, 2-dose schedule for those younger than 15.[1] The first dose can be administered simultaneously with other recommended vaccines for 11- to 12-year-olds (the meningococcal and Tdap vaccines) and the second dose, 6 or 12 months later.[2] The 12-month interval would allow administration, once again, of all required vaccines at the annual visit.

Pivotal immunogenicity study

The new recommendation is based on robust multinational data (52 sites in 15 countries, N = 1,518) from an open-label trial.[3] Immunogenicity of 2 doses of the 9-valent HPV vaccine in girls and boys ages 9 to 14 was compared with that of a standard 3-dose regimen in adolescents and young women ages 16 to 26. Five cohorts were studied: boys 9 to 14 given 2 doses at 6-month intervals; girls 9 to 14 given 2 doses at 6-month intervals; boys and girls 9 to 14 given 2 doses at a 12-month interval; girls 9 to 14 given the standard 3-dose regimen; and girls and young women 16 to 26 receiving 3 doses over 6 months.

The authors assessed the antibody responses against each HPV subtype 1 month after the final vaccine dose. Data from 1,377 participants (90.7% of the original cohort) were analyzed. Prespecified antibody titers were set conservatively to ensure adequate immunogenicity. Noninferiority criteria had to be met for all 9 HPV types.

Trial results. The immune responses for the 9- to 14-year-olds were consistently higher than those for the 16- to 26-year-old age group regardless of the regimen—not a surprising finding since the initial trials for HPV vaccine demonstrated a greater response among younger vaccine recipients. In this trial, higher antibody responses were found for the 12-month dosing interval than for the 6-month interval, although both regimens produced an adequate response.

Immunogenicity remained at 6 months. Antibody levels were retested 6 months after the last dose of HPV vaccine in a post hoc analysis. In all groups the antibody titers declined; however, there was no difference between the 2- and 3-dose cohorts. All levels remained above a threshold required for immunogenicity.

Simplified dosing may help increase vaccination rates

What does this new dosing regimen mean for practice? It will be simpler to incorporate HPV vaccination routinely into the standard vaccine regimen for preadolescent boys and girls. In addition, counseling for HPV vaccine administration can be combined with counseling for the meningococcal vaccine and routine Tdap booster.

Notably, primary care physicians have reported perceiving HPV vaccine discussions with parents as burdensome, and they tend to discuss it last after conversations about Tdap and meningococcal vaccines.[4] Brewer and colleagues[5] documented a 5% increase in first HPV vaccine doses among patients in practices in which the providers were taught to "announce" the need for HPV vaccine along with other routine vaccines. There was no increase in HPV vaccine uptake among practices in which providers were taught to "discuss" HPV with parents and to address their concerns, or in control practices. Therefore, less conversation about HPV and the HPV vaccine, as distinct from any other recommended vaccines, is better.

With the new 2-dose regimen, it should be easier to convey that the HPV vaccine is another necessary, routine intervention for children's health. We should be able to achieve 90% vaccination rates for HPV—similar to rates for Tdap.

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- **Removable whenever she decides—for up to 10 years**[1†]
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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.

*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."[3]

†PARAGARD must be removed by a healthcare professional.[1]

References: 1. PARAGARD® T 380A [Prescribing Information]. North Wales, PA: Teva Women's Health, Inc.; September 2014. **2.** 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. **3.** 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.

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

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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	

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

PAR-41071 10/16

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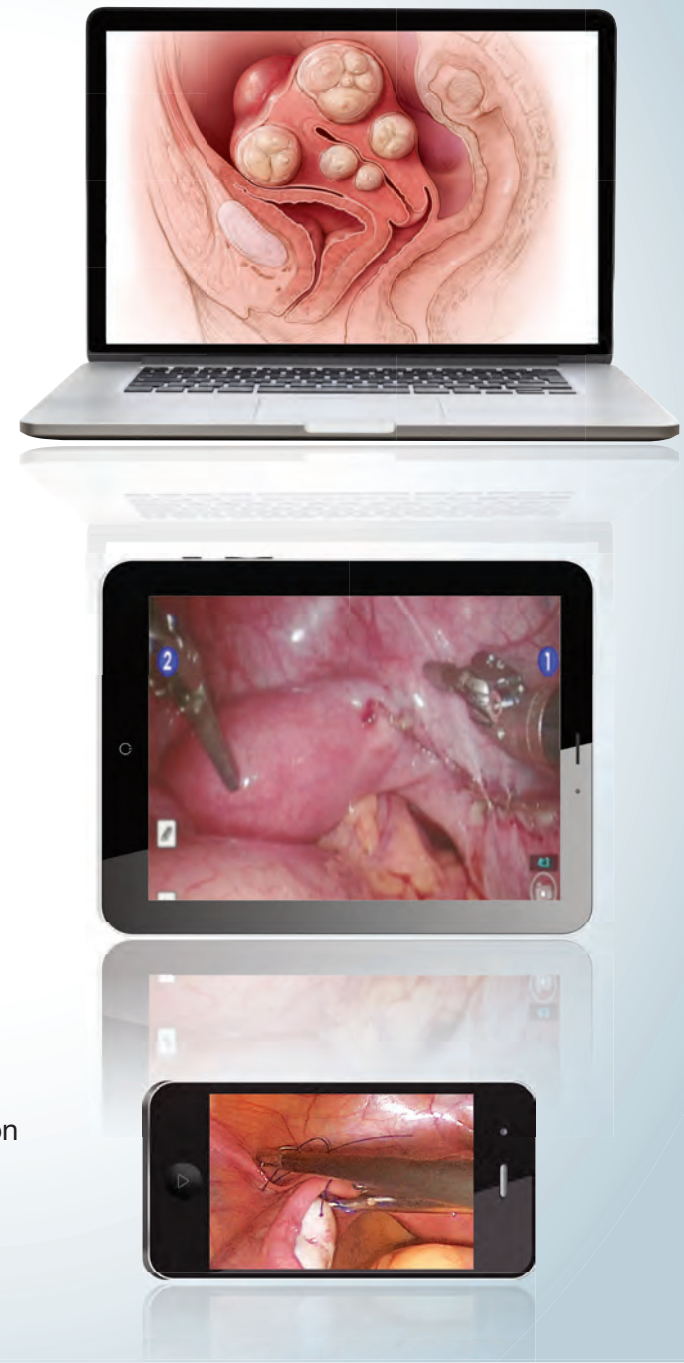

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Vulvovaginal disorders: When to biopsy?

Michael Baggish, MD
Saint Helena Hospital, Saint Helena, California
University of California, San Francisco

Shortly before his presentation on vulvovaginal disorders at the Pelvic Anatomy and Gynecologic Surgery (PAGS) Symposium in December 2016, Dr. Baggish was asked to discuss the circumstances under which he would perform a vulvovaginal biopsy. In this audiocast, he describes several different circumstances where it is absolutely necessary to perform a biopsy of a vulvovaginal lesion. Dr. Baggish comments that if there is a visible lesion and you are not fully confident in what it is, biopsy.

Top 3 things I learned at the PAGS 2016 symposium

Tommaso Falcone, MD
Cleveland Clinic, Cleveland, Ohio

What trend, revealed among PAGS attendees, surprised meeting Co-Chair, Tommaso Falcone? Find out in this 9-minute audiocast in which Dr. Falcone also discusses his other top takeaways related to alternative techniques for safe pelvic tissue extraction and management of vaginal atrophy with use of fractional CO_2 laser technology.

What are the modern cardiovascular risk indicators and how should ObGyns be using them in their practice?

Peter F. Schnatz, DO
President of the North American Menopause Society
Reading Hospital, Reading, Pennsylvania

In his Presidential Symposium at the 2016 annual meeting of the North American Menopause Society (NAMS), Dr. Schnatz described his latest research regarding breast arterial calcifications (BACs) found in the medial layer of breast arteries. In his audiocast, he comments on how BACs may serve as a cardiovascular (CV) risk indicator, adding to such well-known indicators as cholesterol levels, diabetes, hypertension, smoking, race, sedentary lifestyle, and obesity. He also suggests how clinicians should proceed to help a patient who has one or more CV risk factors.

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OBG MANAGEMENT

OVARIAN CANCER

Ovarian cancer remains the most deadly gynecologic malignancy in the United States. What are the practice implications of recent research results on screening, neoadjuvant chemotherapy, and an investigational agent that targets recurrent ovarian cancer?

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Dr. Wright reports that he is a consultant to Clovis Oncology and Tesaro, Inc. Dr. Buskwofie reports no financial relationships relevant to this article.

In 2017, an estimated 22,240 women will be diagnosed with ovarian cancer, and 14,080 women will die of the disease.[1] The high mortality associated with ovarian cancer is due largely to the inability to detect the disease early and the lack of effective therapeutics for women with recurrent disease. In this Update, we review important advances in the diagnosis and treatment of ovarian cancer.

Development of an effective screening tool for women at average risk has been an elusive challenge. The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) examined the efficacy of transvaginal ultrasound and cancer antigen 125 (CA 125) monitoring for ovarian cancer in a large cohort of women.

For women diagnosed with ovarian cancer, treatment paradigms for the initial management of the disease have shifted dramatically. Based on data from multiple randomized controlled trials, neoadjuvant chemotherapy (NACT) is being used more frequently. The American Society of Clinical Oncology and the Society of Gynecologic Oncology developed consensus recommendations for the appropriate use of NACT and primary cytoreductive surgery for women with ovarian cancer.

Finally, all of oncology has moved toward incorporating molecularly targeted therapeutics directed toward individual genetic abnormalities in tumors, so-called precision medicine. In ovarian cancer, poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) has emerged as an important target, particularly for women with *BRCA* gene pathway mutations. We describe a recently published randomized controlled trial of the PARP inhibitor niraparib.

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Investigational PARP inhibitor for maintenance treatment
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Is CA 125 or ultrasound screening appropriate for the general population?

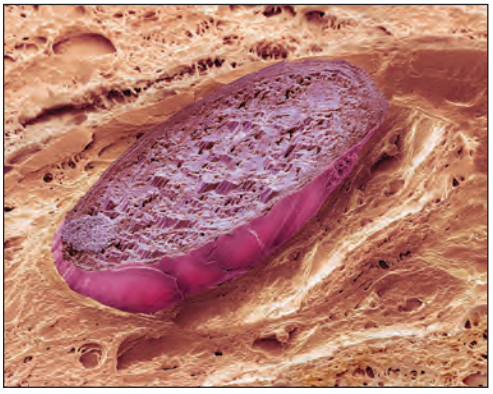
Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2016;387(10022):945–956.

FAST TRACK

The UKCTOCS results have reinvigorated discussions on ovarian cancer screening tools to increase early detection

In the United States, the overall ovarian cancer 5-year survival rate is 46.2%, resulting in more than 14,000 deaths annually.[2] The poor prognosis associated with this malignancy is largely attributable to the fact that almost 75% of women have stage III or stage IV disease at the time of diagnosis.[2] Ovarian cancer is usually associated with vague, nonspecific symptoms as it progresses, which contributes to delayed diagnosis and increased mortality.

Multiple studies have examined pelvic ultrasonography and tumor markers, such as CA 125, as possible screening tools to increase early detection in asymptomatic women. However, neither modality alone or in combination has sufficient sensitivity or specificity to recommend it for use in the general population.[3,4] Nevertheless, the search for an appropriate screening tool continues, and the UKCTOCS trial results have reinvigorated this discussion.[5]



Colored scanning electron micrograph of a section through an ovary showing a dermoid ovarian tumor.

PHOTO: © STEVE GSCHMEISSNER / SCIENCE SOURCE

The UKCTOCS findings

The UKCTOCS was a multicenter, randomized controlled trial in the United Kingdom in which researchers allocated 202,638 women aged 50 to 74 years to 1 of 3 groups: annual multimodal screening (MMS) with serum CA 125 interpreted with the use of the risk of ovarian cancer algorithm, annual transvaginal ultrasound screening (USS), or no screening. The median follow-up was more than 11 years.

The investigators found that equivalent rates of ovarian cancer were diagnosed in each group: 0.7% in the MMS group, 0.6% in the USS group, and 0.6% in the no-screening group. Overall, there was no significant reduction in the mortality rate from ovarian cancer in either of the 2 screening groups compared with the no-screening group.[5]

An important subset discovery

However, in a prespecified subset analysis excluding "prevalent cases" (women with ovarian cancer thought to be present prior to randomization and subsequent screening), ovarian cancer mortality was significantly lower in the MMS group compared with the no-screening group (P = .021). Compared with no screening, MMS was associated with a 20% reduction in mortality rate from ovarian cancer over time, with the most pronounced effects occurring at years 7 to 14 of follow-up, suggesting the possible increased effectiveness of screening over time.[5]

Concordance with other screening trials

While impressive in study magnitude and scope, the UKCTOCS results did not demonstrate a significant mortality benefit associated with MMS or USS when compared with no screening. Although the screening

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

While screening for ovarian cancer remains an important need, there is currently no evidence to suggest that serum tumor marker or ultrasound screening is appropriate in the general population. Studies using more specific screening tests or strategies targeted to higher-risk women are ongoing.

complications were low (<1% in both screening groups), the authors did note a false-positive surgery rate of 14 per 10,000 screens for the MMS group and 50 per 10,000 screens for the USS group. Based on the performance of screening in this trial, 641 women would need to be screened annually using MMS for 14 years to prevent 1 ovarian cancer death.

Like the UKCTOCS, the ovarian cancer–screening arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States was also unable to demonstrate a reduction in mortality rate with screening with CA 125 and transvaginal ultrasound. Importantly, more than one-third of women with a false-positive screen underwent surgery and 15% of them experienced a major complication.[6] Based on these findings, the US Preventive Services Task Force grades screening for ovarian cancer as D, suggesting that the harms of screening may outweigh the benefits.[7]

New clinical practice guideline advises neoadjuvant chemotherapy for certain women with ovarian cancer

FAST TRACK

Appropriate candidates for NACT should be treated with a platinum and taxane doublet and receive interval cytoreduction after 3 to 4 cycles if the response is favorable

Wright AA, Bohlke K, Armstrong DK, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2016;34(28):3460–3473.

It has long been held as a central dogma that primary cytoreductive surgery (PCS) is the preferred initial treatment for women with newly diagnosed ovarian cancer.[8] However, PCS is associated with substantial morbidity, and the ability to achieve optimal cytoreduction (<1 cm of residual disease), an important prognostic factor, is often compromised in women with significant tumor burden.[9,10]

Neoadjuvant chemotherapy, in which chemotherapy is administered prior to surgical cytoreduction, challenges the traditional treatment paradigm for advanced-stage ovarian cancer. Several randomized controlled trials have reported equivalent survival for primary surgical cytoreduction and NACT. Importantly, women who received NACT had fewer complications and were more likely to have optimal cytoreduction at the time of surgery.[11,12] These studies have limitations, however, and the role of NACT remains uncertain.

To help guide clinicians, the Society of Gynecologic Oncology and the American Society of Clinical Oncology convened an expert panel to provide recommendations and guidance on the evaluation of women for and the use of NACT in the setting of advanced ovarian cancer.[13]

Recommendation: Clinical evaluation and patient selection

Strong clinical evidence supports that all women with suspected stage IIIC or

stage IV ovarian cancer should be evaluated by a gynecologic oncologist prior to the initiation of therapy. The evaluation should include at least a computed tomography scan of the chest, abdomen, and pelvis to assess the extent of disease and resectability. A preoperative risk assessment should be performed to assess risk factors for increased morbidity and mortality.

Women who have a high perioperative risk profile or a low likelihood of achieving cytoreduction to 1 cm or less of residual tumor should receive NACT. Prior to the initiation of NACT, histologic confirmation of ovarian cancer should be obtained.[13]

Outcomes for neoadjuvant chemotherapy versus primary cytoreduction

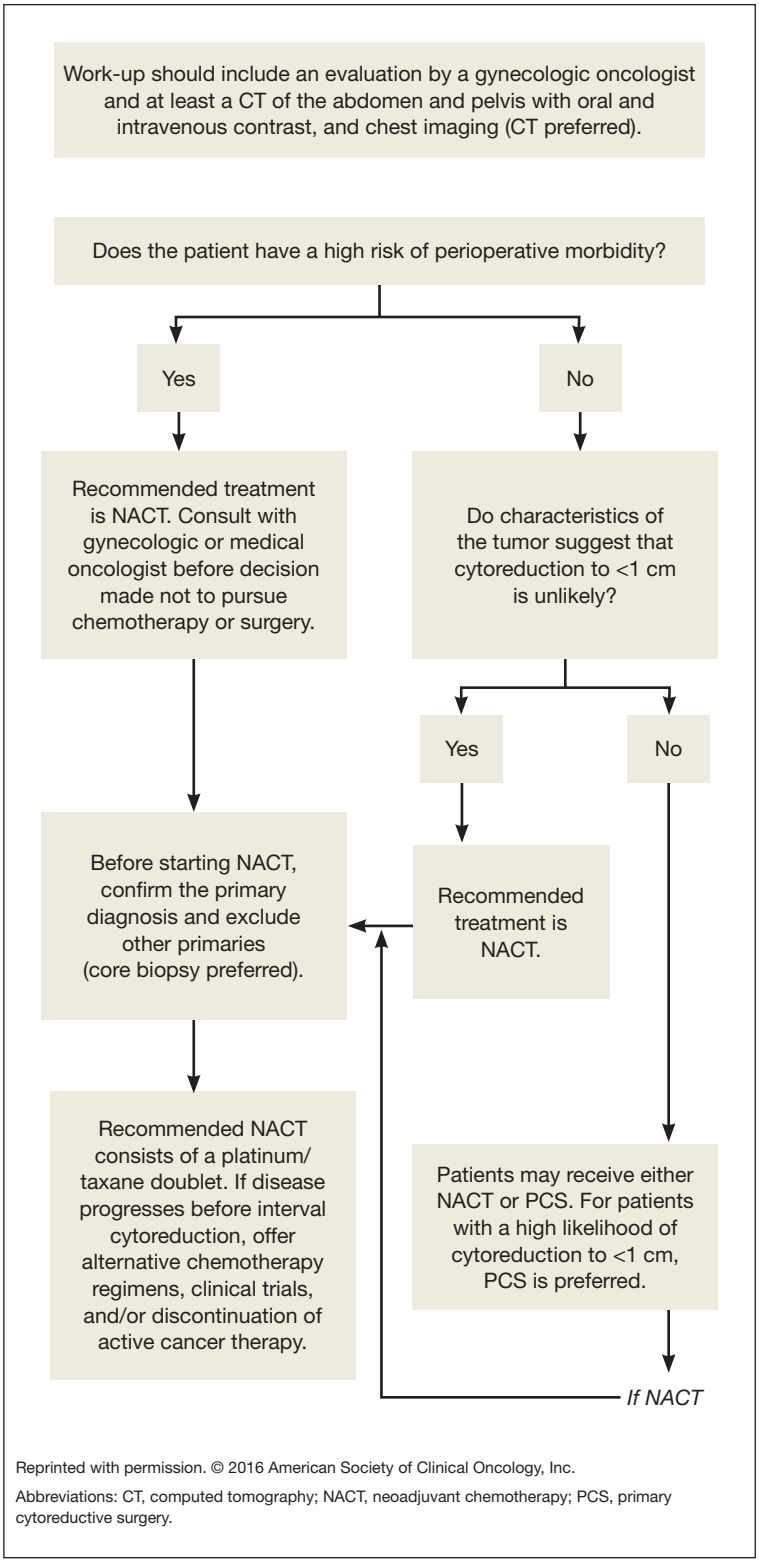
Four phase 3 randomized controlled trials (EORTC 55971, CHORUS, JCOG0602, and SCORPION) suggest that NACT is noninferior to PCS with regard to progression-free survival and overall survival. NACT is associated with less perioperative and postoperative morbidity and mortality and is associated with shorter hospital stays.

To date, complete data are available only from the EORTC and CHORUS trials, which both demonstrated similar progression-free survival and overall survival for NACT and PCS. Critics have noted, however, that both trials have shorter median overall survival for the PCS groups than were previously reported in other phase 3 studies in the United States, suggesting the possibility of different patient populations or less aggressive "surgical effort." Thus, PCS remains the preferred management strategy for women with advanced-stage ovarian cancer in whom there is a high likelihood of optimal cytoreduction.[13]

Recommendation: Use of neoadjuvant chemotherapy

Patients who are appropriate candidates for NACT should be treated with a platinum and taxane doublet and should receive interval cytoreduction following 3 to

FIGURE Suggested algorithm for selection of primary treatment for ovarian cancer[13]



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Abbreviations: CT, computed tomography; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery.

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Neoadjuvant chemotherapy is a noninferior and appropriate treatment option for women who are poor surgical candidates or who have a low likelihood of optimal cytoreduction. When optimal cytoreduction is possible, however, PCS is preferred (see **FIGURE**, page 29). The data on the efficacy of NACT for ovarian cancer have led to increased use of this treatment in the United States.

4 cycles of therapy if a favorable response is noted. Patients whose disease progresses despite NACT have a poor prognosis, and there is little role for surgical treatment with the exception of palliative purposes.[13]

Niraparib is promising as maintenance therapy in ovarian cancer

Mirza MR, Monk BJ, Herrstedt J, et al; for the ENGOT-OV16/NOVA Investigators. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375(22):2154–2164.

FAST TRACK

Hormonal therapies, signal transduction inhibitors, gene expression modulators, and immunotherapies are among the targeted therapies approved for cancer treatment

Approximately 85% of women with ovarian cancer will develop recurrent disease. Women with ovarian cancer are commonly treated with a range of antineoplastic agents over the course of their lifetime. As such, there is a great need for additional active therapeutic agents in this setting. Recently, substantial effort has been directed toward "precision" or "personalized medicine" in oncology.

Precision medicine, targeted therapies in oncology

Precision medicine refers to the customization of medical therapy based on the genetic characterization of the individual patient or the molecular profile of the patient's tumor. As a result of large-scale molecular profiling from projects such as the International Cancer Genome Consortium and The Cancer Genome Atlas, an abundance of molecular data has been generated through the characterization of multiple tumor types. This has led to the discovery of key cancer drivers, alterations, and specific molecular profiles that have distinct prognostic and treatment implications. These data, in combination with the commercial availability of molecular profiling tests, has made precision medicine a reality for women with ovarian cancer.

This wealth of new information has led to development of targeted therapeutics that block the growth and spread of cancer by acting on specific molecules or molecular pathways. Targeted therapies approved for cancer treatment include hormonal therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, and immunotherapies.[14]

How PARP inhibitors work

PARP inhibitors are a class of agents that are emerging as important therapies for ovarian cancer. These agents block the nuclear protein PARP, which functions to detect and repair single-strand DNA breaks with the resulting accumulation of double-stranded DNA breaks.[15] In the setting of DNA damage, the homologous recombination repair pathway is activated for repair. However, homologous recombination deficiencies (HRD) can arise as a result of *BRCA1* or *BRCA2* mutations or *BRCA*-independent pathways, which effectively disable this DNA repair pathway. As a result, when PARP inhibitors are used in patients with HRD, the cell cannot repair

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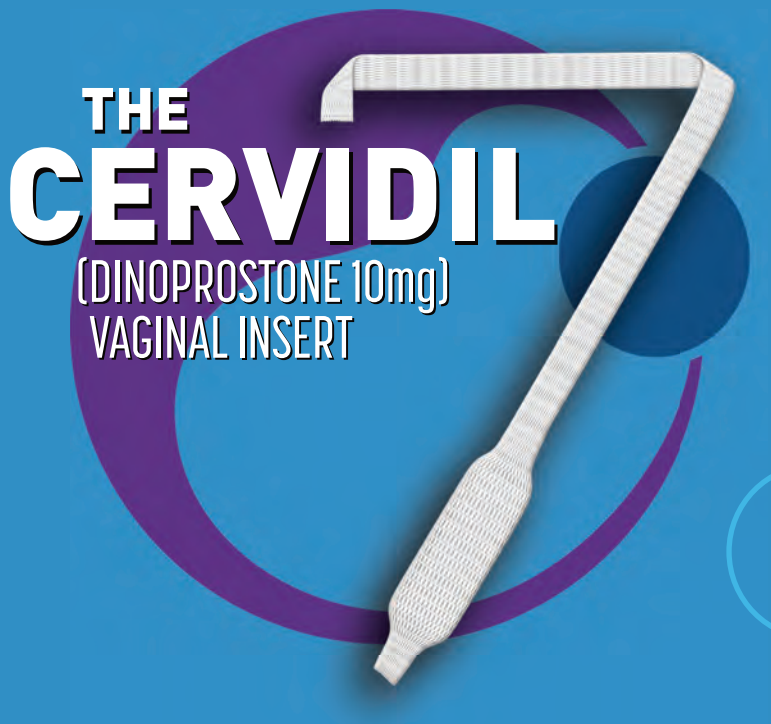

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

This study's results suggest that niraparib has clinical activity against ovarian cancer. Importantly, niraparib was active in women with g*BRCA* mutations, in those with HRD without a g*BRCA* mutation, and potentially in women without HRD. If approved by the US Food and Drug Administration, niraparib will join olaparib and rucaparib as a newly approved therapeutic agent for ovarian cancer. This study provides important evidence that suggests niraparib maintenance therapy may be an efficacious and important addition to the treatment armamentarium for platinum-sensitive ovarian cancer.

double-stranded DNA breaks and this leads to "synthetic lethality."[16]

Understanding this molecular mechanism of PARP inhibitors as well as the frequent abnormalities in the *BRCA* genes and HRD pathways in ovarian cancer has provided an important potential therapeutic target in ovarian cancer. A number of PARP inhibitors are now commercially available and are undergoing testing in ovarian cancer.

Niraparib for ovarian cancer

In a randomized, double-blind, phase 3 trial by Mizra and colleagues, 553 women with platinum-sensitive recurrent ovarian cancer who responded to therapy were divided according to the presence or absence of a germline *BRCA* (g*BRCA*) mutation and randomly assigned to niraparib 300 mg or placebo once daily. Women in the niraparib group had a significantly longer median duration of progression-free survival than did those in the placebo group. This was most pronounced in women in the g*BRCA* cohort (21.0 vs 5.5 months). Importantly, niraparib was associated with improved progression-free survival in HRD-positive patients without g*BRCA* mutations (12.9 vs 3.8 months) as well as in the HRD-negative subgroup (6.9 vs 3.8 months).[17]

Overall, niraparib was well tolerated. About 15% of women discontinued the drug due to toxicity. Significant (grade 3 or 4) adverse events were seen in three-quarters of women treated with niraparib, and they most commonly consisted of hematologic toxicities. Patient-reported outcomes were similar for both groups, indicating no significant effect from niraparib on quality of life.[17]

FAST TRACK

Niraparib-treated women had a significantly longer median progression-free survival compared with those in the placebo group, and this was most pronounced in the g*BRCA* cohort

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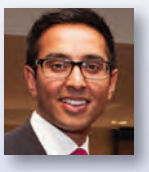

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Commentary

›› Andrew M. Kaunitz, MD

More than one-third of tumors found on breast cancer screening represent overdiagnosis

These findings are according to a new study, but the results are similar to those previously reported

The purpose of screening mammography is to detect tumors when they are small and nonpalpable in order to prevent more advanced breast tumors in women. Overdiagnosis, which leads to unnecessary treatment, refers to screen-detected tumors that will not lead to symptoms. Overdiagnosis cannot be measured directly and, therefore, understanding this concept is problematic for both women and clinicians.

Observations from other types of cancer screening put overdiagnosis in perspective

To help us grasp the overall issue of overdiagnosis, we can consider screening mammography alongside cervical cancer screening and colon cancer screening. For instance, screening with cervical cytology has reduced the incidence of and mortality from invasive cervical cancer.[1] Likewise, colonoscopy repeatedly has been found to reduce colon cancer mortality.[2,3] Decades of media messaging have emphasized the benefits of screening mammograms.[4] However, and in contrast with cervical cytology and colonoscopy, screening mammography has not reduced the incidence of breast cancer presenting with metastatic (advanced) disease.[5] Likewise, as the Danish authors of a recent study published in *Annals of Internal Medicine* point out, screening mammography has not achieved the promised reduction in breast cancer mortality.

New data from Denmark highlight overdiagnosis concerns

Jørgensen and colleagues conducted a cohort study to estimate the incidence of screen-detected tumors that would not become clinically relevant (overdiagnosis) among women aged 35 to 84 years between 1980 and 2010 in Denmark.[6] This country offers a particularly well-suited backdrop for a study of overdiagnosis because biennial screening mammography was introduced by region beginning in the early 1990s. By 2007, one-fifth of the country's female population aged 50 to 69 years were invited to participate. In the following years, screening became universal for Danish women in this age group.

For the study, researchers identified the size of all invasive breast cancer tumors diagnosed over the study period and then compared the incidence rates of advanced tumors (more than 20-mm in size at detection) with nonadvanced tumors in screened and unscreened Danish regions. The investigators took into account regional differences not related to screening by assessing the trends in diagnosis of advanced and nonadvanced tumors in screened and unscreened regions among women older and younger than those screened. This gave them a better estimate of the incidence of overdiagnosis.[6]

Jørgensen and colleagues found that breast cancer screening resulted in an increase in the incidence of nonadvanced tumors, but that it did not reduce the incidence of advanced tumors. They estimated that 39% of the invasive tumors found among women aged 50 to 69 were overdiagnosed.[6]

These Danish study results, that more than one-third of screen-detected tumors represent overdiagnosis, are

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Dr. Kaunitz reports no financial relationships related to this article.

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similar to those found for studies conducted in the United States and other countries.[7,8] The lengthy follow-up after initiation of screening and the assessment of trends in unscreened women represent strengths of the study by Jørgensen and colleagues, and speak to concerns voiced by those skeptical of reported overdiagnosis incidence rates.[9]

Although breast cancer mortality is declining, the lion's share of this decline has resulted from improvements in systemic therapy rather than from screening mammography. Widespread screening mammography has resulted in a scenario in which women are more likely to have a breast cancer that was overdiagnosed than in having earlier detection of a tumor destined to grow larger.[5] In the future, by targeting higher-risk women, screening may result in a better benefit:risk ratio. However, and as pointed out by Otis Brawley, MD, Chief Medical and Scientific Officer of the American Cancer Society, we must acknowledge that overdiagnosis is common, the benefits of screening have been overstated, and some patients considered as "cured" from breast cancer have in fact been harmed by unneeded treatment.[10]

My breast cancer screening approach

As Brawley indicates, we should not abandon screening.[10] I continue to recommend screening based on US Preventive Services Taskforce guidance, beginning biennial screens at age 50.[11] I also recognize that some women prefer earlier and more frequent screens, while others may prefer less frequent or even no screening.

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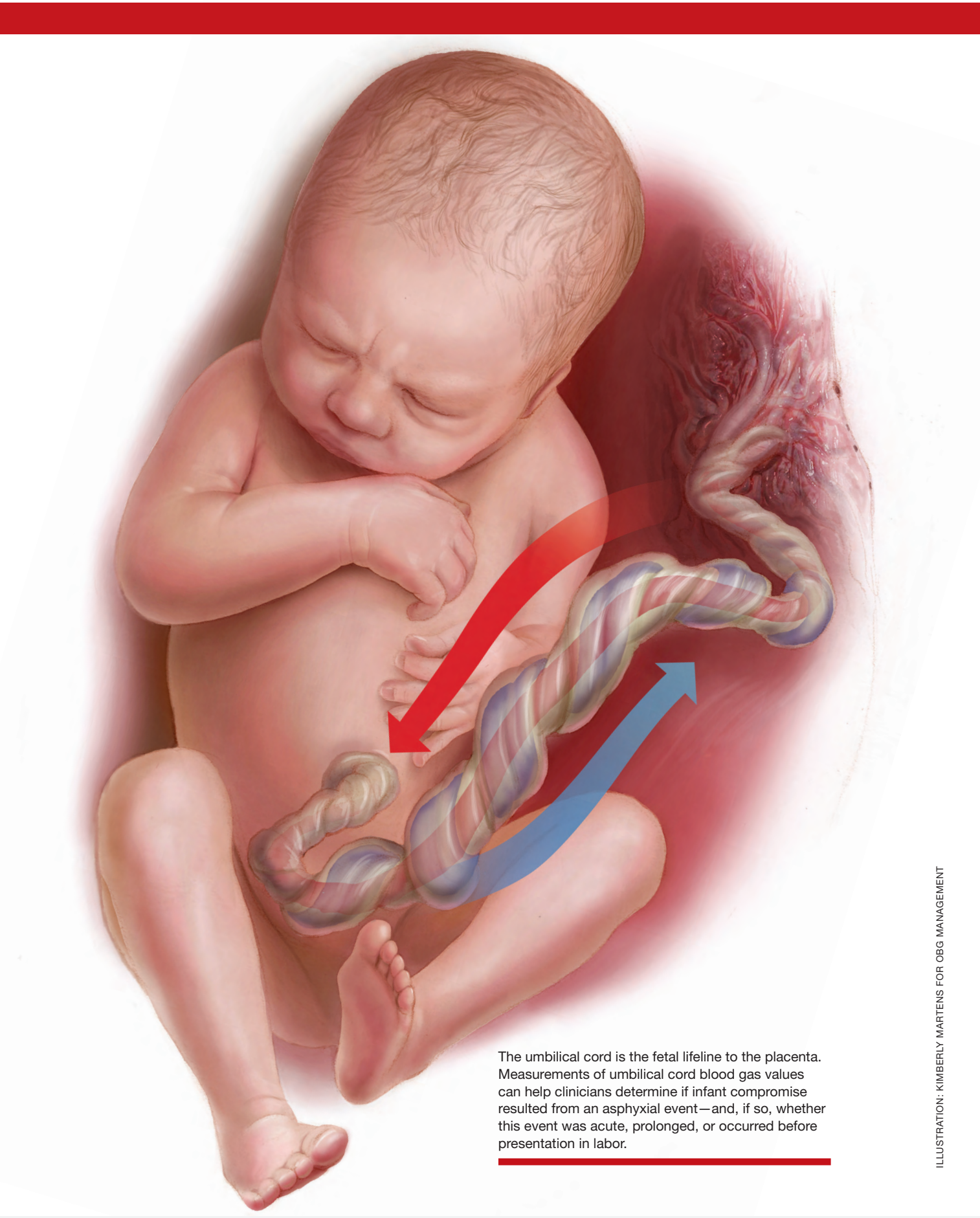

The umbilical cord is the fetal lifeline to the placenta. Measurements of umbilical cord blood gas values can help clinicians determine if infant compromise resulted from an asphyxial event—and, if so, whether this event was acute, prolonged, or occurred before presentation in labor.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

How and when umbilical cord gas analysis can justify your obstetric management

Three cases illustrate how umbilical cord gas values can provide insight into a newborn's status

Michael G. Ross, MD, MPH

Umbilical cord blood (cord) gas values can aid both in understanding the cause of an infant's acidosis and in providing reassurance that acute acidosis or asphyxia is not responsible for a compromised infant with a low Apgar score. Together with other clinical measurements (including fetal heart rate [FHR] tracings, Apgar scores, newborn nucleated red cell counts, and neonatal imaging), cord gas analysis can be remarkably helpful in determining the cause for a depressed newborn. It can help us determine, for example, if infant compromise was a result of an asphyxial event, and we often can differentiate whether the event was acute, prolonged, or occurred prior to presentation in labor. We further can use cord gas values to assess whether a decision for operative intervention for nonreassuring fetal well-being was appropriate (see "Brain injury at birth: Cord gas values presented as evidence at trial" on page 42). In addition, cord gas analysis can complement methods for determining fetal acidosis changes during labor, enabling improved assessment of FHR tracings.[1–3]

I recommend checking umbilical cord blood gas values on all operative vaginal deliveries, cesarean deliveries for fetal concern, abnormal FHR patterns, clinical chorioamnionitis, multifetal gestations, premature deliveries, and all infants with low Apgar scores at 1 or 5 minutes. If you think you may need a cord gas analysis, go ahead and obtain it. Cord gas analysis often will aid in justifying your management or provide insight into the infant's status.

Controversy remains as to the benefit of universal cord gas analysis. Assuming a variable cost of $15 for 2 (artery and vein) blood gas samples per neonate,[4] the annual cost in the United States would be approximately $60 million. This would likely be cost effective as a result of medicolegal and educational benefits as well as potential improvements in perinatal outcome[5] and reductions in special care nursery admissions.[4]

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The author reports no financial relationships relevant to this article.

CASE 1 A newborn with unexpected acidosis

A 29-year-old woman (G2P1) at 38 weeks' gestation was admitted to the hospital following an office visit during which oligohydramnios

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Procedures for cord sampling page 43

Physiology of fetal cord gases page 44

TABLE 1 Normal values for fetal umbilical cord gases[6,7]

	Umbilical artery	Umbilical vein
pH	7.18–7.38	7.25–7.45
Po_2	5.6–30.4 mm Hg	17.4–41.0 mm Hg
Pco_2	32.4–66.0 mm Hg	27.0–49.4 mm Hg
BD_{ECF}, mean (SD)	4.79 (3.46) mmol/L	~4.0 (3.5) mmol/L

Ranges based on mean ±2 SD.

FAST TRACK

The pH, Pco_2, and Po_2 in cord blood are measured, while BD is calculated

(amniotic fluid index, 3.5 cm) was found. The patient had a history of a prior cesarean delivery for failure to progress, and she desired a repeat cesarean delivery. Fetal monitoring revealed a heart rate of 140 beats per minute with moderate variability and uterine contractions every 3 to 5 minutes associated with moderate variable decelerations. A decision was made to proceed with the surgery. Blood samples were drawn for laboratory analysis, monitoring was discontinued, and the patient was taken to the operating room. An epidural anesthetic was placed and the cesarean delivery proceeded.

On uterine incision, there was no evidence of abruption or uterine rupture, but thick meconium-stained amniotic fluid was observed. A depressed infant was delivered, the umbilical cord clamped, and the infant handed to the pediatric team. Cord samples were obtained and values from the umbilical artery were as follows: pH, 6.80; Pco_2, 120 mm Hg; Po_2, 6 mm Hg; and base deficit extracellular fluid (BD_{ECF}), 13.8 mmol/L. Values from the umbilical vein were: pH, 7.32; Pco_2, 38 mm Hg; Po_2, 22 mm Hg; and BD_{ECF}, 5.8 mmol/L. The infant's Apgar scores were 1, 2, and 7 at 1, 5, and 10 minutes, respectively, and the infant demonstrated encephalopathy, requiring brain cooling.

What happened?

Using cord gas values in practice

Before analyzing the circumstances in Case 1, it is important to consider several key questions, including:

- What are the normal levels of cord pH, O_2, CO_2, and base deficit (BD)?
- How does cord gas indicate what happened during labor?
- What are the preventable errors in cord gas sampling or interpretation?

For a review of fetal cord gas physiology, see "Physiology of fetal cord gases: The basics," on page 44.

Normal values: The "20, 30, 40, 50 rule"

Among the values reported for umbilical blood gas, the pH, Pco_2, and Po_2 are measured, whereas BD is calculated. The normal values for umbilical pH and blood gases are often included with laboratory results, although typically with a broad, overlapping range of values that may make it difficult to determine which is umbilical artery or vein (**TABLE 1**).[6,7]

I recommend using the "20, 30, 40, 50 rule" as a simple tool for remembering normal umbilical artery and vein Po_2 and Pco_2 values (**TABLE 2**):

- Po_2 values are lower than Pco_2 values; thus, the 20 and 30 represent Po_2 values
- as fetal umbilical artery Po_2 is lower than umbilical vein Po_2, 20 mm Hg represents the umbilical artery and 30 mm Hg represents the vein
- Pco_2 values are higher in the umbilical artery than in the vein; thus, 50 mm Hg represents the umbilical artery and 40 mm Hg represents the umbilical vein.

Umbilical cord BD values change in relation to labor and FHR decelerations.[8] Prior to labor, the normal fetus has a slight degree of acidosis (BD, 2 mmol/L). During the latent phase of labor, fetal BD typically does not change. With the increased frequency of contractions, BD may increase 1 mmol/L for every 3 to 6 hours during the active phase and up to 1 mmol/L per hour during the second stage, depending on FHR responses. Thus,

TABLE 2 Fetal umbilical cord gases: The "20, 30, 40, 50 rule"

Value, mm Hg	Cord gas measured
20	Umbilical artery Po_2
30	Umbilical vein Po_2
40	Umbilical vein Pco_2
50	Umbilical artery Pco_2

following vaginal delivery the average umbilical artery BD is approximately 5 mmol/L and the umbilical vein BD is approximately 4 mmol/L. As lactate crosses the placenta slowly, BD values are typically only 1 mmol/L less in the umbilical vein than in the artery, unless there has been an obstruction to placental flow (see Case 1).

For pH, the umbilical artery value is always lower than that of the vein, a result of both the higher umbilical artery P_{CO_2} as well as the slightly higher levels of lactic acid before placental clearance. Fetal pH levels typically decrease during labor associated with the increased BD described above. However, short-term effects of increased CO_2 (respiratory acidosis) or CO_2 clearance may cause fluctuations in pH that do not correlate with the degree of metabolic acidosis.

Possible causes of abnormal cord gas values

Because of the nearly fully saturated maternal hemoglobin under normal conditions, fetal arterial and venous P_{O_2} levels cannot be increased significantly above normal values. However, *reduced* fetal P_{O_2} and *increased* fetal P_{CO_2} may occur with poor gas exchange between the maternal and fetal compartments (eg, placental abruption) or maternal respiratory compromise.

In contrast, reduced fetal P_{CO_2} may occur under conditions of maternal hyperventilation and lower maternal P_{CO_2} values. Decreased pH levels may be due to respiratory or metabolic acidosis, the former of which is generally benign. Elevated BD typically is a result of fetal metabolic acidosis, and values approaching 12 mmol/L should be avoided, if possible, as this level may be associated with newborn neurologic injury.[9]

Effect of maternal oxygen administration on fetal oxygenation

Although maternal oxygen administration is commonly used during labor and delivery, controversy remains as to the benefit of oxygen supplementation.[10] In a normal mother with oxygen saturation above 95%,

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Brain injury at birth: Cord gas values presented as evidence at trial

At 40 weeks' gestation, a woman presented to the hospital because of decreased fetal movement. On arrival, an external fetal heart-rate (FHR) monitor showed nonreassuring tracings, evidenced by absent to minimal variability and subtle decelerations occurring at 10- to 15-minute intervals. The on-call ObGyn requested induction of labor with oxytocin, and a low-dose infusion (1 mU/min) was initiated. An internal FHR monitor was then placed and late decelerations were observed with the first 2 induced contractions. The oxytocin infusion was discontinued and the ObGyn performed an emergency cesarean delivery. The infant's Apgar scores were 1, 2, and 2 at 1, 5, and 10 minutes, respectively. Cord samples were obtained and values from the umbilical artery were as follows: pH, 6.86; P_{CO_2}, 55 mm Hg; P_{O_2}, 6 mm Hg; and BD_{ECF}, 21.1 mmol/L. Values from the umbilical vein were: pH, 6.94; P_{CO_2}, 45 mm Hg; P_{O_2}, 17 mm Hg; and BD_{ECF}, 20.0 mmol/L. The infant was later diagnosed with a hypoxic brain injury resulting in cerebral palsy. At trial years later, the boy had cognitive and physical limitations and required 24-hour care.

The parents claimed that the ObGyn should have performed a cesarean delivery earlier when the external FHR monitor showed nonreassuring tracings.

The hospital and physician claimed that, while tracings were consistently nonreassuring, they were stable. They maintained that the child's brain damage was not due to a delivery delay, as the severe level of acidosis in both the umbilical artery and vein could not be a result of the few heart rate decelerations during the 2-hour period of monitoring prior to delivery. They argued that the clinical picture indicated a pre-hospital hypoxic event associated with decreased fetal movement.

A defense verdict was returned.

Case assessment

Cord gas results, together with other measures (eg, infant nucleated red blood cells, brain imaging) can aid the ObGyn in medicolegal cases. However, they are not always protective of adverse judgment.

FAST TRACK

While maternal oxygen supplementation for normal mothers may have nominal benefit for compromised fetuses, it may have marked benefit when maternal P_{O_2} is low

the administration of oxygen will increase maternal arterial P_{O_2} levels and thus *dissolved* oxygen. Because maternal hemoglobin is normally almost fully saturated at room air P_{O_2} levels, there is little change in the *bound* oxygen and thus little change in the maternal arterial O_2 content or maternal uterine venous P_{O_2} levels. As fetal umbilical vein P_{O_2} levels equilibrate to maternal uterine vein P_{O_2} levels, there is minimal change in fetal oxygenation.

However, maternal oxygen supplementation may have marked benefit in cases in which maternal arterial P_{O_2} is low (respiratory compromise). In this case, the steep fetal oxygen saturation curve may produce a large increase in fetal umbilical vein oxygen content. Thus, **strongly consider oxygen supplementation for mothers with impaired cardiorespiratory function**, and recognize that maternal oxygen supplementation for normal mothers may result in nominal benefit for compromised fetuses.

How did the Case 1 circumstances lead to newborn acidosis?

Most noticeable in this case is the large difference in BD between the umbilical artery and vein and the high P_{CO_2} in the artery. Under conditions without interruption of fetal placental flow, either the umbilical artery and/or vein will provide a similar assessment of fetal or newborn metabolic acidosis (that is, BD).

Whereas BD normally is only about 1 mmol/L greater in the umbilical artery versus in the vein, occasionally the arterial value is markedly greater than the vein value. This can occur when there is a cessation of blood flow through the placenta, as a result of complete umbilical cord obstruction, or when there is a uterine abruption. In these situations, the umbilical vein (which has not had blood flow) represents the fetal status prior to the occlusion event. In contrast, despite bradycardia, fetal heart pulsations mix blood within the umbilical artery and therefore the artery generally represents the fetal status at the time of birth.

In response to complete cord occlusion, fetal BD increases by approximately 1 mmol/L every 2 minutes. Consequently, an 8 mmol/L difference in BD between the umbilical artery and vein is consistent with a 16-minute period of umbilical occlusion or placental abruption. Also in response to complete umbilical cord occlusion, Pco_2 values rise by approximately 7 mm Hg per minute of the occlusion, although this may not be linear at higher levels. Thus, **the BD difference suggests there was likely a complete cord occlusion for the 16 minutes prior to birth.**

The umbilical vein BD is also elevated for early labor. This value suggests that repetitive, intermittent cord occlusions (evident on the initial fetal monitor tracing) likely resulted in this moderate acidosis prior to the complete cord occlusion in the final 16 minutes.

Thus, BD and Pco_2 levels can be used to time the onset of umbilical cord occlusion or abruption. Since pH is an inverse logarithmic function, it cannot be used to time the onset or duration of cord occlusion. Remember that BD values should be adjusted for extracellular fluid under conditions of markedly elevated Pco_2.

CASE 2 An infant with unusual umbilical artery values

An infant born via vacuum delivery for a prolonged second stage of labor had 1- and 5-minute Apgar scores of 8 and 9, respectively. Cord gas values were obtained, and analysis revealed that for the umbilical artery, the pH was 7.29; Pco_2, 20 mm Hg; and Po_2, 60 mm Hg. For the umbilical vein, the pH was 7.32; Pco_2, 38 mm Hg; and Po_2, 22 mm Hg.

The resident asked, "How is the Po_2 higher in the artery than in the vein?"

The curious Case 2 values suggest an air bubble

Although it is possible that the aberrant values in Case 2 could have resulted from switching the artery and vein samples, the pH is lower in the artery, and both the artery Po_2 and Pco_2 levels do not appear physiologic. The likely explanation for these values is that an air bubble was contained in the syringe. Since normal room air (21% O_2) has a Po_2 of 159 mm Hg and a Pco_2 of less than 1 mm Hg, exposure of cord blood gases to air bubbles will significantly increase the Po_2 and markedly reduce the Pco_2 values of the sample. Take care to avoid air bubbles in the syringes used to obtain samples for analysis.

CASE 3 A vigorous baby with significant acidosis

A baby with 1- and 5-minute Apgar scores of 9 and 9 was delivered by cesarean and remained vigorous. Umbilical cord analysis revealed an umbilical artery pH level of 7.15, with normal Po_2 and Pco_2 values. What could be the explanation?

Was there a collection error in Case 3?

On occasion, a falsely low pH level and, thus, a falsely elevated BD may result from excessive heparin in the collection syringe. Heparin is acidotic and should be used only to coat the syringe. Although syringes in current use are often pre-heparinized, if one is drawing up heparin into the syringe, it should be coated and then fully expelled.

Umbilical cord sampling: Procedures and equipment

Many issues remain regarding the optimal storage of cord samples. Ideally, a doubly clamped section of the cord promptly should be sampled into glass syringes that can be placed on ice and rapidly measured for cord values.

Stability of umbilical cord samples within the cord is within 20 to 30 minutes. Delayed sampling of clamped cord sections generally has minimal effect on pH and Pco_2 values.[11] The BD does not change to a clinically significant degree over 15 to 30 minutes despite the cord specimen remaining at room temperature. However, one report demonstrated an increase in lactate and BD by 20 minutes under these conditions; this likely was a result of metabolism from endothelial or blood cells.[12] I therefore recommend that clamped cord be sampled as soon as is feasible and ideally not beyond 20 to 30 minutes.

Plastic syringes can introduce interference. Several studies have demonstrated

FAST TRACK

BD and Pco_2 levels can be used to time the onset of umbilical cord occulsion or abruption

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FAST TRACK

Because maternal blood and fetal blood effectively travel in the same direction in the placenta, umbilical vein O_2 and CO_2 equilibrate with that in the maternal uterine vein

Physiology of fetal cord gases: The basics

A review of basic fetal cord gas physiology will assist in understanding how values are interpreted.

Umbilical cord O_2 and CO_2

Fetal cord gas values result from the rapid transfer of gases and the slow clearance of acid across the placenta. Approximately 10% of maternal blood flow supplies the uteroplacental circulation, with the near-term placenta receiving approximately 70% of the uterine blood flow.[1] Of the oxygen delivered, a surprising 50% provides for placental metabolism and 50% for the fetus. On the fetal side, 40% of fetal cardiac output supplies the umbilical circulation. Oxygen and carbon dioxide pass readily across the placental layers; exchange is limited by the amount of blood flow on both the maternal and the fetal side (flow limited). In the human placenta, maternal blood and fetal blood effectively travel in the same direction (concurrent exchange); thus, umbilical vein O_2 and CO_2 equilibrate with that in the maternal uterine vein.

Most of the O_2 in fetal blood is carried by hemoglobin. Because of the markedly greater affinity of fetal hemoglobin for O_2, the saturation curve is shifted to the left, resulting in increased hemoglobin saturation at the relatively low levels of fetal PO_2. This greater affinity for oxygen results from the unique fetal hemoglobin gamma (γ) subunit, as compared with the adult beta (ß) subunit. Fetal hemoglobin has a reduced interaction with 2,3-bisphosphoglycerate, which itself decreases the affinity of adult hemoglobin for oxygen.

The majority of CO_2 (85%) is carried as part of the bicarbonate buffer system. Fetal CO_2 is converted into carbonic acid (H_2CO_3) in the red cell and dissociates into hydrogen (H^+) and bicarbonate (HCO_3^-) ions, which diffuse out of the cell. When fetal blood reaches the placenta, this process is reversed and CO_2 diffuses across the placenta to the maternal circulation. The production of H^+ ions from CO_2 explains the development of *respiratory* acidosis from high PCO_2. In contrast, anaerobic metabolism, which produces lactic acid, results in *metabolic* acidosis.

Difference between pH and BD

The pH is calculated as the inverse log of the H^+ ion concentration; thus, the pH falls as the H^+ ion concentration *exponentially* increases, whether due to respiratory or metabolic acidosis. To quantify the more important metabolic acidosis, we use BD, which is a measure of how much of bicarbonate buffer base has been used by (lactic) acid. The BD and the base excess (BE) may be used interchangeably, with BE representing a negative number. Although BD represents the metabolic component of acidosis, a correction may be required to account for high levels of fetal PCO_2 (see Case 1). In this situation, a more accurate measure is BD extracellular fluid (BD_{ECF}).

Why not just use pH? There are 2 major limitations to using pH as a measure of fetal or newborn acidosis. First, pH may be influenced by both respiratory and metabolic alterations, although only metabolic acidosis is associated with fetal neurologic injury.[2] Furthermore, as pH is a log function, it does not change linearly with the amount of acid produced. In contrast to pH, BD is a measure of metabolic acidosis and changes in direct proportion to fetal acid production.

What about lactate? Measurements of lactate may also be included in blood gas analyses. Under hypoxic conditions, excess pyruvate is converted into lactate and released from the cell along with H^+, resulting in acidosis. However, levels of umbilical cord lactate associated with neonatal hypoxic injury have not been established to the same degree as have pH or BD. Nevertheless, lactate has been measured in fetal scalp blood samples and offers the potential as a marker of fetal hypoxemia and acidosis.[3]

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that collection of samples in plastic may result in an increase in Po_2 values, likely due to the high room air Po_2 diffusing through the plastic to the blood sample.

Use glass, and "ice" the sample if necessary. Although it has been suggested that placing samples on ice minimizes metabolism, the cooled plastic may in fact be more susceptible to oxygen diffusion. Thus, unless samples will be analyzed promptly, it is best to use glass syringes on ice.[13,14]

What if the umbilical cord is torn?

Sometimes the umbilical cord is torn and discarded or cannot be accessed for other reasons. A sample can still be obtained, however, by aspirating the placental surface artery and vein vessels. Although there is some potential variance in pH, Po_2, and Pco_2 levels, the BD values of placental vessels have a high correlation with those of umbilical vessels and therefore can be used when the cord is not available.[15]

How do you obtain cord analysis when delaying cord clamping?

The American College of Obstetricians and Gynecologists (ACOG) now advises delayed cord clamping in term and preterm deliveries, which raises the question of how you obtain a blood sample in this setting. Importantly, ACOG recommends delayed cord clamping only in vigorous infants,[16] whereas potentially compromised infants should be transferred rapidly for newborn care. Although several studies have demonstrated some variation in cord gas values with delayed cord clamping,[17–21] clamping after pulsation has ceased or after the recommended 30 to 60 seconds following birth results in minimal change in BD values. Thus, do not hesitate to perform delayed cord clamping in vigorous infants.

FAST TRACK

If the umbilical cord is unavailable, blood samples for gas analysis can be obtained from placental surface vessels

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She wanted to labor on hands and knees

DURING PRENATAL VISITS, a woman, pregnant with her fourth child, discussed undergoing labor and delivery in any position other than on her back; the ObGyn agreed. When she arrived at the hospital in labor, the patient told the nurse that she preferred to labor on her hands and knees. The nurse disagreed because of the fetal heart-rate monitor.

When the patient began hard labor, she turned herself over onto her hands and knees and again informed the nurse that she could not labor on her back. The nurse flipped the patient onto her back by taking her wrists and pulling the patient's hands out from under her. The nurse then delayed delivery until the ObGyn arrived by putting pressure on the baby's head. During delivery, a second nurse forcibly pressed the patient's left knee back toward her chest, leaving her legs in an asymmetric position.

Two months later, the patient reported chronic severe pelvic pain and was found to have pudendal neuralgia. She underwent nerve blocks and takes medication for chronic pain.

PATIENT'S CLAIM: The ObGyn did not assume responsibility when he arrived for the delivery. The nurses did not follow the standard of care. The patient's injury was the result of tension and compression due to malpositioning of the patient's legs during delivery.

DEFENDANTS' DEFENSE: There was no breach in the standard of care. The patient's injury, if any, had not been caused by the delivery.

VERDICT: A $16 million Alabama verdict was returned.

Late-term abortion: $1.4M award

ALTHOUGH GENETIC TESTING was scheduled for a 37-year-old woman's 15-week prenatal visit, the ObGyn's staff failed to draw blood. At 19 weeks' gestation (April 24), blood was drawn. The ObGyn signed off on test results that showed a high risk for fetal anomaly on May 2, but the patient was not informed until May 22. The ObGyn scheduled amniocentesis for June 3. On May 30, the hospital, based in Illinois, cancelled the test, telling the ObGyn that it was because the patient was over 24 weeks' pregnant and there was no labor and delivery unit to respond if complications arose. Instead of notifying the patient, the ObGyn arranged for amniocentesis to be performed elsewhere on June 3. The ObGyn saw the amniocentesis results on June 13, but did not tell the patient until July 3, when he advised her to terminate the pregnancy because the baby had severe cardiac defects and Down syndrome; he felt the child would not survive or have very poor quality of life. The ObGyn arranged for the patient to undergo a third-trimester abortion in Kansas and paid all expenses. On July 14, the patient began the 5-day abortion process at 30+ weeks' gestation.

PATIENT'S CLAIM: She was never offered additional genetic testing or expedited amniocentesis. She was not told that abortion is illegal in Illinois after 23 6/7 weeks' gestation. The ObGyn had a motive for paying for her abortion. He never counseled her about options to keep the child. She endured extreme pain and emotional trauma during the abortion and was later found to have posttraumatic stress disorder, multidepressive disorder, and anxiety as a result of the experience. She countered the ObGyn's contact information claim by saying that her phone number had not changed.

PHYSICIAN'S DEFENSE: The ObGyn admitted negligence in failing to timely communicate test results but contended that the patient was more than 50% responsible for any delay by failing to update her contact information when she moved. The ObGyn denied causation of any injuries or damage.

VERDICT: A $1,439,250 Illinois verdict was returned.

Did delay in delivery cause infant's death?

A WOMAN PRESENTED to the hospital in labor. During delivery, the patient's ObGyn encountered shoulder dystocia. The infant died shortly after birth.

PARENTS' CLAIM: The ObGyn and hospital nurses were negligent. The nurses failed to monitor labor and properly communicate with the ObGyn. The ObGyn failed to appreciate the baby's large size and order a cesarean delivery. The infant's death was due to a hypoxic event during delivery.

DEFENDANTS' DEFENSE: The baby gained an unexpected amount of weight between the last prenatal visit and labor. There was no reason to expect a complication to vaginal delivery. The nurses denied negligence. The child's sudden death was caused by a genetic cardiac condition.

VERDICT: A Tennessee defense verdict was returned.

These cases were selected by the editors of OBG Management *from* Medical Malpractice Verdicts, Settlements, & Experts, *with permission of the editor, Lewis Laska (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.*

Should the length of treatment for trichomoniasis in women be reconsidered?

Yes. Authors of a meta-analysis found that women who received a single 2-g dose of metronidazole were 1.87 times (95% confidence interval [CI], 1.23–2.82; *P*<.01) more likely to experience a treatment failure than women who received multidose therapy ranging from 200 to 500 mg, two to three times daily, over 5 to 7 days.

Howe K, Kissinger PJ. Single-dose compared with multidose metronidazole for the treatment of trichomoniasis in women: a meta-analysis. Sex Transm Dis. 2017;44(1):29–34.

FAST TRACK

Consider treating women infected with trichomoniasis with a multidose (vs single dose) regimen of metronidazole (500 mg orally twice daily for 7 days)

EXPERT COMMENTARY

Patrick Duff, MD, is Associate Dean for Student Affairs and Professor of Obstetrics and Gynecology in the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville.

Both the Centers for Disease Control and Prevention and the World Health Organization currently recommend that patients with trichomoniasis be treated with a single 2-g oral dose of metronidazole.[1] Following treatment, the reported rates of repeat infection or persistent infection range from 5% to 31%. Repeat infection rates may be even higher in HIV-infected patients.

Repeat infections presumably result from a failure to treat the patient's sexual partner(s) or from the patient's exposure to a new partner. Persistent infections, however, may be the result of inadequate primary therapy, even though inherent resistance of the organism to metronidazole is quite rare. To date, no single study has shown that single-dose therapy is inferior to multidose therapy, but most of these studies lack sufficient power to completely exclude the possibility of a type-2 statistical error.[2] To compare single-dose with multidose therapy for trichomoniasis in a more systematic manner, Howe and Kissinger conducted a meta-analysis, which was recently published in *Sexually Transmitted Diseases*.

The author reports no financial relationships relevant to this article.

Details of the study

The investigators conducted a comprehensive literature search using Embase, Medline, and ClinicalTrials.gov; 6 articles were included in the final results, 4 of which were randomized controlled trials. Approximately 1,300 participants were included in the 6 trials. All of the patients in the single-dose treatment arms received a 2-g oral dose of metronidazole. In the multidose treatment arms for 2 studies the participants received metronidazole 250 mg orally 3 times daily for 7 days, and for 2 studies the dose was 200 mg 3 times daily for 7 days. The fifth study employed a 500-mg oral dose of metronidazole twice daily for 7 days. The final study used a 400-mg oral dose twice daily for 5 days. The key study end point was treatment failure.

Howe and Kissinger demonstrated that women who received the single 2-g dose were 1.87 times (95% CI, 1.23–2.82; *P*<.01) more likely to experience a treatment

failure compared with women who received a multidose regimen. When the one study that focused only on HIV-infected women was excluded from analysis, the results were similar. The relative risk of treatment failure was 1.80 (95% CI, 1.07–3.02; *P*<.03).

Study limitations

The results of this meta-analysis are interesting and provocative. However, the analysis has several important limitations. Five of the 6 studies were published many years ago (1971, 1972, 1979, 1980, and 1982). The most recent study was published in 2010. The investigators used 4 different multidose regimens, with metronidazole doses ranging from 200 mg to 500 mg and duration of therapy ranging from 5 to 7 days. Four of the six investigations used saline microscopy as the definitive diagnostic test of treatment failure. Compared with culture or DNA testing, microscopy is not as accurate. Moreover, the timing of retesting varied in the studies, and some apparent treatment failures actually may have been due to reinfection. In addition, the studies did not consistently track the adequacy of treatment of the sexual partner.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

To be sure, we would benefit from a new comparative study that included a large sample size, a consistent multidose regimen, rigorous treatment of the sexual partner(s), and more sophisticated diagnostic testing to define treatment failure. Pending the publication of such a study, however, I plan to alter my practice pattern and treat infected patients with a multidose regimen of metronidazole. I favor the regimen of 500 mg orally twice daily for 7 days because it is effective against both trichomoniasis and bacterial vaginosis, which is a common co-infection.

The twice-daily regimen is more convenient than the thrice-daily regimen and is not much more expensive than the single-dose regimen ($13 vs $4, http://www.goodrx.com). I will reserve the single 2-g dose of metronidazole for patients in whom treatment adherence is likely to be a problem or for patients in whom an immediate response to treatment is imperative (eg, a patient with preterm premature rupture of membranes or preterm labor).

›› **PATRICK DUFF, MD**

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Novel classification of labial anatomy and evaluation in the treatment of labial agglutination

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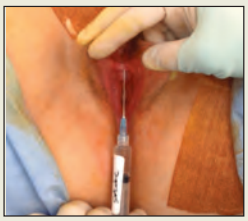

In this video the surgeons suggest a new method of classifying the labia minora and majora into 3 groups based on the vertical height of the labia minora in relation to the height of the genital hiatus. They review vaginal distortion due to labial agglutination from chronic inflammation, a hypoestrogenic state, or local trauma. They then illustrate the use of hydrodissection to treat a 57-year-old woman with a history of recurrent labial agglutination due to lichen planus refractory to methotrexate and oral and topical steroids.

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