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Treatment of Urogenital Symptoms in Individuals With a History of Estrogen-dependent Breast Cancer

Committee on Clinical Consensus–Gynecology. This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Clinical Consensus – Gynecology in collaboration with committee member Betty Suh-Burgmann, MD, and liaison Elizabeth Evans, MD

SUMMARY

With an estimated 3.8 million breast cancer survivors in the United States, obstetrician–gynecologists often are on the front lines of addressing survivorship issues, including the hypoestrogenic-related adverse effects of cancer therapies or early menopause in survivors (1). Although systemic and vaginal estrogen are used widely for symptomatic relief of genitourinary syndrome of menopause in the general population, among individuals with a history of hormone-sensitive cancer, there is uncertainty about the safety of hormone-based therapy, leading many individuals with bothersome symptoms to remain untreated, with potential negative consequences on quality of life (2). An effective management strategy requires familiarity with a range of both hormonal and nonhormonal treatment options, knowledge about the pharmaceutical mechanisms of action, and the ability to tailor treatment based on individual risk factors. This clinical consensus document was developed using an a priori protocol in conjunction with two authors specializing in urogynecology and gynecologic oncology. This document has been updated to review the safety and efficacy of newer hormonal treatment options as well as nonhormonal modalities.

BACKGROUND

Purpose

With an estimated 3.8 million breast cancer survivors in the United States, obstetrician–gynecologists often are on the front lines of addressing survivorship issues, including the hypoestrogenic-related adverse effects of cancer therapies or early menopause in survivors (1). The term *genitourinary syndrome of menopause* (GSM) will be used in this document to refer to a constellation of symptoms that relate to hypoestrogenic effects on the genital epithelium, such as genital dryness, burning, and irritation; potential downstream effects of vulvar and vaginal atrophy such as dyspareunia; urinary symptoms such as urgency or dysuria; and recurrent urinary tract infections (3). Although systemic and vaginal estrogen are used widely for symptomatic relief of GSM in the general population, among individuals with a history of hormone-sensitive cancer, there is uncertainty about the safety of hormone-based therapy, leading many individuals with bothersome symptoms to remain untreated, with potential negative consequences on quality of life (2). An effective management strategy requires familiarity with a range of both hormonal and nonhormonal treatment options (Table 1), knowledge about the pharmaceutical mechanisms of action, and the ability to tailor treatment based on individual risk factors. This document has been updated to review the safety and efficacy of newer hormonal treatment options as well as nonhormonal modalities.

The American College of Obstetricians and Gynecologists recognizes and supports the gender diversity of patients who seek obstetric and gynecologic care, including people who are cisgender, transgender, gender nonbinary, or otherwise gender expansive. Its goal is to use language that is inclusive of gender-diverse individuals. When describing research findings, this document uses the gender terminology reported by the investigators. Therefore, this document uses the terms "woman," "women," "patient," and "individual." The American College of Obstetricians and Gynecologists advocates for inclusive, thoughtful, affirming care, including the use of language that reflects a patient's identity.

Epidemiology

On average, more than 250,000 women will be diagnosed with invasive breast cancer in the United States each year (4). The vast majority of cancers are hormone receptor–positive, with 80% demonstrating estrogen receptors and 65% demonstrating progesterone

Table 1. Nonhormonal and Hormonal Treatment Options		
Formulation	**Composition**	**Dosages**
Nonhormonal options		
Lubricants	Water-, silicone-, and polycarbophil-based products	See product labeling
Moisturizers	Hyaluronic acid Polyacrylic acid Polycarbophil-based vaginal moisturizer	5 mg daily for 2 weeks, then 3–5 times per week 3 g daily 2.5 g 3 times/week
Vaginal suppositories	Vitamin E Vitamin D	30–200 international units 1,000 international units
Lidocaine	4% aqueous lidocaine	Fully saturated cotton ball applied to the vulvar vestibule for 3 minutes
Hormonal options		
Vaginal insert	Prasterone*	One 6.5-mg vaginal insert once daily
Vaginal cream	17β-estradiol†	The usual dosage range is 1 to 4 g (marked on the applicator) daily for 1 or 2 weeks, then gradually reduced to one-half initial dosage for a similar period; a maintenance dosage of 1 g, 1 to 3 times a week, may be used after restoration of the vaginal mucosa has been achieved‡
Vaginal cream	Conjugated equine estrogen	• Evidence-based regimen: twice weekly administration of 0.5 g intravaginally (eg, Monday and Thursday) for treatment of moderate-to-severe dyspareunia • Dosage regimens of 1 g every night for 2 weeks, then twice a week or 0.5 g twice a week are commonly used‡§
Vaginal ring	17β-estradiol	7.5 micrograms/day for 90 days
Vaginal tablet or insert	Estradiol hemihydrate	• 10 micrograms/day for 2 weeks, then 10 micrograms/day 2 times a week • A vaginal insert containing 4 micrograms is available, although not used in included studies
Vaginal cream	Testosterone	• 300 micrograms or 150 micrograms applied daily for 28 days • 300 micrograms or 150 micrograms applied daily for 2 weeks, then 3 times a week

*The product label contains the following warning and precaution for those with a current or past history of breast cancer: "Estrogen is a metabolite of prasterone. Use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer. [It] has not been studied in women with a history of breast cancer." Additional data have been published on this population since the U.S. Food and Drug Administration approval of this medication.

†Known, suspected, or history of breast cancer is listed as a contraindication in the product label.

‡U.S. Food and Drug Administration–approved dosages of conjugated estrogen and estradiol creams may be higher than dosages commonly used in clinical practice.

§Study protocol: cyclic administration of 0.5 g intravaginally (daily for 21 days then off for 7 days) for treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

receptors. Although the overall median age at diagnosis is 62 years, 30% of cancers will be diagnosed in women younger than 50 years of age and 7% will be diagnosed in those younger than 40 years of age (5). Although the likelihood of having a hormone receptor negative breast cancer is higher for premenopausal individuals, the majority of breast cancers in premenopausal individuals are still hormone receptor–positive.

Endocrine therapy is a central component of treatment for those with hormone receptor–positive cancers. Following local management of early-stage cancers, most premenopausal individuals are treated with at least 5

years of tamoxifen, whereas postmenopausal individuals are commonly treated with up to 10 years of an aromatase inhibitor (AI). Tamoxifen acts as a selective estrogen antagonist in the breast, blocking estrogen at the receptor level, whereas AIs block peripheral estrogen biosynthesis from androstenedione and testosterone. Both forms of endocrine therapy are associated with GSM resulting from low estrogen levels. Although symptoms related to tamoxifen may be more pronounced owing to patient age, estrogen levels for those on AIs are lower than levels typically associated with menopause. Because of their mechanisms of action, the effects of exogenous estrogens on breast tissue would be expected to be blocked in those taking tamoxifen but not in those taking AIs.

Traditionally, oral or transdermal estrogen is used to treat systemic menopausal symptoms such as hot flushes and night sweats and for prevention of postmenopausal osteoporosis, whereas vaginal estrogen is used to treat urogenital symptoms. Although systemic estrogen also can be used to treat GSM, its use is generally considered contraindicated in individuals with a history of hormone receptor–positive breast cancer based on the potential for systemic estrogen to increase the risk of recurrence. Therefore, this document focuses on the use of vaginal estrogen and other local vaginal treatment options.

Health Inequities

Many of the data on the use of nonhormonal and hormonal approaches are overwhelmingly from White study participants. When demographic data were reported, most studies lacked racial and ethnic diversity, which could limit their generalizability. Although studies specifically evaluating disparities in the treatment of GSM in those with a history of breast cancer are lacking, the average age of diagnosis of breast cancer is slightly younger in Black women (56 years) when compared with White women (59 years) (6), suggesting that endocrine therapy may result in more severe symptoms among Black women, because younger women may experience a greater change in estrogen levels. Lower initiation and adherence rates to endocrine therapy have been reported among Black, Hispanic, and Asian women compared with White women; this is attributable to many potential factors, including lack of recommendation by health professionals, fear of adverse effects, and cost (7). In a survey study of 743 breast cancer survivors, 40% of those who discontinued endocrine therapy cited adverse effects as the main reason for stopping (8). Because adjuvant endocrine therapy has been shown to reduce the risk of breast cancer recurrence by approximately 40%, nonadherence due to adverse effects may lead to an increased risk of recurrence (9). Additionally, structural issues, such as health insurance, out-of-pocket cost of medications, and socioeconomic status, can affect access to available treatment options. Health care professionals who treat breast cancer survivors should be knowledgeable about adverse effects associated with endocrine therapy, as well as the systemic barriers that may prevent use and adherence, and take a proactive approach to mitigating potential negative effects of therapy on quality of life to support adherence to therapy. Studies on the treatment of GSM should strive to include a diverse cohort of participants to ensure that the lived experiences of all individuals with GSM are accounted for in the literature used to inform care.

METHODS

This clinical consensus document was developed using an a priori protocol in conjunction with two authors specializing in urogynecology and gynecologic oncology. A full description of the Clinical Consensus methodology is published separately (10). The description below is specific to this Clinical Consensus.

Literature Search

The foundation for the evidence base were studies found by the 2000–2020 literature search. American College of Obstetricians and Gynecologists' medical librarians searched in EMBASE, PubMed, and MEDLINE human-only studies written in English. The full reference list from ACOG Committee Opinion No. 659, *The Use of Vaginal Estrogen in Women With a History of Estrogen-Dependent Breast Cancer*, was provided to the authors for review and inclusion in the document. MeSH terms and keywords can be found in Appendix 1 (available online at http://links.lww.com/AOG/C482). Search terms for racial and ethnic disparities and implicit bias in the setting of vaginal estrogen treatment for women with estrogen-dependent breast cancer were incorporated into the literature review, and recommendations were drafted with the intent to promote health equity and reduce these disparities. A bridge literature search was completed in June 2021.

Study Selection

Qualifying studies that passed both title and abstract screen and full-text screen were conducted in countries ranked very high on the United Nations Human Development Index (11). Studies that focused on populations with cancer of any kind, as opposed to specifically breast cancer, were excluded. Only treatments for GSM commonly used in the United States were reviewed. Animal studies, basic science nonclinical studies, and opinion pieces were excluded. All other study designs were included in the evidence review. Studies that passed full-text screen by the authors were included in a

summary evidence map (Appendix 2, available online at http://links.lww.com/AOG/C483).

Consensus Voting and Recommendation Development

At a meeting of the Committee on Clinical Consensus-Gynecology, a quorum of two thirds of eligible voting members was met and the committee held a formal vote for each proposed recommendation. All recommendation statements met or exceeded the 75% approval threshold required for consensus.

CONSENSUS RECOMMENDATIONS AND DISCUSSION

Nonhormonal Approaches

Nonhormonal methods should be considered first-line treatment for urogenital symptoms in individuals with a history of estrogen-dependent breast cancer.

Although hormonal-based treatments may be an option for individuals with a history of breast cancer, because many nonhormonal treatments are low-cost and low-risk, an initial trial of these options can be useful (12, 13).

Gynecologists should be familiar with different nonhormonal treatment options because trials of multiple options may be needed to find effective treatment for any individual patient.

Patients' concerns about GSM vary in terms of nature and severity, ranging from mild vulvovaginal irritation to dyspareunia related to introital discomfort or deep penetration, frequent urinary tract infection, and atrophy-related vaginal bleeding. Symptoms also may interact with other issues, such as overall health, nutrition, and psychosocial factors. Therefore, there is no "one-size-fits-all" treatment that will be appropriate for all individuals. Trials of different treatments may be needed before finding a therapy that is effective for and tolerated by an individual patient.

Nonhormonal treatments that have been reported to be effective in treating vulvovaginal symptoms include silicone-, polycarbophil-, and water-based lubricants; hyaluronic acid; polyacrylic acid; and vitamin E and D vaginal suppositories. There are insufficient data to indicate that one approach is superior to others.

Vaginal dryness and irritation, which often are contributing factors to dyspareunia, may be effectively treated

Summary of Consensus Recommendations

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Nonhormonal treatments that have been reported to be effective in treating vulvovaginal symptoms include silicone-, polycarbophil-, and water-based lubricants; hyaluronic acid; polyacrylic acid; and vitamin E and D vaginal suppositories. There are insufficient data to indicate that one approach is superior to others.

Hormonal Approaches: Vaginal Estrogen

If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen. For individuals taking aromatase inhibitors (AIs), low-dose vaginal estrogen can be used after shared decision making between the patient, gynecologist, and oncologist.

Dehydroepiandrosterone and Testosterone

If vaginal estrogen is not an option, vaginal dehydroepiandrosterone (DHEA) or testosterone may help with dyspareunia and improve vaginal tissue health.

Ospemifene/Selective Estrogen Receptor Modulators

Ospemifene, an orally administered selective estrogen receptor modulator (SERM), has been found to improve symptoms in a general population of menopausal individuals and may be considered as an option for individuals with a history of estrogen-dependent breast cancer. Although there is no indication that ospemifene is associated with increased risk of recurrence, long-term safety data are limited.

with nonhormonal topical treatments. Several over-the-counter lubricants exist, and data demonstrate the effectiveness of vaginal moisturizers (eg, gels and creams) for the temporary relief of vaginal dryness, urogenital atrophy, and dyspareunia (14–19). In a randomized controlled trial of breast cancer survivors (N=45), a polycarbophil-based vaginal lubricant was similar to a water-based lubricant in treating vaginal dryness but was superior in reducing dyspareunia (20). A cohort study of sexually active postmenopausal breast cancer patients (N=38) found that a silicone-based lubricant provided greater symptomatic relief compared with water-based lubricant (21). More recently, lubricants containing polyacrylic acid or hyaluronic acid have become available. In a small trial of women taking tamoxifen (N=52), those randomized to polyacrylic acid reported a decrease in sexual dysfunction from 96% to 24%, compared with 88.9% to 55.6% for women using standard lubricant (22). Small studies have demonstrated relief of vaginal atrophy symptoms with the use of hyaluronic acid, particularly when dosed three to five times per week (23–25). Another small, randomized trial of breast cancer survivors (N=64) receiving tamoxifen and experiencing symptoms of vaginal atrophy found that both vitamin D and E suppositories were associated with improved vulvovaginal symptoms and lower vaginal pH compared with placebo (24). Oil-based lubricants should not be used with condoms, though most water-based and silicone-based lubricants can be used effectively with barrier methods (26). Patients should be counseled to review a product's package insert before using with barrier methods.

The use of topical lidocaine may be particularly effective for dyspareunia related to introital pain. In a double-blind trial of 46 breast cancer survivors with severe penetrative dyspareunia, the use of 4% aqueous lidocaine applied to the introitus for 3 minutes before vaginal intercourse was associated with a reduction in dyspareunia of 88% compared with 38% for those randomized to saline placebo (27). Aqueous lidocaine also was helpful in reversing vestibular sensitivity in a similar patient population (28). Data are lacking on the efficacy of other nonhormonal topical treatments, such as formulations that combine known effective therapies with olive oil or oligopeptides and antioxidants (29, 30), although, there have been no indications that such treatments cause harm.

Hormonal Treatment Options

If nonhormonal treatments have failed to adequately address symptoms, after discussion of risks and benefits, low-dose vaginal estrogen may be used in individuals with a history of breast cancer, including those taking tamoxifen. For individuals taking AIs, low-dose vaginal estrogen can be used after shared decision making between the patient, gynecologist, and oncologist.

Obstetrician–gynecologists can play an important role in the shared decision-making process by providing data on the safety of low-dose vaginal estrogen to patients and their medical oncologists. Clear communication with a patient's medical oncologist, if possible, will support the shared decision-making process. Low-dose vaginal estrogen includes local (not systemic) products such as an estradiol-releasing vaginal ring, 10-microgram estradiol vaginal tablets or inserts, and comparable low doses of vaginal estrogen cream (31). To date, there is no evidence to indicate harm from these types of local treatments (32, 33). Formulations that have been shown to be associated with serum estradiol levels of less than 20 pg/mL are 4-microgram estradiol insert, 7.5-microgram estradiol ring, and 10-microgram estradiol inserts and tablets (34). Other low-dose regimens included in this document's review were estriol 0.25 mg twice a week and 12.5-microgram estradiol vaginal tablets twice a week. Dosing regimens were not provided in all studies. These low-dose vaginal estrogens have been reported to be highly effective at relieving symptoms of urogenital atrophy (35–40) compared with placebo (41) or water-based personal lubricant (19). Improved objective measures of vaginal health also have been demonstrated, including improved vaginal maturation index, pH, and vaginal cytology (19, 41–43), as well as improved sexual function as measured by the Female Sexual Functioning Index, which assesses symptoms related to dyspareunia as well as other factors (41). However, there are insufficient data to establish one formulation of low-dose estrogen as superior to others. Additionally, although a common recommendation is to apply vaginal estrogen after vaginal intercourse to avoid potential exposure for a male partner, data are lacking on partner absorption (26).

Unlike tamoxifen, AIs do not block the effects of exogenous estrogens on breast tissue. With the concomitant use of both estrogen and an AI, there is the potential for elevated serum estrogen levels to stimulate estrogen receptors in breast tissue. However, when serum estradiol levels were evaluated in 10 studies, most demonstrated either only a transient increase (resolving within 12 weeks) or no increase at all in serum estrogen levels (35, 37, 38, 40–42, 44–47). Although the duration of use varied across studies, only one study reported sustained increases in serum estrogen levels in two of six participants at 7 and 12 weeks of use (37).

Regardless of serum estradiol levels, the main question is whether vaginal hormonal treatment increases the risk of breast cancer recurrence. Although studies that

answer this question definitively are lacking, increased recurrence was not seen in seven studies (36, 45, 48–52) totaling more than 4,000 breast cancer survivors over a median follow-up of 2–7 years. These studies included women taking tamoxifen and women taking AIs and had varied follow-up time. Additionally, no change in breast density or Bi-RADS scores was observed in a cohort study of menopausal women after 1 year of estrogen use (53).

If vaginal estrogen is not an option, vaginal dehydroepiandrosterone (DHEA) or testosterone may help with dyspareunia and improve vaginal tissue health.

Prasterone is a vaginal DHEA insert (6.5 mg daily) that is approved by the U.S. Food and Drug Administration (FDA) for the treatment of moderate-to-severe dyspareunia due to menopause. Dehydroepiandrosterone can be converted to androstenedione, which, in turn, can be converted to estrogen through aromatization. Because estrogen is a metabolite of prasterone, there is concern about its use in individuals with a history of breast cancer. The product label notes that the use of exogenous estrogen is contraindicated in women with a known or suspected history of breast cancer and that manufacturers have not studied prasterone in this population (54). A randomized controlled trial of 464 women with a history of breast or gynecologic cancer compared both 6.5 mg and 3.25 mg of vaginal DHEA with plain moisturizer (55). Both the DHEA and moisturizer arms reported improvement in either dryness or dyspareunia, with no statistically significant difference between the arms. However, study participants receiving the higher (6.5-mg) dose reported better sexual health outcomes based on Female Sexual Functioning Index scores when compared with the 3.25-mg dose or moisturizer. No differences in adverse effects were reported among the three arms. Increases in serum estradiol were seen only among women receiving the 6.5-mg dose who were not on AI therapy. Of these 464 women, 345 contributed blood samples and 46 contributed vaginal cytology and pH values. Compared with plain moisturizer, DHEA resulted in increased DHEA-S and testosterone levels, although they were still in the lowest half or quartile of the postmenopausal range and was associated with greater improvement in vaginal cytology. Estrogen concentrations in women taking AIs were not changed (56).

Testosterone can help with proliferation of vaginal epithelium. Because the conversion of testosterone to estrogen is blocked in individuals using AIs, it is thought that testosterone may improve atrophy without interfering with the benefits of AIs. Though limited, there are promising data on the use of vaginal testosterone to improve symptoms of vulvovaginal atrophy, dyspareunia, and sexual dysfunction in those taking AIs (35, 57–61), including data from two randomized clinical trials and two systematic reviews. In a 2017 randomized clinical trial, 69 postmenopausal women were randomized to a vaginal estrogen ring or intravaginal testosterone. Only four women in the intravaginal testosterone cream arm (12%) had persistent elevation in estrogen at the end of the 12-week study (35). A phase I/II study of 21 postmenopausal breast cancer patients with symptoms of vaginal atrophy taking AIs reports continued suppression of estrogen during 1 month of use of vaginal testosterone cream (either 300 micrograms or 150 micrograms per day) (62). Because most studies reviewed only 4 weeks of testosterone use, studies with longer duration are needed. The use of testosterone in women for this indication is considered off-label use.

Other Approaches to Treatment

Ospemifene, an orally administered selective estrogen receptor modulator, has been found to improve symptoms in a general population of menopausal individuals and may be considered as an option for individuals with a history of estrogen-dependent breast cancer. Although there is no indication that ospemifene is associated with increased risk of recurrence, long-term safety data are limited.

Ospemifene is a selective estrogen receptor modulator approved by the FDA for the treatment of postmenopausal vulvovaginal atrophy. In randomized placebo-controlled trials of more than 1,000 women from the general postmenopausal population, ospemifene use ranging from 12 weeks to 1 year in duration was associated with improved vaginal pH and vaginal tissue health as well as decreased patient reports of dyspareunia (63, 64). Currently, the FDA-approved label includes a warning for its use in those with a history of breast cancer and states that, "it should not be used in women with known or suspected breast cancer" (65). In Europe, the drug is approved for use among women with a history of breast cancer who have completed all treatment (66). However, the FDA warning against its use in women with a history of breast cancer is controversial (67), because data published since ospemifene's FDA approval have not demonstrated an increased risk of recurrence with its use (68) and may indicate higher patient satisfaction and adherence when compared with other local therapies (69). Furthermore, although ospemifene has an estrogen agonist effect on vaginal tissues as well as bone, available data indicate that it acts as an antagonist in breast tissue. Clinicians should discuss the label warning with patients and use clinical judgment to assess the appropriateness of its use.

Although ospemifene is not an estrogen, because of concerns about its potential estrogenic effects on the uterus, the label includes a black box warning about the potential increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. However, three double-blind, placebo-controlled clinical trials report that no cases of endometrial cancer or atypical endometrial hyperplasia were observed over a treatment period of 52 weeks (70).

Laser therapy.

There is emerging interest in treating GSM with laser therapy to potentially improve vaginal mucosal thickness, lubrication, and elasticity (71). The theory behind the mechanism of action is that fractional beams of light create small wounds in the epithelium and lamina propria that then lead to the stimulation of collagen, remodeling, and regeneration. It also is thought to increase blood flow to this area, improving tissue quality. Currently available data are based on largely observational studies with either small numbers of participants or limited follow-up (71, 72); its efficacy has not been compared with other treatment options.

CO_2 and erbium laser therapy have been reported to improve vulvovaginal symptoms, including improved Vaginal Health Index measurements (73–75), subjective GSM symptoms (75–80), and sexual function (73, 75, 78, 79, 81–84). Laser therapy has shown promise in a research setting, with small trials demonstrating benefit, especially in the population of breast cancer survivors who may be hesitant to pursue hormonal therapy and often have more severe atrophic symptoms. However, consistent training and certification procedures for its use are lacking and concerns exist regarding the potential for scarring and long-term safety (85). Laser therapy is neither FDA-approved nor FDA-cleared for the treatment of symptoms related to menopause (86). It also is costly and not covered by insurance, making it inaccessible to many individuals. Additional research is warranted before recommending laser therapy for this indication.

FURTHER RESEARCH

Available evidence suggest that low-dose vaginal estrogen is safe in individuals with a history of hormone receptor–positive breast cancer who are at low risk of recurrence. However, given the low incidence of recurrence as well as the extended length of follow-up needed to detect recurrence in this population, large prospective longitudinal studies of breast cancer survivors are needed to definitively address the question of whether these treatments are associated with any increased risk of recurrence. In addition, further research is needed on psychological interventions (eg, cognitive behavioral therapy and antidepressants), the safety and efficacy of newer agents such as ospemifene, and alternative treatments such as laser therapy to manage GSM in this population. Finally, because existing studies have evaluated the effectiveness of treatment among predominately White patients, additional studies are needed to understand whether the findings are generalizable to all racial and ethnic groups.

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APPENDICES

1. Literature Search Strategy: http://links.lww.com/AOG/C482
2. Evidence Map: http://links.lww.com/AOG/C483

CONFLICT OF INTEREST STATEMENT

All ACOG committee members and authors have submitted a conflict of interest disclosure statement related to this published product. Any potential conflicts have been considered and managed in accordance with ACOG's Conflict of Interest Disclosure Policy. The ACOG policies can be found on acog.org. For products jointly developed with other organizations, conflict of interest disclosures by representatives of the other organizations are addressed by those organizations. The American College of Obstetricians and Gynecologists has neither solicited nor accepted any commercial involvement in the development of the content of this published product.

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