This educational supplement discusses updated treatment guidelines for bacterial vaginosis (BV) and reviews literature on the association of BV and the risk of sexually transmitted infections that supports the need for proper BV treatment, whether symptomatic or asymptomatic.

Read the supplement: contemporaryobgyn.net/vaginosis
BV affects over 21 million women between the ages of 15 and 44 years in the United States annually, with recurrence rates as high as 58%
ENDOMETRIOSIS IT'S NOT FOR ADULTS ONLY

Marc R. Laufer, MD
and Jessica Y. Shim, MD,
NAMS 2020 ANNUAL MEETING

The mountains are calling and I must go.
—JOHN MUIR

Please join us at the
GAYLORD ROCKIES HOTEL
Denver, Colorado
SEPTEMBER 30 — OCTOBER 3
www.menopause.org
CHAIRMAN’S LETTER

On to other topics

The official start of summer has brought with it signs that in some areas of the country, restrictions associated with COVID-19 are being lifted. Coverage of the pandemic in these pages has lessened to some extent, but our online content buttresses what you have read here in the past few months with compelling video interviews and access to resources for managing your practice.

One of the more interesting highlights over the past few weeks has been the report, “Placental Pathology in COVID-19” from the American Journal of Clinical Pathology, with findings of maternal vascular malperfusion in the placentas of patients positive for the virus that causes Sars-CoV-2. Visit https://www.contemporaryobgyn.net/covid-19/covid-19-and-pregnancy-mmv-evidence-found-to-watch-an-interview with Emily Miller, MD, MPH, an author of the study.

Beyond COVID-19, timely clinical topics covered in this issue include cesarean scar pregnancy (CSP), a complication that occurs when an early pregnancy implants in the scar from a previous cesarean delivery. Editor-in-Chief Catherine Y. Spong, MD, provides her commentary based upon the Consult Series #49 from the Society for Maternal-Fetal Medicine, in which experts analyze the incidence, pathogenesis, and risk to patients who present with CSP.

In “Endometriosis: Not for adults only,” authors Marc R. Laufer, MD, and Jessica Y. Shim, MD, discuss how a painful condition impacts younger patients, and presents much differently in this age group than it does in adults.

We want to hear your thoughts on any of these topics, especially if you have encountered them clinically. Please email Senior Editor Angie DeRosa at aderosa@mjhlifesciences.com. ■

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
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FOR THE TREATMENT OF MODERATE TO SEVERE VASOMOTOR SYMPTOMS DUE TO MENOPAUSE IN WOMEN WITH A UTERUS

BIJUVA IS THE FIRST AND ONLY FDA-APPROVED COMBINATION OF BIO-IDENTICAL* ESTROGEN + MICRONIZED PROGESTERONE
IN A SINGLE ONCE-DAILY ORAL CAPSULE

BIJUVA is a combination of estradiol and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

INDICATION

BIJUVA is a combination of estradiol and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

ESTROGEN PLUS PROGESTIN THERAPY

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

• The Women's Health Initiative (WHI) estrogen plus progestin substudy reported increased risks of stroke and deep vein thrombosis (DVT), pulmonary embolism (PE), and myocardial infarction (MI)

• The WHI estrogen plus progestin substudy reported an increased risk of diabetes mellitus in women 65 years of age or older

ESTROGEN-ALONE THERAPY

• There is a increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens

• Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia

• The WHI estrogen-alone substudy reported increased risks of stroke and DVT

• The WHIMS estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older

CONTRAINDICATIONS

• BIJUVA is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of cancer of the breast; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (for example, stroke, MI), or a history of these conditions; known anaphylaxis reaction, angioedema, or hypersensitivity to BIJUVA or any of its ingredients; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

• Monitor thyroid function in women on thyroid replacement therapy. Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs.

• Estrogens increase the risk of gallbladder disease.

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

• Monitor thyroid function in women on thyroid replacement therapy.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) for BIJUVA are breast tenderness (10.4%), headache (3.4%), vaginal bleeding (3.4%), vaginal discharge (3.4%) and pelvic pain (3.1%).

Please note that this information is not comprehensive. Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following pages.

References:
1. BIJUVA [package insert]. Boca Raton, FL: TherapeuticsMD, Inc; 2019

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BIJUVA® 1mg/100mg (estradiol and progesterone) capsules

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TherapeuticsMD
For Her. For Life.
In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted (see Clinical Studies (14.4) in full prescribing information). Should stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately. Subgroup analysis of women 50 to 59 years of age suggested no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (19 versus 21 per 10,000 women-years).

Coronary Heart Disease

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years). An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 (see Clinical Studies (14.4) in full prescribing information).

In the WHI estrogen-alone substudy, no overall effect on CHD events was reported in women receiving estrogen-alone compared to placebo (see Clinical Studies (14.4) in full prescribing information).

In postmenopausal women with documented heart disease (n = 2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary artery disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not through the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open-label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS II, HERS I, and overall.

Venous Thromboembolism

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE (DVT and PE) was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (55 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (16 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted (see Clinical Studies (14.4) in full prescribing information). Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately. In the WHI estrogen-alone substudy, the risk of VTE was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (36 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years (see Clinical Studies (14.4) in full prescribing information). Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

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

Malignant Neoplasms

Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.88, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CEE (0.625 mg)-alone group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups (see Clinical Studies (14.4) in full prescribing information).

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80] (see Clinical Studies (14.4) in full prescribing information).

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer in estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

In a one-year trial, among 1,684 women who received a combination of estradiol plus progestin ( Estradiol 1 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 100 mg progesterone or 0.5 mg estradiol plus 50 mg progesterone or 0.25 mg estradiol plus 50 mg progesterone) or placebo (n=151), six new cases of breast cancer were diagnosed, two of which occurred among the group of 419 women treated with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg. No new cases of breast cancer were diagnosed in the group of 151 women treated with placebo.
Endometrial Cancer

Endometrial hyperplasia (a possible precursor of endometrial cancer) has been reported to occur at a rate of approximately 1 percent or less with BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg.

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in women with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk was associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more, and this risk has been shown to persist for at least 6 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring vaginal bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestogen to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

The WHI estrogen plus progestin substudy report a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.38 (95% confidence interval [CI], 0.77 to 2.34). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,101 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% CI, 1.32 to 1.51); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years) or by the type of hormone used to estrogen. In a large, randomized cancer diagnosis. The relative risk associated with combined estrogen and progestin use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

Probable Dementia

In the WHIMS estrogen plus progestin ancillary study of WHIMS, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE 0.625 mg plus MPA 2.5 mg or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.55 (95% CI, 1.21 to 3.34). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

In the WHIMS estrogen-alone ancillary study of WHIMS, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE 0.625 mg or placebo. After an average follow-up of 3 years, 40 women in the CE group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE versus placebo was 1.48 (95% CI, 0.83 to 2.66). The absolute risk of probable dementia for CE versus placebo was 37 versus 25 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication is discontinued.

Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

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When data from the two populations in the WHIMS estrogen-alone and estrogen plus progesterin ancillary studies were pooled as planned in the WHIMS protocol, the overall relative risk for probable dementia was 1.76 (95% CI, 1.19 to 2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

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As we are now incorporating the new post-COVID-19 “normal” into our routines, I was reflecting on the parallels of the changes that went into play with the identification and management of patients with HIV. As was done then, we are moving from an elite team approach to incorporation of patients with COVID-19 into our service, with everyone using the appropriate precautions to prevent transmission. We recognize that personal protective equipment is now part of our daily lives. As such, learning must continue.

This issue of Contemporary OB/GYN includes an expert article on cesarean scar pregnancy (CSP) by the Society for Maternal-Fetal Medicine (SMFM). Our valued partnership with SMFM gives us the ability to bring readers of our magazine the most up-to-date and topical information on conditions they face in practice. CSP is one of those topics.

The rise in cesarean deliveries coupled with the widespread use of ultrasound, especially in the first trimester, provided the opportunity to identify and diagnose this condition. Cesarean delivery as the mode of delivery rose from 1996 to 2009, peaking at 32.9%.

Concurrent with the rise in cesarean deliveries was the rise in use of ultrasound. By 2001, 67% of women with live births received an ultrasound during pregnancy, an increase from 47.7% in 1989. In addition, at the same time, first-trimester ultrasound was actively being evaluated for detection of aneuploidy. The number of articles on CSP inversely mirrors the US national cesarean rate (Figure).

The authors of the SMFM article reviewed the literature and provide recommendations based on evidence and expert opinion, the latter in the setting where evidence is not available. A PubMed search documents the recent onset of CSP. The first article was published in 1998 and there are only 398 articles in total (Figure). As expected, articles with concerning outcomes predominate, which is the case with any condition; normal outcomes rarely are published. Importantly, expert opinion is essential in guidance about new areas, to provide a reasoned approach for the practitioner when data are not available. As the article describes, CSP is an accepted precursor to placenta accreta spectrum (PAS), and affected pregnancies are at increased risk for hemorrhage as a result. Risk of uterine rupture, however, is less clear. As we take this information, we

PubMed search of ‘cesarean scar pregnancies’ vs United States Cesarean Delivery rate.
must be cautious and appreciate the similarities to other situations in obstetrics. Consider for example the “genetic sonogram” initially performed only in those women at high risk for fetal anomalies. As ultrasound technology improved, more could be visualized, and soft markers were identified in these high-risk women, associating the soft markers with aneuploidy. As the use of ultrasound expanded to low-risk women, it was found that many of these soft markers are normal variants, and that they alone do not increase the risk of aneuploidy.

As the SMFM experts note, “The true incidence of CSP is unknown, as the condition is likely underdiagnosed and underreported.” There are limited studies available following the course of CSPs to determine the outcome with expectant management. A key question is whether only a subset of these patients might require immediate treatment to avoid uterine rupture. In the remainder of cases, if indeed they are at risk for PAS alone, it might be beneficial to have a discussion that incorporates shared decision-making, given the lack of evidence, and particularly because the pregnancy is likely to be the woman’s last. One recently published study attempts to address this question. However, the women were identified at 10 to 13 weeks’ gestation, which is later than the expert opinion recommends, and it is not clear that all met the criteria for CSP. Interestingly, this study found that only eight of the 40 women required a hysterectomy and 82% delivered vaginally.4 We should be attentive to these findings as we become more comfortable identifying and diagnosing CSP.

Current research on CSPs is extremely limited. Searching the National Institutes of Health Reporter database revealed no currently funded studies. A search of clinicaltrials.gov identified six trials, of which two are recruiting and none are in the United States.

We appreciate the partnership with SMFM, and the help from their experts with our practice.

Dr. Spong, editor in chief, is Professor and Vice Chair in the Department of Obstetrics and Gynecology and Chief of the Division of Maternal-Fetal Medicine at UT Southwestern Medical Center in Dallas. She holds the Gillette Professorship of Obstetrics and Gynecology.

Email her at cspong@mjhiflsciences.com

REFERENCES
Introduction
Fertility awareness-based contraceptive methods (FABM) are behavioral methods of contraception that are used by approximately 2.2% to 3.2% of sexually active women.1 This low usage rate may be due to provider and patient knowledge and beliefs. One concern providers may have is that the typical use efficacy rate is lower than for other contraceptive methods. In addition, providers may be uncomfortable counseling patients about appropriate usage.2 Women who use FABM may choose it because they have values and/or beliefs that are aligned with using non-pharmacologic contraception. However, we must consider that the best form of contraception is the one the patient feels works for her. Given that FABM may be used as a contraceptive, and that there are patients who will choose it, ob/gyns must be familiar with it and ready to counsel about its use.

Considerations
Nonjudgmental and open conversation with patients about their priorities is critical to all contraceptive counseling, particularly when discussing FABM. Generally, FABM is most suitable for patients who have regular menses (although some methods, such as TwoDay, may not require this) and for whom variance in efficacy of a method—and therefore the real possibility of an unplanned pregnancy—is acceptable. As such, an important part of counseling is reviewing medical comorbidities, obstetric history, and current medications so that the patient understands the risks of unplanned pregnancy to their health and the health of the fetus. Given that FABM requires abstinence or use of barrier methods on certain days, the ability to have open communication with a partner is paramount. Considering this, FABM may work best for patients whose partner(s) is highly motivated to avoid pregnancy and willing to avoid unprotected sex on certain days. Thirty-six percent of women in the United States suffer sexual violence and coercion3; behavioral methods cannot protect
against pregnancy in these cases. In addition, FABM does not offer protection against sexually transmitted infections.

It is important to note that studies of FABM effectiveness vary in quality, which makes it difficult to compare efficacy between specific methods. Overall, FABM collectively has a 15% typical-use first-year failure rate, but it can vary as much as 2% to 23%. There are many factors that impact effectiveness of FABM. These include the ability of the provider to adequately counsel on how to use the method and the ability of the patient to follow and use the method instructions appropriately. Given that most studies show high first-year discontinuation rates for FABM, shared decision-making and clear instructions on how to properly use each technique are critical to successful patient use.

### Avoiding fertilization

The crux of FABM is understanding the menstrual cycle and using biological knowledge and cues to predict when fertilization is most likely. We know that ovulation most often occurs in the middle of a menstrual cycle; given that sperm can persist for 3 to 5 days in the female reproductive tract and the ovum has a lifespan of 12 to 24 hours, the fertile window lasts for approximately 6 days. In cycles with lengths of 26 to 32 days, 78% of women will have a fertile window between Days 8 and 21. There are various methods that can be used to predict the fertility window—and therefore the period of “at-risk” days for pregnancy—during a menstrual cycle. In addition to counseling patients how to predict these days, it is vital to discuss how they will avoid unprotected intercourse during the 10 to 17 “at-risk” days of their menstrual cycle. If they are interested in barrier methods (condom, diaphragm), ensuring proper instruction on how to use them is needed to ensure effectiveness of FABM.

### Case

Elena is a 28-year-old G0 who is considering pregnancy in the next 1 to 2 years. She and her husband prefer a method that does not involve exogenous hormones or medical devices. She asks you about using a fertility awareness-based method (FABM) for contraception. She has tracked her regular periods for many years and is detail-oriented. Elena has no medical problems and takes a multivitamin daily. Which of the following do you tell her is important to the success of using an FABM method?

A. Meticulous, daily recording
B. Ability to avoid unprotected intercourse
C. Adequate knowledge about how to determine “at-risk” days

All of the above

Patients are most likely to have success using FABM if they are able and committed to meticulous, daily attention and recording of various aspects of their cycle (depends on what method), able to avoid unprotected intercourse, and are well-informed about the specific method they are using. For these reasons, we recommend the Standard Days® (CycleBeads®) method or the TwoDay® method, as they are the most straightforward methods for providers and patients.

The Standard Days Method® requires 6 months of menstrual cycle tracking prior to initiation. It requires that a menstrual cycle is between 26 and 32 days long. Patients who are breastfeeding or who have recently stopped hormonal contraception may not have an-
## Table 1.

<table>
<thead>
<tr>
<th>Method</th>
<th>How It Works(^6,8)</th>
<th>Effectiveness (% 1st-year failure rate)</th>
<th>Important Counseling Pearls</th>
</tr>
</thead>
</table>
| **Calendar/rhythm** (requires regular menstruation) | Identify shortest and longest menstrual cycle in 6– to 12-month period, then perform specific calculation to identify “at-risk” window in which intercourse is avoided or other contraceptive method is used. | Varies widely based on study: 14–19\(^{9,11}\) | - Effectiveness may be increased because of increased compliance with method if barrier method used on at-risk days.\(^{12}\)  
- Given the complexity of proper use and varied failure rate of this method, we recommend using Standard Days if calendar-based method desired. |
| **Standard Days Method\(^5\)** (CycleBeads) | Utilizes color-coded beads to track fertile days. Requires that menstrual cycle length is 26-32 days.\(^7\) Unprotected intercourse is permitted on Days 1* through 7 and from day 20 until end of menstrual cycle. On Days 8-19, must abstain or use barrier method. | PERFECT USE: 5%  
TYPICAL USE: 12%\(^{13}\) | - Method can be used for both contraception and fertility prediction — effectiveness may improve with provider counseling experience.\(^{14}\)  
- Can purchase physical beads online or use software versions such as iCycleBeads (IOS) or CycleBeads (Android). |
| **Billings ovulation**          | Uses cervical mucus changes to predict “at-risk” window.                            | PERFECT USE: 3%  
TYPICAL USE: 22%\(^{10,15,16}\) | - Requires specific and detailed instruction on how to evaluate secretions in addition to special chart for tracking.  
- Approved by the WHO.\(^{17}\)  
- Must avoid actions that may interfere with mucus evaluation, such as intercourse on consecutive days.  
- Vaginal infections may interfere with identification of secretions.  
- Method can be used for both contraception and fertility prediction. |
| **TwoDay Method\(^6\)**          | Simplified version of Billings method where patient evaluates if secretions of any type were present “Today” or “Yesterday.” Patient must have two consecutive secretion-free days to have unprotected intercourse. | PERFECT USE: 3.5%\(^{14}\)  
TYPICAL USE: 14%\(^{14,18}\) | - Method allows for cycle-cycle variation.  
- Must allow 3 days in between coital events because ejaculate will interfere with secretion evaluation.  
- Effectiveness may improve with provider counseling experience.\(^{13}\) |
| **Symptothermal**              | Combined method that utilizes cervical secretions and basal body temperature (BBT)\(^1\) to identify “at-risk” time. | PERFECT USE: 0.4%  
TYPICAL USE: 12-20%\(^{19,20}\) | - BBT must be taken using a BBT thermometer first thing in the morning, before rising, after at least 3 hours of sleep.  
- Requires specific chart for tracking.  
- Can be used for both contraception and fertility prediction. |

*Day 1: first day of menstrual bleeding  
\(^1\)BBT alone will not offer advanced warning of ovulation and is not suitable as a contraceptive method on its own.
ticipated efficacy with this method and should wait to observe their cycles before starting. The Standard Days Method\textsuperscript{9} relies on the fact that unprotected intercourse has a low likelihood of causing pregnancy on menstrual cycle Days 1 to 7 and from Day 20 until the end of the cycle. The patient should abstain from intercourse or use a barrier method on Days 8 to 19. Cyclebeads\textsuperscript{8} are a helpful way for a patient and her partner to keep track of cycles together; bead colors may indicate fertile and less fertile days, so they know when unprotected intercourse will avoid pregnancy. She can place the beads in a common area as a way to communicate with her partner. With perfect use, this method is 95% effective and with typical use, it is 88% effective.

The TwoDay Method\textsuperscript{9} relies on a patient’s comfort, awareness, and tracking of vaginal secretions and on the fact that thin, watery, secretions make it possible for sperm to travel through the female reproductive tract and survive for several days. The cervical fluid around the time of ovulation is particularly characteristic in that it is abundant, clear, and stretchy.\textsuperscript{15,18} Therefore, when a patient is dry or lacks vaginal secretions, it has been theorized she is less likely to become pregnant. A patient may use touch to assess for secretions, or observe them on underwear or a menstrual pad. If she does not experience vaginal secretions for 2 days in a row, the risk of pregnancy is low. Patients should abstain from or use barrier methods for 3 days following unprotected intercourse, as the ejaculate interferes with the ability to assess for presence of vaginal secretions. Benefits of this method are that it can be used by women who have irregular cycles and that it is simple to understand and execute. Patients should be warned that vaginal infections can interfere with symptom assessment. With perfect use, the TwoDay Method\textsuperscript{9} is 97.5% effective, and with typical use, it is 86% effective.

For Elena, we can counsel her that both of these methods have similar perfect and typical use, are easy to understand, can help her prevent pregnancy for now, and can aid in achieving pregnancy in the future. Educating her about the Standard Days Method\textsuperscript{9} may provide her with more information about ovulation and a fertile window, while the TwoDay Method\textsuperscript{9} can inform her about the role of cervical mucus in fertility. Ultimately, we can discuss which method she feels most comfortable with and provide her with supplemental reading material.

Conclusion

The world of contraception is constantly changing, with improving technologies, new devices, and more options than ever before. In addition to staying up to date within the evolving field of Family Planning, ob/gyns should also be prepared to counsel and support patients who choose to use FABM. These methods require an ob/gyn to be knowledgeable about it and able to engage in shared decision-making with the patient to determine which method is appropriate. There are many resources ob/gyns can use to refresh their knowledge about these methods—many of which are cited in this review. We feel the Standard Days Method\textsuperscript{9} (CycleBeads\textsuperscript{8}) and TwoDay Method\textsuperscript{9} are the simplest to use and counsel about and the easiest for patients to understand. With proper counseling and education, FABM may be a satisfactory option for your patient.

For references visit contemporaryobgyn.net/fabm

COVID-19: DR. EMILY MILLER DISCUSSES PLACENTAL CHANGES

Emily Miller, MD, MPH, with Northwestern Medicine in Chicago, has been involved in what may be the most interesting clinical findings to date for the impact of COVID-19 to pregnancy. There are changes to the placenta, including evidence of maternal vascular malperfusion (MVM).

In this exclusive video interview with Senior Editor Angie DelRosa, Miller discusses MVM and what she has seen in clinical practice and research, including the impact of socioeconomic status to how patients are able to socially distance.

To watch the full interview visit contemporaryobgyn.net/covid-19/covid-19-and-pregnancy-dr-emily-miller
Endometriosis: Not for adults only

Tricky to diagnose and treat in younger women, the painful condition is the leading cause of secondary dysmenorrhea.

by MARC R. LAUFER, MD, AND JESSICA Y. SHIM, MD

Endometriosis is classically diagnosed by presence of endometrial glands and stroma outside the uterine lining. While it may be a more common entity diagnosed among adults, endometriosis is the leading cause of secondary dysmenorrhea and chronic pelvic pain in adolescents. The symptoms can be debilitating, limiting adolescents in their participation in school or extracurricular activities. The presentation of endometriosis in this population also can be misleading, as its signs and symptoms differ from those in adult women. Awareness of and early intervention in adolescent endometriosis is critical to avoid diagnostic delay and progression of disease.

Evaluation of endometriosis

Evaluation of endometriosis begins in the office with a thorough medical history. Unlike adults, adolescents rarely present with endometriomas or infertility. Endometriosis most commonly is identified in adolescents who present with pelvic pain. In a survey of adult women affected by endometriosis, two-thirds of respondents reported their first pelvic symptoms before age 20, and one in three women had pain before age 15. While endometriosis is typically considered to be a disease that manifests after years of menstruation, symptomatic cases have been reported prior to menarche without an associated obstructive anomaly, and also as soon as one month after menarche. These instances suggest alternative hypotheses to Samson’s theory on retrograde menstruation as the cause of endometriosis.

Endometriosis in adults presents with dysmenorrhea but adolescents may exhibit other symptoms. A study from our institution in the 1990s identified that the classic adult symptom of cyclic pain was present by itself in only 9.4% of adolescents, whereas 28.1% of patients had acyclic pain alone, and 62.5% had both cyclic and acyclic pain. Therefore, the majority of adolescents with endometriosis (90.6%) had acyclic pain. Endometriosis is also associated with gastrointestinal (GI) symptoms such as diarrhea or constipation, and urinary symptoms such as urgency and dysuria. In a case series of adolescents with laparoscopically diagnosed endometriosis, over half the patients reported at least one GI symptom (56%) or one genitourinary symptom (52%). Adolescents affected by endometriosis also have a higher prevalence of migraines compared to their peers without endometriosis.

Several red flags in a patient’s history
should raise suspicion for endometriosis. Endometriosis appears to have a hereditary component; a young woman with a first-degree relative affected by endometriosis has a four to seven times higher risk of developing endometriosis than that in the general population. A history of childhood sexual and physical abuse has also been found to have an association with increased risk of endometriosis. Endometriosis is associated with obstructive Mullerian anomalies, such as imperforate hymen, transverse vaginal septum, and agenesis of the lower vagina. Even if a patient were to have surgical correction of an obstructive anomaly, that might not resolve their risk of endometriosis.

A recent systematic review of observational, population-based studies suggests an increased comorbidity risk of autoimmune diseases including systemic lupus erythematosus, Sjögren’s syndrome, rheumatoid arthritis, autoimmune thyroid disorder, celiac disease, multiple sclerosis, inflammatory bowel disease, and Addison’s disease.

After obtaining a thorough history, a physical exam should be performed to assess for any other etiologies of the pain; these may include gastrointestinal, urinary, or musculoskeletal etiologies, or a pelvic mass or reproductive tract anomaly. In an adolescent, particularly one who has no genital complaints, a pelvic exam is not always necessary. Uterosacral nodularity or distorted anatomy are findings of more advanced stage or deep infiltrating disease, which is less common in adolescents. If there is concern for an obstructive anomaly or a mass, a rectal-abdominal exam may be performed, or a Q-tip can be inserted into the vagina to assess for vaginal patency. A physical exam may not exclude endometriosis, but it is an opportunity to exclude alternative explanations for a patient’s complaints.

Imaging does not need to be routinely obtained in adolescents with dysmenorrhea, but ultrasound imaging may be helpful when other gynecologic pathologies such as an adnexal cyst, torsion, or a reproductive tract anomaly need to be excluded. Transvaginal imaging is unnecessary and invasive, and it can be traumatic for a younger and/or non-sexually active teen; a transabdominal ultrasound (U/S) of the pelvis is acceptable. Magnetic resonance imaging may be indicated if the exam or U/S findings are concerning for a complex congenital anomaly of the reproductive tract. More than likely, endometriosis will not be appreciated on imaging as it is typically superficial peritoneal disease (stage I or II disease) and only deeply infiltrative disease, adhesions or endometriomas will be appreciated on U/S. In addition, endometriomas are less common in adolescents than in adults. Currently, there are no specific blood tests or serum markers to identify endometriosis. Other laboratory tests that may be helpful to obtain include a pregnancy test, sexually transmitted infection testing, and a urinalysis.

Diagnosing endometriosis

A clinical diagnosis of endometriosis should be considered if the evaluation of the patient’s symptoms, history, physical examination, and/or imaging raise suspicion. A recent call to action proposes moving from a histological diagnosis of endometriosis to a clinical diagnosis. This shift in focus may help lessen diagnostic delay, and it emphasizes the chronic, inflammatory, and progressive nature of endometriosis. When there is a concern for endometriosis, a trial of nonsteroidal anti-inflammatory drugs, progestin-only or estrogen/progestin therapy should be offered. We do not
routinely initiate a first-line trial of empiric gonadotropin-releasing hormone (GnRH) agonist or antagonist therapy in adolescents due to the potential detrimental effects on bone marrow density with long-term use. A trial of combination estrogen/progestin or progestin therapy is typically at least 3 months in duration.

If a patient’s pain persists despite medical therapy, laparoscopy may be indicated prior to 3 months of medical therapy. If pain persists on one combination pill, changing to another pill is not usually useful and will only delay diagnosis and surgical treatment. Laparoscopy is supported by the American College of Obstetricians and Gynecologists. The provider should feel comfortable operating on adolescents and knowledgeable about the visual appearance of superficial peritoneal lesions typically found in adolescents (Figures 1 to 3). The variable appearance of endometriosis has been described in the revised American Society for Reproductive Medicine Classification of Endometriosis. Red and clear vesicular lesions are frequently appreciated in adolescent endometriosis and are often the most painful lesions. “Powder-burn” lesions represent older, more advanced implants and are less commonly identified in adolescents. We have found that adjusting the magnification and moving the laparoscope closer to the peritoneum may identify subtle lesions. Another technique for visualization of lesions is by filling the pelvis with irrigation fluid (e.g. normal saline or lactated Ringer’s) and submerging the laparoscope underneath the fluid; subtle, clear lesions may be seen floating under the fluid. If no suspicious lesions are identified, random cul-de-sac biopsies may be beneficial as endometriosis may be microscopic in appearance.

Management of endometriosis
There is no medical or surgical cure for endometriosis. Surgery can provide significant pain relief, but because there is no cure from surgery, medical therapy is needed after surgery. During surgery, after identification
of endometriotic lesions in the pelvis, the surgeon should feel comfortable with destroying/removing as much of the disease as possible and attempting to restore normal anatomy. Lysis of adhesions should also be performed if needed. Implants can be treated via electrocautery, endocoagulation, laser ablation, or excision. At our institution, we destroy superficial peritoneal disease with a monopolar L-hook electrode instrument, and excise deeper infiltrating lesions. “Radical excisional surgery” or “peritoneal stripping” should not be used in adolescents as it may increase extensive adhesive formation and has not been shown to have clinical benefit.20

Patients should be managed after surgery with medical therapy to prevent recurrence or progression of disease. Combined surgical-medical management has been demonstrated to retard disease progression in adolescents who elected a subsequent laparoscopic procedure.21 We recommend that patients stay on hormonal therapy long-term until they want to become pregnant. Hormonal therapy includes combination estrogen/progestin therapy, progestin-only therapy, exogenous androgens, and GnRH agonists or antagonist. When prescribing continuous combination oral contraceptives (COC), we prefer to use monophasic regimens because multi-phasic regimens will be less successful in suppressing menstruation. There are no data suggesting one combination estrogen/progestin pill formulation treats endometriosis-associated symptoms better than another. Alternatives to COCs, including the vaginal ring and transdermal patch, are also acceptable and may be more tolerable for patients who are not compliant with daily pill use. All these methods can be administered in extended fashion or continuously to suppress menses and endometriosis-associated pain.

Progestin-only methods include the “mini-pill,” (norethindrone), norethindrone acetate, medroxyprogesterone acetate, the etonogestrel implant, and the levonorgestrel intrauterine system (LNG-IUS). Norethindrone acetate (5-15 mg daily) is an effective treatment that can be titrated to achieve amenorrhea and pain relief.22 Norethindrone acetate is different from noretindrone in that it is not a US Food and Drug Administration-approved contraceptive, and there is small peripheral conversion of norethindrone acetate to ethinyl estradiol.23 Medroxyprogesterone acetate can be used, with administration every 3 months, in intramuscular or subcutaneous formulation. Patients may experience unwanted side effects from progestins, such as irregular bleeding, weight gain, and mood changes; we therefore recommend a trial of oral progestins prior to injectables or long-acting reversible contraception as these can be quickly discontinued if poorly tolerated. Limited studies have evaluated use of the implant or the LNG-IUS in adolescents with endometriosis, but both treatments appear to be effective in reducing endometriosis-associated pain.24 We have noticed the systemic level of hormone from the LNG-IUS may not be high enough to treat endometriosis-associated pain and potential disease progression, therefore we often use the device in conjunction with continuous low-dose estrogen/progestin or progestin-only therapy.25 In our experience, adolescents have tolerated the LNG-IUS well and we offer placement in the outpatient setting or at time of laparoscopy, to eliminate the possible inseritional pain. We do not routinely use the subdermal implant given the risk of unwanted menstrual changes.26
Exogenous androgens used in treatment of endometriosis include danazol and methyltestosterone. Both of these methods have effects that are dose-dependent, such as acne, hirsutism, and weight gain, and some that may be irreversible, such as deepening of the voice. We do not routinely prescribe these medications due to their side effect profiles, however, transgender male patients may find these side effects desirable and preferable compared to the side effects from estrogen/progestin or progestin-only therapies.

Second-line options for treatment of adolescent endometriosis-associated symptoms include GnRH agonists or antagonists. GnRH agonist therapy is generally reserved for adolescents above age 16 because of the potential detrimental effects on bone mineral density (BMD). GnRH agonists are available in many formulations, but we prefer the nasal spray or the 3-month injectables to improve patient compliance. When starting GnRH agonist therapy, patients should be warned about the “flare effect;” pain and withdrawal bleeding may occur 21 to 28 days post-initiation due to an initial production of follicle stimulating hormone and luteinizing hormone prior to down-regulation. If pain and bleeding persist beyond the first month, obtaining estradiol levels may be helpful in determining if up-titrating the GnRH agonist is necessary. Add-back therapy should be initiated with the start of GnRH agonist therapy to decrease hypoestrogenic side effects. We found the combination of norethindrone acetate (5 mg/day) plus conjugated equine estrogen (0.625 mg/day) add-back to be more effective for increasing total body BMD compared to norethindrone acetate monotherapy. COCs are not an appropriate add-back therapy as they negate the effects of the GnRH agonist. Bone density surveillance should be performed with dual energy X-ray absorptiometry, beginning at 8 months and repeating at least every 2 years on therapy. Discontinuation of GnRH agonist therapy is advised if a patient experiences unwanted symptoms or a decrease in BMD.

GnRH antagonists are a newer alternative to agonist therapies. The oral antagonist Elagolix is approved for moderate to severe endometriosis-related pain, however, its clinical trials did not include adolescents younger than age 18. Antagonist therapies are effective immediately and do not cause a “flare effect.” Elagolix does not always suppress ovulation and is not approved as a contraceptive. In addition, women may still experience menstrual bleeding as the incidence of amenorrhea varied from 13.9 to 65.6% in their clinical trials.

Other treatments include use of aromatase inhibitors. The use of letrozole has been endorsed by ACOG as an option for treatment of endometriosis-associated pain.

Complementary treatments can be helpful in addition to medical management of endometriosis. Japanese-style acupuncture is an effective and safe adjuvant therapy for adolescent endometriosis. A multidisciplinary approach to endometriosis is also helpful and includes referral to pain medicine and physical therapy specialists to address pelvic pain sensitization and pelvic floor trigger point pain. While alternative therapies warrant further research, it should be emphasized that medical therapy is the mainstay to prevent progression of disease.

Conclusion
Endometriosis is a chronic and currently incurable disease with frequent onset in adolescence. Early diagnosis and intervention can help prevent progression of the disease and significantly improve quality of life. A variety of surgical, medical, and complementary treatment modalities exist to help manage endometriosis. Treatment should be tailored to the individual adolescent, to improve patient compliance and decrease any unwanted side effects. In our experience, most clients diagnosed early, disease progression can be retarded, one surgical procedure is performed during their lifetime, and they have no difficulty conceiving a pregnancy. Adolescents can obtain patient educational information on endometriosis at youngwomenshealth.org and bostoncenterendometriosis.org with specific information relating to the diagnosis, treatments emotional support, and college planning. We also offer monitored, monthly chat rooms for safe, educational, and age-based discussions.

DISCLOSURES Dr. Laufer is the Director of the Boston Center for Endometriosis, which receives funding from the J. Willard and Alice S. Marriott Foundation. He is also on the International Advisory Board of AbbVie Pharmaceuticals, an advisor for NextJane Gen, and an author for UpToDate.

FOR REFERENCES VISIT contemporaryobgyn.net/ad-endo
Physical training can preserve and even significantly bolster bone mass in the hip and femoral neck of individuals under caloric restriction, according to a systematic review and meta-analysis of 13 randomized clinical trials. “It is uncertain if an exercise program reduces the adverse effects of calorie restriction-induced weight loss in adults,” wrote the authors in *Critical Reviews in Food Science and Nutrition*.

**Methods**
To evaluate the differences in bone mass between adults who enrolled in a calorie-restriction-alone (CR) weight loss group versus an exercise plus-calorie-restriction (CR-E) weight loss group, PubMed and Scopus libraries were searched for randomized clinical trials published up through February 2020. The 13 studies selected comprise 852 participants, mostly postmenopausal females, with a mean age of 56.6 years and a mean body mass index (BMI) of 32.5 kg/m².

Individuals decreased their caloric intake by 250 to 1500 kcal/day, compared to their pre-restriction total energy intake.

**Findings**
The review found significantly higher body mass density (BMD) at the hip (weighted mean difference [WMD]: 0.03 g/cm²; 95% confidence interval [CI]: 0.01 to 0.04; *P* < 0.001), femoral neck (WMD: 0.03 g/cm²; 95% CI: 0.01 to 0.05; *P* < 0.001) and total body bone mineral content (BMC) (WMD: 0.13 kg/cm²; 95% CI: −0.10 to 0.36; *P* < 0.001) in the CR-E weight loss group compared to the CR weight loss group. On the other hand, none of the changes in total body BMD (WMD: 0.00 g/cm²; 95% CI: −0.01 to 0.02; *P* = 0.57) and lumbar spine BMD (WMD: 0.00 g/cm²; 95% CI: −0.01 to 0.01; *P* = 0.89) were statistically significant.

Dramatic BMD improvements in the hip and femoral neck were particularly noticeable in participants aged 65 or older who engaged in combined exercise training lasting more than 200 days.

**Conclusions**
The protective effect that an exercise-induced weight loss program has on hip BMD in older adults can prevent or reduce incidence of hip fracture in this population. Although the mechanism by which concurrent exercise training improves BMD is not entirely understood, it is believed that the additional mechanical loading provided by aerobic exercise promotes an osteogenic response in bone.

The underlying mechanism that links age and increased BMD in the hip with exercise is also not well established, but could be due to proinflammatory cytokines and anti-inflammatory cytokines produced mainly by T cells, monocytes, and stromal cells in bone microenvironments. During aging, it is believed that osteoclastogenic-inducing proinflammatory cytokines and hence bone resorption are increased. Exercise prevents their production.

This inhibition is mediated especially by estrogen production. Losing body fat protects bones from osteoporosis by reducing proinflammatory cytokine production and increasing transforming growth factor beta in bone. In women, exercise has been demonstrated to have a positive effect on estrogen concentration, but the level of impact largely depends on factors like age, fitness, and intensity of regular exercise.

Two limitations are the inability to evaluate for sex differences and the lack of subgroup analysis based on menopausal status. “Further preliminary studies are required to assess bone quality in response to both calorie restriction and exercise training with reference to different time points, sex differences, hormonal and also adipokines level changes,” the authors concluded.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

**SOURCE**
Cesarean scar pregnancy (CSP) is a complication in which an early pregnancy implants in the scar from a prior cesarean delivery. Incidence and recognition of this condition appear to have increased over the past two decades, perhaps due to high worldwide cesarean delivery rates. The clinical presentation is variable, and many women are asymptomatic at presentation. CSP can be difficult to diagnose in a timely fashion. Ultrasound is the primary imaging modality for CSP diagnosis. Expectantly managed CSP is associated with high rates of severe maternal morbidity such as hemorrhage, placenta accreta spectrum (PAS), and uterine rupture. Given these substantial risks, pregnancy termination is recommended after CSP diagnosis. Several surgical and medical treatments have been described for this disorder, but at this time, optimal management remains uncertain.

Q: What is cesarean scar pregnancy, and what is its incidence?
CSP occurs when an embryo implants in the fibrous scar tissue of a prior cesarean hysterotomy. Although sometimes called a “cesarean ectopic pregnancy,” these gestations are, in fact, within the uterine cavity and, unlike true ectopic pregnancies, may result in a liveborn infant. This condition presents a substantial risk for severe maternal morbidity complicated by challenges in securing timely diagnosis, as well as uncertainty regarding optimal treatment once identified.

Q: What is the pathogenesis of CSP?
Although the pathogenesis of CSP is incompletely understood, the mechanism has been postulated to involve blastocyst implantation within a microscopic dehiscence tract in the scar from a prior cesarean delivery. Due to the fibrous nature of scar tissue, these inherently deficient implantation sites are at risk for dehiscence, PAS, and hemorrhage as the CSP enlarges. CSP and placenta accreta appear to be increasing, likely as a result of high contemporary cesarean delivery volume. Other factors, including improved imaging with ultrasound and magnetic resonance imaging (MRI), increased utilization of transvaginal ultrasonography (TVUS), and possibly increased physician awareness, may also contribute to a perceived increase in incidence.
have similar disease pathways and may exist along a common disease continuum. Histopathologic analyses for both groups are characterized by myometrial or scar tissue villous invasion with little or no intervening decidua.

Implantation patterns of CSP can be categorized as either endogenic (also referred to as “on the scar”) or exogenic (“in-the-niche”). Endogenic is defined as growing within the uterine cavity and exogenic as arising from a gestational sac deeply implanted into the scar that may grow toward the bladder or abdominal cavity (Figure 1). These ultrasonographic appearances may influence obstetric prognosis. It has been suggested that early first-trimester determination of whether a CSP is growing “on the scar” or “in the niche” of the prior cesarean hysterotomy may be used to predict subsequent pregnancy outcomes. In one small, retrospective experience, patients with pregnancies growing “on the scar” had variable obstetric outcomes, whereas those with pregnancies growing “in the niche” all underwent hysterectomy with PAS at delivery.1

**How does CSP present clinically, and are there known risk factors?**

Although second-trimester diagnoses have been reported, CSP usually presents in the first trimester. In one review of published CSP case series, the average gestational age at diagnosis was 7.5 +/- 2.5 weeks.2 The clinical presentation is variable, ranging from asymptomatic ultrasonographic detection to a presentation with uterine rupture and hemoperitoneum, typically in the absence of a timely diagnosis. In the review mentioned above, about one-third of cases were asymptomatic, and approximately one-third presented with painless vaginal bleeding. Nearly one-quarter of presentations involved pain, with or without bleeding. Women with a ruptured CSP may also present with hemodynamic collapse.

Although by definition prior cesarean delivery is a prerequisite for CSP development and placenta previa may modify this risk, it is not clear if the number of prior cesarean deliveries further increases risk. A review of the literature reveals that 52% of CSP cases occur in women with a single prior cesarean delivery.3,4 Previous delivery for breech presentation appears to be a more common indication in women who later develop CSP. No published data exist regarding an association between hysterotomy closure technique and CSP.

**How is CSP diagnosed?**

TVUS is the optimal modality for evaluation of suspected CSP, as it provides the highest image resolution (Figures 2 and 3). Grayscale combined with color Doppler ultrasound is recommended for CSP diagnosis. One group suggests combining TVUS with a transabdominal ultrasonogram with a full maternal bladder to provide a “panoramic view” of the uterus and the relationship between the gestational sac and bladder.5 The initial finding of a low, anteriorly located gestational sac should raise concern for a possible CSP and warrants further investigation. When evaluating women with suspected CSP, a high degree of clinical suspicion is needed as a missed or delayed diagnosis can result in uterine dehiscence, hemorrhage, loss of fertility, or maternal death.

Diagnostic criteria have been proposed to enhance ultrasonographic detection of CSP.6,7 One approach proposes the following ultrasonographic criteria to diagnose CSP: (1) an empty uterine cavity and endocervix; (2) placenta, gestational sac, or both embedded in the hysterotomy scar; (3) a triangular (≤8 weeks of gestation (Figures 2 and 3). Grayscale combined with color Doppler ultrasound is recommended for CSP diagnosis. One group suggests combining TVUS with a transabdominal ultrasonogram with a full maternal bladder to provide a “panoramic view” of the uterus and the relationship between the gestational sac and bladder.5 The initial finding of a low, anteriorly located gestational sac should raise concern for a possible CSP and warrants further investigation. When evaluating women with suspected CSP, a high degree of clinical suspicion is needed as a missed or delayed diagnosis can result in uterine dehiscence, hemorrhage, loss of fertility, or maternal death.

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tation) or rounded or oval (> 8 weeks of gestation) gestational sac that fills the scar “niche” (the shallow area representing a healed hysterotomy site); (4) a thin (1-3 mm) or absent myometrial layer between the gestational sac and bladder; (5) a prominent or rich vascular pattern at or in the area of a cesarean scar; and (6) an embryonic or fetal pole, yolk sac, or both with or without fetal cardiac activity (Figure 4). All of these criteria may not be observed. Especially with very early diagnosis and before fetal cardiac activity, the woman must have confirmation of pregnancy (for example, a positive pregnancy test result). Bulging or ballooning of the lower uterine segment in the midline sagittal transabdominal view has also been considered to be supportive of CSP diagnosis.

Distinguishing CSP from other clinical entities with a similar ultrasonographic appearance is challenging. CSP may be misdiagnosed as either cervical ectopic pregnancy, spontaneous abortion in transit, or low implantation of an intrauterine pregnancy. Given the importance of prompt diagnosis, referral to an experienced center for a second opinion may be preferable to ongoing follow-up examinations that are likely to lead to a delay in diagnosis.

Q: Are other modalities useful for diagnosis?

Transvaginal three-dimensional (3D) ultrasound and 3D power ultrasound have been used in an attempt to enhance accuracy of CSP diagnosis. However, data are insufficient to support a benefit of routine use of 3D ultrasound for diagnosis or management of CSP. Magnetic resonance imaging (MRI) has been used as an adjunct to ultrasound for diagnosis of CSP, although its incremental benefit over ultrasound alone is unknown. MRI may provide useful information regarding the degree of invasion and whether there is evidence of PAS. Most authors do not recommend MRI as a routine component of CSP evaluation. In cases in which ultrasound imaging is inconclusive, MRI could be considered as an adjunct study. Given the risks associated with delayed diagnosis, use of multiple ultrasound imaging approaches, as well as modalities such as MRI, are likely preferable to serial ultrasound examinations.

Hysteroscopy and laparoscopy can be used to confirm a diagnosis at the time of planned operative intervention. With laparoscopic examination, CSP has been described as an echymotic bulge with a “salmon-red” appearance beneath the bladder at the level of the prior cesarean scar with an otherwise normal-appearing uterus.

Q: What is the natural history of CSP?

Although few recognized CSPs continue to a viable gestational age, some
CSPs have resulted in live births often associated with PAS, cesarean hysterectomy, and massive hemorrhage at delivery. Series describing outcomes of expectantly managed CSPs all involve small case numbers and high hysterectomy rates, ranging from 50% to 100% and usually associated with PAS. In case series of women managed expectantly, most required additional treatment, and more than 50% had severe complications.9–13

Due to the high risk of severe maternal morbidity, expectant management is not recommended for a recognized CSP, and pregnancy termination is generally advised as soon as the diagnosis is confirmed. For cases in which a CSP is suspected but the diagnosis is not certain, short-interval follow-up, a second opinion, or additional imaging with MRI should be considered to make a timely diagnosis without undue delay. We recommend against expectant management of cesarean scar pregnancy (GRADE 1B).

An exception to the recommendation against expectant management involves early CSP that is definitively diagnosed as nonviable. In this situation, expectant management may be pursued with serial ultrasound surveillance, quantitative beta-hCG measurements, and repeat imaging.

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### Table 1.

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<th>Method</th>
<th># of studies</th>
<th>Number of patients</th>
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<th>Complications</th>
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<tr>
<td>Laparoscopy</td>
<td>7</td>
<td>69</td>
<td>97.1%</td>
<td>0</td>
</tr>
<tr>
<td>Local MTX</td>
<td>2</td>
<td>74</td>
<td>64.9%</td>
<td>4.1%</td>
</tr>
<tr>
<td>HIFU</td>
<td>1</td>
<td>16</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>HIFU + hysteroscopic suction curettage</td>
<td>1</td>
<td>52</td>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>Cervical ripening double-balloon catheterf</td>
<td>2</td>
<td>48</td>
<td>97.7%g,h</td>
<td>4.2%g,h</td>
</tr>
</tbody>
</table>

---

*Unless otherwise noted, data from reference 14.
*Women who did not need additional treatment
*Severe complications such as hemorrhage, hysterectomy
*11 women also had systemic MTX and hysteroscopy
*12 women also had systemic MTX and transvaginal resection
*34 women also had systemic MTX
*Reference 15
*16.

Abbreviations: D&C, dilation and curettage; HIFU, high-intensity focused ultrasound; MTX, methotrexate; UAE, uterine artery embolization.
surements, and monitoring for ma-
ternal symptoms such as bleeding or pelvic pain. It can take several months for a nonviable CSP to resolve sponta-
neously, and expectant management of nonviable CSP has been associated with development of a uterine arte-
riovenous malformation (AVM). Uterine AVM in this clinical context has been associated with persistent, se-
vure vaginal bleeding and may require umbilical artery embolization or even hysterectomy.

**What CSP treatment modalities have been reported?**

Surgical, medical, and minimally invasive therapies, as well as various combi-
 nations of such treatments, have been described, including hysterosc-
opy, laparoscopy, laparotomy, open surgery, transvaginal surgery, dilation and curettage (D&C, including both sharp and vacuum aspiration tech-
niques), uterine artery embolization (UAE), methotrexate (MTX) (both lo-
cal guided injection and systemic ad-
mistration), direct potassium chlor-ide (KCI) injection, needle-guided sac decompression, high-intensity fo-
cused ultrasound (HIFU), and use of balloon catheters, and combinations of these methods (Table 1).14-16

The optimal treatment is not known. Systematic reviews have been incon-
sistent with regard to identification of a single optimal CSP treatment modal-
ity that best balances procedural suc-
cess and risks. Data regarding optimal CSP therapy consist primarily of case series with varying levels of clinical experience, institutional capability, pro-
vider skill, and case complexity. Ran-
donized controlled trials comparing treatment approaches are limited, as are those comparing medical and sur-
gical approaches.

CSP treatment decisions are guided by a principal goal of preserving ma-
ternal health, followed by a secondary goal of preserving fertility when pos-
sible. Management decisions should be determined after considering preg-
nancy viability, gestational age, ma-
ternal health, future family planning wishes, physician skill and experience, and institutional resources. Preferred management may differ between in-
stitutions based upon resources, per-
sonnel, and clinical experience. Even with efforts to tailor treatment strate-
gies to individual patients and clinical presentations, there remains a sub-
stantial risk of complications with any management approach.

**What are the recommended treatment approaches for CSP?**

**SURGICAL TREATMENT**

Among surgical management options, transvaginal and laparoscopic CSP re-
section appear to have low complica-
tion rates.17-19 A potential advantage of these approaches is that the scar tissue can be excised and the surrounding myometrium reapproximated at the
time of CSP removal. It is unknown if this practice decreases risk of CSP reoccurrence.

D&C alone, without adjuvant treatments, has been associated with high complication rates, including hemorrhage and perforation, due to an inability to completely access and remove trophoblastic tissue outside of the endometrial cavity and because scar tissue contracts poorly after curettage. As with PAS, sharp curettage may sever deeply invading blood vessels, exposing the patient to ongoing bleeding. In addition to a high complication rate, additional treatment is reported to be required after 52% of D&C cases. It should be noted that the published literature incompletely distinguishes between sharp curettage and vacuum aspiration, which may provide different success and complication rates with CSP management. We suggest operative resection (with transvaginal or laparoscopic approaches when possible) or ultrasound-guided vacuum aspiration be considered for surgical management of CSP and that sharp curettage (D&C) alone be avoided (GRADE 2C).

While sharp curettage alone is not recommended as a primary CSP treatment, higher efficacy and lower complication rates have been reported with ultrasound-guided vacuum aspiration. Shirodkar placement as an adjunct to D&C has also been described, in which the cerclage suture is placed prior to D&C and only secured in the setting of hemorrhage to minimize bleeding.

Gravid hysterectomy is an alternative surgical option that may be considered for definitive management of CSP. This approach may be particularly appropriate for early second-trimester CSP presentations or for women who do not desire future fertility.

MEDICAL TREATMENT

When pursuing medical treatment of CSP, local or intragestational injection of MTX is a preferred approach, with or without accompanying systemic MTX. Standalone systemic MTX is not recommended due to a higher reported risk of complications. Although a small randomized trial of systemic versus local MTX demonstrated no difference in overall cure rates, reviews suggest a high risk of complications with intramuscular MTX alone, and local MTX appears to be a more effective approach. In a literature review by Cheung et al, of 96 cases of intragestational MTX for CSP, success was achieved in 73.9% after a single local MTX injection and increased to 88.5% after an additional local or intramuscular MTX injection. Intragestational injection is typically performed with a 20-gauge needle under ultrasound guidance using a transvaginal approach. Sac aspiration may be performed prior to injection to verify appropriate needle placement. Optimal dosing for local MTX injection ranges...
from doses of 1 mg/kg of maternal weight to 50 mg. Varying dosages of systemic MTX have been reported in management of CSP; in general, these dosages are comparable to those used for ectopic pregnancy. **We suggest intragestational MTX for medical treatment of CSP, with or without other treatment modalities (GRADE 2C). We recommend that systemic MTX alone not be used to treat CSP (GRADE 1C).**

When following women with CSP who have been treated medically, the gestational mass can take weeks to months to resolve. A transient increase in beta-hCG levels and CSP mass size can be observed after MTX therapy. One study of 22 women following local conservative CSP treatment reported a mean time to resolution of 88 days (range 26-177). An understanding of this anticipated posttherapy course may help to minimize unnecessary additional treatments. During the post-treatment observation period, patients should be monitored for concerning symptoms such as hemorrhage or uterine AVM development. Interval ultrasonographic surveillance may be helpful to observe for CSP resolution.

Intragestational KCl has also been described for treatment of CSP in a small number of cases. This approach may be particularly appropriate for management of CSP heterotopic pregnancies with a coexisting intrauterine pregnancy, as MTX exposure may have embryocidal or teratogenic consequences for the intrauterine cotwin. As with MTX, ultrasound-guided KCl injection can be accompanied by sac aspiration. Hysteroscopic and laparoscopic approaches for treating CSP heterotopic pregnancies have also been described.

**ADJUNCT TREATMENT OPTIONS**

UAE is a minimally invasive procedure that has been used in various combinations to treat CSP. It has been reported as a standalone procedure, as well as in combination with D&C, MTX, and hysteroscopy, which complicates comparisons between studies. UAE may be a uterine- and fertility-preserving procedure, although reported outcomes in the setting of CSP vary significantly, and its role as an adjunct to other management approaches requires further study.

Ultrasound-guided placement and inflation of balloon and Foley catheters to tamponade a CSP gestational sac complicated by bleeding or as a prophylactic measure has been reported. Limited experience shows that this technique may be well tolerated and efficacious, supporting a potential option that warrants further study.

Q | How should CSP be managed in women who decline treatment?

Women who decline treatment of a CSP should be counseled about risk of significant obstetric complications, including PAS, massive hemorrhage, uterine rupture, severe maternal morbidity, and potentially maternal death. Management of such cases should include a very high index of suspicion for PAS with appropriate antepartum management and delivery planning. Women should be counseled regarding signs and symptoms of preterm labor or any symptoms suggesting uterine rupture. Repeat cesarean delivery is recommended between 34 0/7 and 35 6/7 weeks of gestation. As with other medically indicated late preterm births, betamethasone administration is recommended prior to delivery. **In women who choose expectant management and continuation of a CSP, we recommend repeat cesarean delivery between 34 0/7 and 35 6/7 weeks of gestation (GRADE 1C).**

We recommend that women with a CSP be advised of the risks of another pregnancy.

Q | How does a history of a CSP impact future pregnancies?

Women can become pregnant after uterine-preserving management of a CSP, although there appears to be an increased risk for recurrent CSP and other severe maternal morbidities. High rates of complications and severe maternal morbidity, including PAS, recurrent CSP, gravid hysterectomy, and uterine rupture, have been reported. Women considering pregnancy after a CSP should be informed that there is a significant risk of recurrence and severe maternal morbidity. **We recommend that women with a CSP be advised of the risks of another pregnancy and counseled regarding effective contraceptive methods, including long-acting reversible contraception and permanent contraception (GRADE 1C).**
Although a short interval between successful conservative CSP management and subsequent pregnancy may increase risk of recurrent CSP or PAS, there is no consensus about how long to wait before attempting another pregnancy for women who desire another pregnancy after counseling regarding the risks. Some experts have recommended waiting 12 to 24 months before attempting to become pregnant again, although there is limited supporting evidence.

Given the increased risk of CSP recurrence, some advocate evaluation of the uterus and cesarean scar by saline infusion sonohysterography prior to a subsequent pregnancy. However, it is not clear whether the detection of a defect is associated with higher risks and should influence counseling regarding the advisability of another pregnancy. Interpregnancy repair or revision of a cesarean scar has been reported using a variety of surgical modalities. However, data are insufficient to support a benefit to this practice.

Should a woman with a history of a CSP become pregnant, close ultrasonographic monitoring is recommended to confirm the presence of an intrauterine pregnancy and to exclude recurrent CSP or PAS. An initial ultrasound examination is recommended on presentation to prenatal care, ideally before 8 weeks of gestation, to confirm a normal intrauterine location. Repeat cesarean delivery is recommended between 34 0/7 and 35 6/7 weeks of gestation, prior to the onset of labor. Betamethasone administration is recommended prior to anticipated late preterm delivery. The delivery team should be prepared for obstetric hemorrhage and the potential need for cesarean hysterectomy.

**Conclusion**
Due to high worldwide cesarean delivery rates, an increased incidence of CSP has been recognized. CSP can be difficult to diagnose in a timely fashion, and this diagnosis should be considered in women with a prior cesarean delivery who are undergoing early first-trimester ultrasonography. Several surgical and medical treatments have been described for this disorder, but at this time, optimal management remains uncertain. For this reason, an international registry has been created for providers to submit data on diagnosis, natural history, and management (https://csp-registry.com).

**Summary of Recommendations**

<table>
<thead>
<tr>
<th>Number</th>
<th>Recommendations</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>We recommend against expectant management of cesarean scar pregnancy.</td>
<td>1B</td>
</tr>
<tr>
<td></td>
<td>Strong recommendation, moderate-quality evidence</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>We suggest operative resection (with transvaginal or laparoscopic approaches when possible) or ultrasound-guided vacuum aspiration be considered for the surgical management of CSP and that sharp curettage (D&amp;C) alone should be avoided.</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Weak recommendation, low-quality evidence</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>We suggest intragestational MTX for medical treatment of CSP, with or without other treatment modalities.</td>
<td>2C</td>
</tr>
<tr>
<td></td>
<td>Weak recommendation, low-quality evidence</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>We recommend that systemic MTX alone should not be used for the treatment of CSP.</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Strong recommendation, low-quality evidence</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>In women who choose expectant management and continuation of a CSP, we recommend repeat cesarean delivery between 34 0/7 and 35 6/7 weeks of gestation.</td>
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</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
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<td>We recommend that women with a CSP be advised of the risks of another pregnancy and counseled regarding effective contraceptive methods, including long-acting reversible contraception and permanent contraception.</td>
<td>1C</td>
</tr>
<tr>
<td></td>
<td>Strong recommendation, low-quality evidence</td>
<td></td>
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</tbody>
</table>
A 45-year-old female presents to her primary care physician complaining of changes in her vulvar skin with intermittent irritation and some bleeding. She had recently experienced severe pruritus and white discharge which she treated with an over-the-counter antifungal cream for vulvovaginal candidiasis. However, her symptoms were only partially alleviated. On examination, she was noted to have thickening and wrinkling of the skin of the labia majora. Excoriations were seen.

The diagnosis is typically made based on history and physical examination. It is critical to obtain information about how the pruritus began, when the patient is scratching and rubbing with what. We have had patients report using items as extreme as a wire brush. Patients will often report that there is temporary relief from the pruritus with scratching or rubbing. In addition, patients may often complain of painful urination or defecation and sexual activity which is typically related to the excoriations that can occur as a result of repetitive scratching or rubbing. You should also collect information about potential inciting events as well as current vulvar hygiene practices such as the type of underwear, frequency of showers/baths, whether tight clothing is worn, and whether soaps or other feminine hygiene products are utilized on the vulvar skin as well as fragrance or dyes in detergents for clothing.

A wet mount or yeast culture should be performed to rule out candidiasis. You should also consider a biopsy if the patient does not improve with initial therapies, or the gross appearance is concerning. A tissue biopsy can help to rule out other causes of pruritus and skin changes such as lichen sclerosus, lichen planus, and pre-cancers or cancers of the vulva. It can also be provoked by metabolic conditions such as diabetes mellitus or iron deficiency anemia. These triggers then result in a cycle of itching and scratching that ultimately compromises the skin’s protective barrier and results in inflammation. The altered skin barrier also increases the risk for secondary infection.

Diagnosis
The diagnosis is typically made based on history and physical examination. It is critical to obtain information about when the pruritus began, when the patient is scratching and rubbing with what. We have had patients report using items as extreme as a wire brush. Patients will often report that there is temporary relief from the pruritus with scratching or rubbing. In addition, patients may often complain of painful urination or defecation and sexual activity which is typically related to the excoriations that can occur as a result of repetitive scratching or rubbing. You should also collect information about potential inciting events as well as current vulvar hygiene practices such as the type of underwear, frequency of showers/baths, whether tight clothing is worn, and whether soaps or other feminine hygiene products are utilized on the vulvar skin as well as fragrance or dyes in detergents for clothing.

A wet mount or yeast culture should be performed to rule out candidiasis. You should also consider a biopsy if the patient does not improve with initial therapies, or the gross appearance is concerning. A tissue biopsy can help to rule out other causes of pruritus and skin changes such as lichen sclerosus, lichen planus, psoriasis, high grade squamous intraepithelial lesions, and cancers. On histology, a tissue biopsy from a patient with lichen simplex chronicus will display thickening of epidermis (acanthosis) and hyperkeratosis. You may also see increased mitotic
activity without cellular atypia in the hyperplastic epithelium and a lymphocytic infiltrate within the dermis.²

Management (Table 1)

At the University of Michigan Center for Vulvar Diseases, we utilize a multi-step approach to treat this diagnosis. It begins with education on appropriate vulvar care which includes keeping the area dry, avoiding potential irritants such as soaps, detergents, and fabric softener with dyes or fragrance, wearing cotton underwear, and avoiding tight clothing. We also recommend against using products with benzocaine given the risk of developing contact dermatitis from this medication.³ In addition, we advise our patients to utilize vulvar comfort measures focused on reducing scratching or rubbing such as tap water soaks in tepid water followed by application of a barrier to protect the skin (e.g. petroleum jelly). Patients are encouraged to wear cotton gloves at night to prevent scratching and wear a nightgown without underwear or cotton pajama pants with a string.⁴ Our treatment protocol also includes using medications to help with nighttime pruritus such as amitriptyline or gabapentin or hydroxyzine. Of note, if the patient complains of an allergy. Do not forget to utilize an antifungal medication, such as oral fluconazole, if candida is discovered as part of your workup. In some cases, a patient may require a longer course of topical corticosteroids for maintenance. In addition, recurrence is common even with complete resolution.⁵ Although, this inflammatory dermatitis does not increase the risk of malignancy, it can have significant ramifications for a patient’s quality of life.⁶ Thus if a patient is not responding to the treatment regimen, consider referral to a vulvar specialist.

Table 1

<table>
<thead>
<tr>
<th>Severe itch-scratch cycle treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nighttime medications; some aid with sleep</strong></td>
</tr>
<tr>
<td>Amtryptiline 10-25 mg po 2 hours prior to bedtime, may increase by 10-25 mg weekly up to a max dose of 150 mg per day. CAUTION: Start at 10 mg for elderly patients, avoid alcohol use. taper dose when discontinuing or Gabapentin 300 mg po nightly for 3 days, then BID for 3 days, then TID for 3 days; then the patient may increase by 300 mg each week up to a max dose of 1200 mg po TID. The dose taken at one time should not exceed 1200 mg. CAUTION: Taper dose when discontinuing or Hydroxyzine 25 mg po qhs as needed; this can be increased if needed to 50 mg po qhs. If necessary, the patient may use 25 mg po q 6 to 8 hours pm.</td>
</tr>
<tr>
<td><strong>Systemic corticosteroid burst</strong></td>
</tr>
<tr>
<td>Prednisone 40 mg po in the morning for 5 days then 20 mg po in the morning for 10 days. If oral Prednisone fails, consider Triamcinolone 1 mg/kg intramuscular injection into the gluteus muscle monthly up to 3 months. Do not exceed 80 mg per injection.</td>
</tr>
<tr>
<td><strong>Antibiotic for secondary inflammation</strong></td>
</tr>
<tr>
<td>Cefadroxil 500 mg po twice daily for 10 days or Clindamycin 300 mg po twice daily for 10 days if unable to use cefadroxil</td>
</tr>
<tr>
<td><strong>Vulvar comfort measures</strong></td>
</tr>
<tr>
<td>Nightgown without underwear or cotton pajama pants with string</td>
</tr>
<tr>
<td>Cotton gloves at night</td>
</tr>
<tr>
<td>Tap water soaks in tepid water after bath and then apply petroleum jelly</td>
</tr>
<tr>
<td><strong>Topical corticosteroids</strong></td>
</tr>
<tr>
<td>Clobetasol propionate ointment 0.05% at bedtime for 1 month then transition to Triamcinolone acetonide ointment 0.1% at bedtime or twice daily for 1-3 months based on clinical response or Tacrolimus 0.03% or 0.1% alternating days with topical corticosteroid CAUTION: Tacrolimus can cause burning</td>
</tr>
<tr>
<td><strong>Anti-fungal if positive yeast culture</strong></td>
</tr>
<tr>
<td>Fluconazole 150 mg po weekly for 2 to 3 weeks CAUTION: Do not use if patient on amitriptyline or topical antifungals</td>
</tr>
</tbody>
</table>

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SOURCE: https://umich.app.box.com/s/fj6rs7hbn3vq8t61hp77qyip5hnedk4
Lessons learned from postmenopausal hormone therapy

by BOB KRONEMYER

The timing of postmenopausal hormone therapy (HT) significantly impacts coronary risk and overall benefit-to-risk profile, according to an overview of Women’s Health Initiative (WHI) results in the journal Menopause.

WHI evaluated oral conjugated equine estrogens (CEE) taken with or without medroxyprogesterone acetate (MPA) for prevention of chronic disease in postmenopausal women aged 50 to 79 at enrollment. The key findings were that women younger than age 60 or no more than 10 years since the onset of menopause achieved better outcomes from HT than older women or those further past the menopausal transition. A total of 16,608 women with an intact uterus were randomized to either CEE + MPA therapy or placebo for a median of 5.6 years, while 10,739 women with hysterectomy were randomized to either CEE-alone therapy or placebo for a median of 7.2 years. Both cohorts, with a combined initial average age of 63, have been followed for 18 years.

“We find that there are significant age-related trends for coronary heart disease and for all-cause mortality with HT,” said JoAnn Manson, MD, DrPH, NCMP, a professor of medicine at Harvard Medical School, who is the principal investigator of the Boston site of WHI. “This is particularly true in the estrogen-alone trial. Estrogen therapy had more favorable effects on heart disease and all-cause mortality among younger and more recently menopausal women.”

For example, women who were younger than age 60 had about a 40% lower risk of heart attack or coronary heart disease with estrogen-alone therapy compared to no reduction or a slight increase in risk among women aged 70 and older. Similarly, for all-cause mortality, women below age 60 had roughly a 30% risk reduction, whereas older women did not have a reduction in mortality risk.

Comparable results were observed for the number of years since menopause. “The women who were within 10 years of the onset of menopause tended to have more favorable results from HT on coronary heart disease and all-cause mortality than women who were more than 10 years past the onset of menopause,” Dr. Manson told Contemporary OB/GYN.

In addition, the combination of CEE and MPA was linked to an approximately 24% to 30% increased risk of breast cancer, with risk elevation emerging after 4 to 5 years of treatment. “But estrogen alone was not associated with an increased risk of breast cancer; in fact, with long-term follow-up there was close to a 20% reduction,” Dr. Manson said.

Women younger than age 60 with prior bilateral oophorectomy particularly benefited from estrogen-alone therapy, resulting in a 32% reduction in all-cause mortality over long-term follow-up.

The overview underscores the importance of considering a woman’s age and time since menopause for clinical decision-making about the use of hormone therapy.

“Systemic HT has an acceptable, even favorable, safety profile for menopause management when initiated among healthy women who are younger or recently menopausal and not at elevated risk for cardiovascular disease or breast cancer,” Dr. Manson said. However, she believes more research is needed on the clinical effects and risk/benefit profiles of other formulations of HT therapy, particularly transdermal estradiol and low-dose products.

DISCLOSURES Dr. Manson reports no relevant financial disclosures.

Bob Kronemyer is a freelance writer for Contemporary OB/GYN.

SOURCE Manson JE, Chlebowski RT, Stefanick ML et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women’s health initiative randomized trials. JAMA 310 (13), 1353-1368 (2013).
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Did contraindicated hysterectomy lead to HIT and limb loss?

**Factual Summary**
On April 2, 2014, the patient was seen in the gynecology outpatient clinic by Defendant OB. She had a history of fibroid uterus, which she complained caused her urinary tract irritative symptoms and back pain, and dilated pelvic vessels in the left adnexal region, obscuring the left ovary. Magnetic resonance imaging (MRI) was ordered for evaluation. A 9.9-cm exophytic fibroid arising from the posterior uterine body with focal cystic degeneration was seen.

On Sept. 22, 2015, the patient underwent a supracervical hysterectomy, right salpingectomy, lysis of adhesions, and control of massive pelvic hemorrhage. By way of indications for the surgery, the Defendant OB documented that the patient was a 45-year-old PI with a history of a symptomatic fibroid uterus who desired definitive treatment with hysterectomy. Intraoperatively, he described that the uterus was 7-to 8-weeks in size and there was a large, pedunculated fibroid on the fundus, which measured 10 X 12 X 8 cm with necrosis. Intraoperatively, the Defendant OB noted that when attempting to remove the lap pad that had been packed into the right pelvis, there was noted to be “massive amounts of venous bleeding.” The source of the bleeding was not well visualized and an intraoperative vascular consult was obtained from the Defendant Vascular Surgeon. This surgeon noted that the patient was bleeding “profusely from pelvic veins” and that “the patient was hypotensive, lost several liters of blood, there was bleeding from the deep pelvic veins as well as uterine veins on the right side. This was very difficult to control.” Eventually, hemostasis was achieved. The patient was hypotensive, received pressors, and had an estimated blood loss of 4.5 L. At deposition, the Defendant OB explained that the Ligasur “slipped” off the uterine vein as he was ligating.

The patient was hypotensive, received pressors, and had an estimated blood loss of 4.5 L.

Upon arrival to the Surgical Intensive Care Unit (SICU), the patient was hemodynamically unstable and, as such, it was decided to administer packed red blood cells and fresh frozen plasma and to continue with aggressive resuscitation. The resident described that the patient was stable and was to receive fentanyl for pain control and subcutaneous heparin for deep vein thrombosis (DVT) prophylaxis. That was held until the afternoon of Sept. 23, secondary to “massive bleeding.” The patient’s platelet count on Sept. 22 was 196,000 (Hgb) and hemoglobin and hematocrit (Hct) were 10.4/31.4.

On Sept. 23, 2015, the gynecology service noted that the patient was stable. Heparin was given at 2:27 p.m. on Sept. 24, the patient was described as critically ill, and she was undergoing resuscitation with volume and products. The resident noted that the patient denied chest pain, shortness of breath, nausea, vomiting, lower extremity pain, or calf tenderness. The resident’s plan included re-starting subcutaneous heparin for DVT prophylaxis as the patient was at high risk for DVT. The patient was seen by the Defendant OB, who agreed with the resident’s plan of care. DVT prophylaxis included 5000 units of subcutaneous heparin, sequential circumferential compression devices, and having the patient out of bed and ambulating as tolerated.

*Andrew I Kaplan, Esq* is a partner atAaronson, Rappaport, Feinstein & Deutsch, LLP and a regular contributor to this column.
Heparin was given at 6:34 a.m.; 2 p.m.; and 10 p.m. On Sept. 23, the patient’s platelet count dropped to 128 and then to 100 (HGB/HCT 9.5/27.3), and on the Sept. 24 the platelet count dropped to 82 and the HGB/HCT to 8.5/24.5.

On Sept. 25, 2015, the SICU resident noted no acute events overnight and that the patient was in no apparent distress. The patient’s subcutaneous heparin was to be 7500 units every 8 hours and she was to undergo a DVT sonogram. The study was interpreted as being negative for any evidence of acute DVT. The patient was transferred to the floor. The Defendant OB noted that the patient would be discharged home on enoxaparin sodium for up to 6 weeks. The patient’s morning dose of heparin was held, and doses were given at 3:08 p.m. and 10:54 p.m. Her platelet count dropped to 79,000 and Hgb/Hct was 7.3/21.3 (as of 11:00 p.m. on Sept. 24).

On Sept. 26, the gynecology resident noted that the patient denied light-headedness, shortness of breath, and/or chest pain. No labs were repeated on that day. On Sept. 27, 2015, the resident examined the patient and noted that she was doing well and ready to be discharged later that evening. The patient denied chest pain, shortness of breath, and was ambulating without difficulty. Her platelet count that evening was 133,000 and H/H was down to 6.4/18.5. An enoxaparin sodium injection was given at 1:00 p.m.

The next day, the patient reported swelling in her legs and that they felt tight and sore with walking. At 12:21 a.m., she was seen by the Defendant OB who noted that the patient felt light-headed at times but she denied chest pain and/or shortness of breath and was able to ambulate well. Hgb/Hct was 6.5/19 (critical values) and platelet count was 169,000. Enoxaparin sodium injection was given at 9:30 a.m.

The patient failed to appear for her Sept. 30, 2015, follow-up visit in the gynecology clinic. She testified that the reason she did not show up was because she was in too much pain and unable to walk. On Oct. 7, 2015, the resident called the patient regarding her missed post-operative appointment. The patient did not answer the phone and a voice mail message was left. The resident called the patient on Oct. 9 and, again, a message was left asking that the patient call back. On Oct. 14, 2015, the resident spoke to the patient in the presence of the Defendant OB. The patient advised that she had been admitted to another hospital with bilateral DVTs and had undergone an above-the-knee amputation of the left lower extremity. She stated that she had continued to take the enoxaparin sodium daily after discharge.

**Codefendant hospital admission**

On Oct. 3, 2015, the patient presented to the codefendant hospital and was admitted for bilateral leg swelling and pain. In the emergency department, she was found to be anemic (Hgb 6.4) and thrombocytopenic (platelets 16). A hematology consult noted the patient’s clinical findings were concerning for HIT (heparin-induced thrombocytopenia) and that she was in need of argatroban. A CT scan came back and showed multiple DVTs in the femoral vein and lower left leg. Thereafter, an infusion of argatroban was started.

On Oct. 6, 2015, the patient was seen by a surgeon. Bilateral leg swelling was noted, left greater than right, with tenderness to palpitation. The patient was experiencing severe pain on passive extension of her left foot. The recommendation was for venous mechanical thrombectomy as soon as possible. On the same day, the HIT assay came back positive as did the serotonin release assay. The next day, a resident was called as the patient was having severe pain in her left lower extremity with burning. The surgeon advised that pain with burning sensation after thrombectomy was common due to re-perfusion. The Vascular Service was called to evaluate the patient’s left foot and the service opined that the patient had phlegmasia cerulea and needed an emergency amputation.


**The patient underwent an above-the-knee amputation (AKA) on Oct. 7, 2015.**

**Allegations**

The plaintiff alleged that she suffered left AKA; multiple surgeries to both legs; wheelchair dependence; needed physical, occupational, and psychological therapy; suffered emotional distress; and was unable to perform the activities of daily living. She asserted that the defendants were negligent in performing unnecessary hysterectomy as the patient was asymptomatic at the time of
surgery; that the patient was at high risk for clot formation given prior DVT and her body mass index, further contraindicating surgery. She also alleged that the Defendant OB failed to properly control bleeding during the surgery, resulting in massive hemorrhage and significantly increasing the risk of clot burden postoperatively; that the defendants failed to consider, diagnose or treat HIT during the patient’s admission; failed to consult vascular surgery before or after the surgery; and that the patient was negligently discharged from defendant Hospital with undiagnosed and untreated critical anemia and DVTs, despite complaints of leg pain and swelling on the date of discharge.

**Discovery**

At his deposition, the defendant OB pointed out that the patient had confirmed dilated vessels preoperatively and was at increased risk for bleeding, which was discussed as part of her consent. He disagreed that she was asymptomatic preoperatively and refuted the suggestion that menopause or medical management were acceptable alternatives to surgery. The “slip” of the Ligasur was unfortunate but unpreventable and properly managed with tamponade and consult with a vascular surgeon. He disagreed that the patient was suffering from HIT during her admission, testifying that her initial diminution in platelet count was secondary to her significant intraoperative bleeding, and pointing to her escalating platelet count in the 2 days prior to discharge. The patient’s leg swelling and edema at the time of discharge were secondary to third-spacing and hemodilution, and there was no complaint or evidence of pain at that time. The patient failed to appear for her outpatient visit or call, at a time when they may have been able to intervene and save her leg. He conceded he was not an expert on coagulopathy but did not consult a vascular surgeon before the surgery or with regard to the patient’s post-operative anticoagulation.

Our obstetric expert felt that, pre-operatively, there was little documentation regarding plaintiff’s history of having had a DVT in 2008 including what, if any, work-up the plaintiff underwent. He opined that the plaintiff was an appropriate surgical candidate for the hysterectomy. He further noted that other medications were not good alternatives to surgery as they would not have addressed the plaintiff’s complaint of pain and/or could have caused early menopause. The intra-operative bleeding encountered was a known and accepted risk of surgery. He did not believe that there was strong evidence of HIT prior to the plaintiff’s discharge and indicated that the plaintiffs low platelet count was reasonably attributable to the blood loss that occurred intra-operatively. Further, plaintiff’s platelet count was trending upward by the time she was discharged. He was critical, however, of discharging the patient with critical anemia and complaints of leg swelling and discomfort without further evaluation.

Our hematology expert opined that it generally takes 5-10 days for a Heparin sensitivity reaction to reveal itself. With a credible alternate explanation and rising platelet count on the 27th and 28th, he would not have considered HIT. He felt it was appropriate to discharge the patient on Sept. 28 despite her anemic labs as they were stable, to be expected after her blood loss and resuscitation, and she was to follow up in the clinic in a few days. He felt her HIT started after she was discharged.

**Result**

We moved for dismissal of the matter, primarily on the basis that the patient did not have HIT during the defendant hospital admission and it developed only after her discharge. Plaintiff opposed with experts of her own in ob/gyn and hematology. Given the high-exposure nature of the case, the decision was made to mediate the matter while the motions were pending and we were able to resolve it for less than half of plaintiff’s initial settlement demand.

**Analysis**

This case presented a number of challenges that would have made it difficult to defend before a lay jury. First and foremost, the defense begins “behind the eight ball” in having to explain how a young woman could present for hysterectomy and wind up losing her leg. If there were one or two focused issues to defend medically, that might have made it more tenable. However, the constellation of decisions and issues to defend – pre-op workup, consent, intra-op complication, anticoagulation management, decision to discharge, follow-up – made it increasingly risky to put in the hands of a lay jury when the known outcome was limb loss. Ultimately, defendant OB preferred to resolve the case if the opportunity arose to do so reasonably, and once it did, we acted.

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PARTNER PERSPECTIVES

Cervical Cancer Screening in Australia
A new policy may undermine prevention

By Brian Cox, MBChB, PhD, and Michael Randell, MD

Beginning in December 2017, the Australian Government implemented changes in its National Cervical Screening Program (NCSP). These changes came from an assessment of potential screening pathways, tests, and intervals called the Renewal.1 Previously, women between the ages of 18 and 70 years were screened for cervical cancer using a cytologic (Papanicolaou [Pap]) test every 2 years. These changes, however, meant shifting to human papillomavirus (HPV) testing alone every 5 years, including for women as young as age 25 years. A study by Cox and Sneyd to estimate the impact of the changes on cancer prevention predicted an increase in the incidence rate of cervical cancer with primary HPV screening every 5 years compared with prior cytologic screening methodology.2 In addition, the study predicted this Renewal policy would result in cervical cancer overdiagnosis, increase unnecessary colposcopy referrals, and delay reporting results to patients. In this report, we review findings from that study and discuss their relevance to cervical cancer screening strategies in the United States based on recent evidence that shows potential harmful consequences for women derived from the Australian experience.

Renewal policy of the Australian National Cervical Screening Program

The Renewal policy of the Australian NCSP represents a valuable opportunity to assess the true impact of adopting HPV testing alone every 5 years.1 The policy was based on simulation models that do not accurately reflect the impact HPV testing every 5 years may have on public health in Australia.2 The models used detection sensitivity, defined as the probability that a test will detect its target: cervical intraepithelial neoplasia (CIN). The potential for HPV testing to preferentially detect nonprogressive CIN was not assessed, however, and would require measurement of cervical cancer incidence between screening events. The simulation models assumed that HPV testing has greater screening sensitivity than cytology based on the probability that the test detects the subset of disease that will progress to life-threatening invasive cancer when it is present and that reliance on HPV testing will decrease cervical cancer incidence and mortality. Mere HPV detection does not predict the fate of an infection (ie, whether it will spontaneously resolve, cause a cancer lesion, or persist with no clinical consequences). Not distinguishing among these outcomes hinders accurate prediction of the likelihood of cancer.

Risk of increasing cervical cancer incidence

Several clinical studies have compared HPV testing with cytology screening, yielding mixed results.3–7 A rigorous analysis was conducted to determine the relative impacts of HPV testing and cytology on public health using results from an earlier randomized health services study on cervical cancer screening in Finland.2,5 This study did not introduce the analytic bias of excluding women previously diagnosed with CIN detected by cytology, which reduces the potential pool of cytology-detectable lesions prior to randomization, thus biasing the comparison against cytologic screening.
Cytologic screening and primary HPV testing were evaluated in the context of well-accepted estimates of the effects of screening frequencies on cervical cancer incidence combined with published age-specific data on the frequency with which women are actually screened. The study showed that women age 30 to 64 years screened under the prior (every 2 years) cytologic protocol would be expected to have a cervical cancer incidence of 7.5% relative to the 100% incidence expected in unscreened women. Anticipated reductions in cervical cancer risks with cytology every 2 years and HPV testing every 5 years would be approximately 93% and 84%, respectively (Figure 1). Thus, the risk of cervical cancer would increase with the new HPV testing protocol versus the prior cytology screening program.

Women differ in their adherence to screening protocols. Based on data from the Australian NCSP, 17% of Australian women age 20 years and older had not been screened in the previous 5 years or had never been screened. The estimated proportions without screening or with more than 10 years between screening tests varied significantly by age: from 9% to 16% in women age 30 to 54 years and from 21% to 34% in those age 55 to 69 years. When applying the relative protection from screening to the different screening frequencies of different age groups, the cervical cancer risks for women age 30 to 69 years were reduced by only 67% with HPV testing every 5 years versus 76% with cytologic screening every 2 years.

The overall incidence of cervical cancer in women in Australia was predicted to increase by 39% with HPV testing every 5 years versus cytologic screening every 2 years as a result of screening inadequacy. This translates to an additional 222 women developing cervical cancer each year for the next 10 years. For relatively screening-compliant women with less than 10 years since their last negative test, the new HPV testing protocol was predicted to increase the annual incidence of cervical cancer in women screened to 121% of that attained with the prior cytologic screening protocol. Even if the new protocol resulted in a 10% increase in the proportion of women screened, the overall incidence of cervical cancer in

These findings should prompt additional research to further evaluate the success of various screening protocols at providing protection against cervical cancer.

Figure 1. Estimated percentage reduction in cervical cancer incidence

<table>
<thead>
<tr>
<th>Age adjusted 30-69 years</th>
<th>2 year cytology</th>
<th>5 year HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Cancer Incidence Reduction (%)</td>
<td>93</td>
<td>84</td>
</tr>
</tbody>
</table>

Australia would be expected to rise 30% due to screening inadequacy. Based on these figures, the transition to the HPV testing protocol would be detrimental to women in the absence of better evidence of at least equivalent public health outcomes.

Overdiagnosis and treatment delays

The Renewal policy includes HPV testing in women age 25 to 69 years and is based on high estimates of detection sensitivity. Because the vast majority of HPV infections regress spontaneously within 2 years, the increased sensitivity of HPV testing would amount to overdiagnosis, which in turn would result in overtreatment (ie, use of colposcopies). The study findings suggest that this overtreatment would increase the treatment burden on women who would not have ultimately progressed to invasive cancer.

It is important to note that since implementation of the Renewal policy, a colposcopy clinic in Australia reported that the volume of referrals has increased sixfold. This increase likely stems from increased sensitivity of the HPV test combined with its inability to predict which lesions will progress to cancer. The increased colposcopy volume prolonged the waiting times for women to be seen in the colposcopy clinic to approximately 12 months. Overdiagnosis and unnecessary colposcopies and biopsies could harm a woman’s fertility or ability to carry a child to term.

These findings should prompt additional research to further evaluate the success of various screening protocols at providing protection against cervical cancer. Based on lack of conclusive evidence on the most protective screening program, it would be advisable to implement a cotesting screening protocol, during which time the information lacking to assess the effectiveness of HPV testing on reducing cervical cancer compared with the prior cytologic protocol could be collected.
findings of the study analysis do not support lengthening the cervical cancer screening interval, especially in conjunction with a change in testing method.²

Identifying a preferred screening option for cervical cancer

Human papillomavirus testing is often used as an adjunct to cytologic screening, a strategy known as cotesting.⁸ A debate is currently under way as to the best method for cervical cancer screening. Screening with an HPV test alone was shown to be less effective than cotesting in the largest real-world retrospective study, showing that 1 of 5 cases of cervical cancer were missed with HPV screening alone.¹¹

Joint guidelines from the American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology, and American Cancer Society issued in 2012 recommend cytologic screening every 3 years in women younger than age 30 years and cytologic screening every 3 years or cotesting every 5 years in women age 30 years and older.¹² Cotesting is the preferred method, and HPV testing alone every 5 years is discouraged. Subsequent 2016 guidance from the American College of Obstetricians and Gynecologists also recommends cotesting as the preferred screening method.¹³ More recently in 2018, the US Preventive Services Task Force endorsed cytologic screening every 3 years, HPV testing every 5 years, and cotesting as acceptable options.¹⁴

Implications for US screening

The Renewal policy was partially driven by the high HPV vaccine uptake in Australia relative to most countries, including the United States.¹⁵ Human papillomavirus testing is most efficacious in screening cohorts with complete HPV vaccine coverage.¹⁶ HPV infection occurs primarily in young adulthood, however, and vaccination after infection does not reduce risk of cervical cancer. Therefore, vaccination will provide no reduction in risk for most women currently age 30 years or older. Cotesting is the best test method in populations of variable vaccine uptake across all age groups.¹³ Unvaccinated women who are screened with the HPV test tend to have more “false positives” versus those screened with cotesting.¹⁷

Despite differences in healthcare programs between the United States and Australia, which has a universal healthcare system, the cervical cancer incidence rates are comparable.¹⁸,¹⁹ For Australia, the 2015 age-adjusted incidence rate for cervical cancer was 6.9 cases/100,000 women per year.¹⁸ For the United States, the 2012–2017 age-adjusted incidence rate of cervical cancer was 7.3 cases/100,000 women per year.¹⁹ These incidence rates suggest that similar factors may influence success in cervical cancer screening between the two countries and that lessons learned from the Australian experiment can provide cautionary guidance.

Based on the study analysis of Australia’s Renewal policy, findings from previous studies, as well as concerning implications for both healthcare providers and patients, adoption of HPV testing alone every 5 years is not advisable in any country, including the United States.

Other factors that could limit the efficacy of HPV screening should be considered in addition to increased colposcopies and the associated costs demonstrated in the Australian study.²⁰ There is currently a lack of healthcare provider support in the United States for HPV primary screening because the impact on clinical practice has not been rigorously studied. For example, the psychosocial impact of HPV screening on cervical cancer prevention is not understood.²¹ Changes in clinical practice and screening strategy would require significant investment in patient reeducation and may negatively affect testing compliance, which would contribute to increased cervical cancer incidence.

Based on the study analysis of Australia’s Renewal policy, findings from previous studies, as well as concerning implications for both healthcare providers and patients, adoption of HPV testing alone every 5 years is not advisable in any country, including the United States. The current accepted strategy of cytology for women age 21 to 29 years and cotesting for those age 30 to 65 years should continue to ensure the best possible protection and compliance among both healthcare providers and their patients, and ultimately guarantee what is best for women.

Note: The study on HPV screening, invasive cervical cancer, and screening policy in Australia is not affiliated with Hologic and was conducted independently.

References


Authors’ Biographies

Dr. Brian Cox is a medical epidemiologist and public health physician with specific training in cancer screening and epidemiology. He was also the New Zealand representative to the International Cancer Screening Network of the National Cancer Institute for over 20 years. Dr. Cox was involved in the design and establishment of the National Cervical Screening Program (NCSP). He also established the independent monitoring groups of the national cervical and breast screening programs of New Zealand and was their inaugural chair. Dr. Cox is Director of the Hugh Adam Cancer Epidemiology Unit of the Department of Preventive and Social Medicine of the Dunedin School of Medicine.

Dr. Michael Randell is a Board-Certified Obstetrician and Gynecologist in a private practice in Atlanta, Georgia and on the Medical Staff at Emory Saint Joseph’s Hospital. He earned his Bachelor of Science degree from Emory University in Atlanta and received his Medical degree with research distinction from the University of Miami School of Medicine in Miami, Florida. Dr. Randell is an expert in laparoscopic and robotic gynecologic surgery. His research interests include managing cancer during pregnancy, the effects of barometric pressure changes on the initiation of labor, and the treatment of atypical Pap tests have led to award winning presentations at scientific meetings. Dr. Randell is a Diplomate of the American Board of Obstetrics and Gynecology and the National Board of Medical Examiners. He is also a Fellow of the American College of Obstetricians and Gynecologists.