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A black and white photograph of a woman's profile, looking thoughtfully to the side with her hand near her face.

# the Omnia CME Journal

A CME SELF-STUDY ACTIVITY

## GENITAL HERPES

Common questions about diagnosis and transmission

» Gary A. Richwald, MD, MPH

## FEMALE SEXUAL DYSFUNCTION

A vexing problem in women's health

» Andrea J. Singer, MD

## PELVIC ADHESIONS

Prevention through adjunctive therapies

» Kaylen M. Silverberg, MD

This supplement was submitted by Omnia Education. Selected topics resulted from a process that included a review of needs assessments, quality improvement data, an expert-needs survey, which included medical advisory board input, and peer-reviewed literature.

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# GENITAL HERPES:

## Common questions about diagnosis and transmission

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### Educational Objectives

At the conclusion of this activity, participants should be able to:

- Discuss current approaches to testing for herpesvirus (HSV) infection to improve the diagnosis of genital herpes (GH) and to reduce the risk of transmission
- Encourage the counseling of HSV-infected patients and their partners by providing a better understanding of the natural history of GH and viral shedding to reduce the risk of transmission of HSV

### Credit Designation:

Omnia Education, Inc. designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit(s)<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

### Disclosure:

Dr Richwald has disclosed affiliation with GlaxoSmithKline and Merck & Co., Inc.

Renewed interest in genital herpes (GH) began in 1981 with the commercial introduction of acyclovir, the first oral antiviral medication.<sup>1,2</sup> This breakthrough was followed by a number of key developments, including the following:

- Recognition that women outnumber men with herpesvirus-2 (HSV-2) infection 2 to 1.<sup>3</sup>
- Approval of 2 new, longer-acting viral agents, valacyclovir and famciclovir
- Greatly improved testing in the form of amplified DNA swab tests and type-specific serologic (antibody) tests
- The emergence of herpesvirus-1 (HSV-1) as a major cause of genital herpes
- Advances in understanding the natural history of infection and disease including antiviral shedding, HSV/HIV interactions, and the successful use of antivirals to help prevent further transmission of infection<sup>4-7</sup>

The following commonly asked questions focus on clinical presentation, diagnosis, asymptomatic viral shedding and transmission of infection in non-pregnant women and their sexual partners.

### Q: How common is GH and what are its clinical characteristics?

**A:** GH is a very common viral infection. Approximately 50 million people in the United States are infected with HSV-2, and an estimated 10 to 15 million have genital HSV-1.<sup>3,8,9</sup> Following initial infection, these viruses become nerve-based in the trigeminal ganglion in the face (HSV-1) and sacral ganglia in the lower back

## What is the difference between genital herpes caused by HSV-2 and by HSV-1?

HSV-2 GH is caused by viral transmission following penile-vaginal and penile-anal intercourse.<sup>1</sup> Of the 50 million infected individuals, 15% to 20% (8 to 10 million people in the United States) have the easily recognizable, classic clinical presentations. The remaining 40 million people with HSV-2 appear to have recurrent lower genital tract inflammation that, because of the absence of ulcerative GH lesions, is rarely associated with GH by either the patient or clinician. The majority of these 40 million individuals have recurrent lower genital tract inflammation without ulcerative lesions. Patients with so called “atypical GH” can present with itching, redness, mild to moderate pain, discharge, rash, and dysuria.<sup>2,3</sup> In response to these symptoms, patients often use a variety of over-the-counter non-prescription remedies including antihemorrhoidals, antibacterial and antifungal creams, ointments and sprays, and topical corticosteroids.

HSV-1 GH is often much less inflammatory in its clinical presentation than is HSV-2. It is usually caused by transmission of HSV-1 from the lips to the genitals during oral sex.<sup>4</sup> Initial HSV-1 GH outbreaks are shorter than those caused by HSV-2 (1 to 3 days vs 1 to 2 weeks), less recurrent in the first few years (annual outbreaks vs every 2 to 4 months), and less likely to be associated with AVS.<sup>5-7</sup> Many clinical cases may be undiagnosed due to a short first outbreak period and infrequent clinical recurrences. Acquisition of HSV-1 GH through penile-vaginal or penile-anal intercourse is less likely than through oral sex due to infrequent outbreaks and limited viral shedding in the genital area associated with HSV-1 infection of the sacral ganglia. It is difficult to accurately estimate the number of individuals with sexually acquired HSV-1 GH since about two-thirds of Americans are infected

with orolabial HSV-1 during early childhood.

Approximately half of those infected with HSV-1 will go on to develop cold sores or fever blisters, usually beginning in the peripubertal period. This extensive level of pre-sexually acquired HSV-1 infection may help explain the milder clinical course and less frequent rate of viral reactivation of HSV-1 GH compared to HSV-2 GH.

Also, increased and earlier oral-genital sexual activity among adolescents and young adults are thought to account for increasing rates of HSV-1 GH infection. Although HSV-2 GH infection is responsible for at least 95% of recurrent GH clinical outbreaks, GH due to HSV-1 infection accounts for an increasing proportion of first clinical GH episodes reaching 50% or more in some groups such as university students.<sup>8-10</sup>

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(HSV-2 and HSV-1). In these nerve-based locations, herpesviruses are apparently protected from full clearance by the immune system, hence their designation as lifelong infections.

Clinical characteristics of GH include recurrent symptoms in the genital area, such as itching, burning, and pain accompanied first by erythema and then classic inflammatory vesicular lesions that ultimately progress to ulcers and crusting, finally healing to normal-appearing skin.

### Q: Which patients are at greatest risk of acquiring GH?

**A:** Approximately 1 in 4 women are infected with GH—about twice as many as men.<sup>9,10</sup> The greater susceptibility of women to GH compared to men may reflect anatomic, immunologic, and unexplained differences. Unlike bacterial STDs, in which socioeconomic characteristics significantly impact infection rates, in the United States, married people, college graduates, and higher-income (more than



\$100,000) adults have rates similar to the overall rate of GH infection. Significant racial disparities in prevalence exist, especially for African Americans and, to a lesser degree, Hispanic Americans, for reasons that have remained largely unexplained.<sup>9</sup>

Differences in sexual and preventative behaviors (eg, number of sex partners, use of condoms) that may explain the risk of acquiring bacterial STDs such as chlamydia or gonorrhea, do not predict who will become infected with HSV-2. With one-quarter or more of prospective sexual partners infected with HSV-2, the risk of acquiring HSV-2 is less dependent on the number of sex partners than on whether sex partners have been infected. The common belief that patients who acquire GH have a substantially larger number of sex partners than those who are not infected is incorrect, when considering the vast majority of those infected with GH.<sup>11</sup>

In the typical primary care and women's health practice, about 3% to 4% of patients have a history of GH, which largely reflects those with classic GH signs and symptoms. This contrasts with the 25% or more who are actually infected with genital HSV-2, most with unrecognized atypical or asymptomatic GH. This difference in percentages contributes to the misconception that GH is rarely seen in primary care.

## Diagnosing genital herpes

**Q:** Why do so many GH infections remain undiagnosed?

**A:** For decades, clinicians have used the appearance of vesiculoulcerative lesions and associated symptoms to make a diagnosis of GH. This syndromic approach is highly problematic for a number of reasons. Even in the hands of experienced clinicians, more than 1 in 5 patients presenting with classic GH signs and symptoms do not actually have GH. In addition, patients with a history of genital irritation may not have lesions or symptoms at the time of their office visit. Some may not have classical stigmata, instead presenting with nonspecific symptoms such as genital itching, burning, dysuria, discharge, and atypical lesions such as rashes or fissures. Patients with GH often will report what they think they have

**TABLE Clinical scenarios for serologic testing and screening for genital herpes**

- To confirm a visual diagnosis, especially with a negative GH culture or no culture performed
- When patients have recurrent lower genital-tract clinical symptoms suggesting GH but not classic GH lesions
- In the absence of GH lesions
- To determine whether the current or previous sex partners of a patient with GH also have GH
- As part of STD screening and when a patient has another STD, reflecting the increased risk of also having GH
- When a patient requests his or her GH infection status

GH, genital herpes; STD, sexually transmitted disease.

Department of Health and Human Services, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. MMWR. 2006;55:1-94. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 46. Gynecological Herpes Simplex Virus Infections. Obstet Gynecol. 2004;104:1111-1117.

as other conditions including urinary tract infection, vaginitis, yeast infection, vulvitis, perineal and perianal irritation, condom and spermicidal allergies, and postcoital soreness.<sup>12,13</sup>

Failure by the CDC and other guideline-setting groups to agree which STD tests should be included in a standard STD screening panel and to make recommendations for routine inclusion of HSV-2 serologic testing when performing STD evaluation, further contribute to under diagnosis of GH.<sup>12</sup>

**Q:** Why is it important to know which herpesvirus (HSV-2 or HSV-1) is responsible for the patient's GH?

**A:** GH caused by HSV-2 infection generally has more serious clinical consequences than HSV-1, with much higher rates of viral shedding, longer and more frequent recurrences, and greater likelihood of genital-to-genital transmission. HSV-2 is more likely to present as an atypical outbreak than HSV-1; it is often associated with reactivation during and particularly at the end of pregnancy as well as with neonatal infection. In addition, compared to patients with HSV-1, patients with HSV-2 infection are much more likely to receive daily antiviral therapy to reduce the frequency of clinical outbreaks and to prevent transmission to uninfected partners.

**Q: Why should swab tests be used and how accurate are they?**

**A.** HSV cultures are inexpensive but the yield can be low, often less than 50%, especially if the specimen is not obtained during the first few days after the outbreak begins. In addition to low sensitivity (high rates of false negatives), cultures can suffer from transport problems and prolonged result-reporting times, sometimes in excess of a week.<sup>14</sup> Some laboratories fail to report positive culture results by type, either HSV-1 or HSV-2, which delays a type-specific diagnosis and requiring a second specimen.

Amplified DNA swab tests, often referred to as PCR (polymerase chain reaction) assays, are able to identify smaller amounts of viruses later in the course of the outbreak and are less dependent on careful sampling and transport. In addition, results can be available in a day or two.<sup>15,16</sup> Although clearly superior to culture in diagnosing GH, PCR assays are usually far more expensive and also may not be reimbursed by some third-party payers when used in outpatient care. PCR assays are not approved by the US Food and Drug Administration (FDA) for genital specimens but because of better sensitivity, they are recommended for this use by most viral disease experts.<sup>17</sup>

**Q: How should serologic tests be used and interpreted?**

**A.** The 2006 US Centers for Disease Control (CDC) STD Treatment Guidelines expand on previous recommendations regarding the key role type-specific serologic (antibody) tests play in diagnosis of HSV infection.<sup>12</sup> These tests accurately distinguish HSV-2 antibodies from those of HSV-1 without cross-reactivity problems.<sup>18</sup>

Newer HSV glycoprotein G-based, type-specific serologic tests can be sent to medical laboratories or performed at the point-of-care. The most commonly used antibody tests for GH are the HerpeSelect-2 and HerpeSelect-1 for HSV-2, and HSV-1 IgG (immunoglobulin G) long-term antibodies, respectively.

A positive HSV-2 antibody test means that the patient has genital herpes. In general, a positive HSV-1 antibody test usually means that the patient

has orolabial herpes, since about two-thirds of the population have HSV-1 trigeminal nerve infection by adolescence, whereas a much smaller percent are HSV-1 positive due to HSV-1 GH.

In terms of test interpretation, the window period for the HerpeSelect-1 and HerpeSelect-2 tests is approximately 3 weeks for the earliest appearance of antibodies after infection and 16 weeks for the point by which the vast majority of those infected have acquired IgG antibodies.<sup>19,20</sup>

For point-of-care testing, the new, more accurate and easier-to-perform HerpeSelect Direct, as well as the older Biokit HSV-2 Rapid Test and SureVue HSV-2 kit, can be used to detect HSV-2 antibodies from capillary blood or serum during an office visit.<sup>21</sup>

While some clinicians order IgM (immunoglobulin M) antibody tests to differentiate initial from recurrent GH infection, IgM antibody tests are not type-specific, are unreliable, and should not be used in making a GH diagnosis.<sup>20</sup> Patients with reported positive IgM antibodies for HSV-1 and HSV-2 in the presence of persistently negative IgG serologic tests for HSV-2 and HSV-1 are very unlikely to have genital herpes.

## Call for mainstream testing

The CDC recently issued recommendations to mainstream the use of HIV tests, with the goal of reaching those who have HIV but are unaware of it. A similar approach is warranted for HSV-2 infection. It is far better for patients to have an antibody test and learn their HSV-2 status prior to infecting a sex partner. Such knowledge provides patients with the opportunity to practice prevention and to inform sex partners of their HSV-2 infection status prior to sexual intercourse.<sup>22</sup> Studies show that the latter behavior is associated with reduced transmission. In addition, adverse psychosocial consequences are more likely to occur among patients who inadvertently discover they have GH by infecting a sex partner who then develops clinical GH.<sup>23,24</sup>

**Q: Is there a simple algorithm for the use of swab and serologic tests in diagnosing patients with suspected GH lesions?**

**A:** Swab tests (herpes culture or PCR assay) should always be performed when suspected classic or atypical GH lesions are present. A negative swab test does not rule out that genital lesions are caused by HSV-2 or HSV-1.<sup>14</sup>

There are 2 approaches to using antibody testing to evaluate patients with suspected GH lesions. Clinicians first perform a swab test, and if the test is negative, they perform another antibody test the following week. The alternative is to perform HSV-2 antibody testing at the same time as the swab test. Many clinicians prefer this approach because the swab test is often negative even in the presence of herpesviruses, and delaying an HSV antibody test may delay the diagnosis of GH. Also, more than half of patients with a first GH outbreak already have GH antibodies. This is because their initial GH infection was asymptomatic or unrecognized, and their first lesional outbreak does not represent true primary infection but, rather, the first clinical outbreak of a previously acquired GH infection.<sup>10,13,25,26</sup>

In terms of whether to test for HSV-2 antibodies only or both HSV-1 and HSV-2 antibodies, the former approach often makes more sense. A positive HSV-1 antibody test usually reflects orolabial infection acquired in early childhood rather than GH due to HSV-1. If the initial HSV-2 antibody test is negative, it should be repeated 3 months later. A positive HSV-2 antibody test at 3 months following an initial negative HSV-2 test reflects true primary infection. A persistently negative HSV-2 test at 3 months suggests that the original suspected GH lesion was most likely due to HSV-1.

Alternatively, if both HSV-1 and HSV-2 antibody tests are performed, and the HSV-1 antibody test is initially negative, and then three months later after retesting is positive, this reflects true primary GH infection due to HSV-1. If the initial HSV-1 antibody test is positive and initial and follow-up HSV-2 tests are negative, this reflects an HSV-1 infection at either an orolabial or genital site, and a GH diagnosis cannot be made. In cases where the diagnosis or site of GH infection is indeterminate, re-swabbing subsequent lesions may be of value in making a definitive diagnosis.

**Q:** How often does asymptomatic viral shedding occur?

**A:** Asymptomatic viral shedding (AVS) occurs frequently and is responsible for up to 70% of GH transmission to uninfected sex partners.<sup>27</sup> AVS is not only common and occurs frequently in almost all patients, it occurs even in those with longstanding, recognized GH and clinically silent infection.<sup>12</sup> The presence of herpesviruses in the genital area in the absence of lesions is a challenging concept for many patients.

Although asymptomatic AVS was previously thought to occur only at the principal clinical outbreak location or locations during non-outbreak periods, it is now known that AVS can occur in multiple locations in the lower genital tract (cervix, vagina, vulva, penis, scrotum, perineum, urethra, and perianal region), either simultaneously with clinical outbreaks or independent of them. As a result, patients cannot predict if, when, or where they may have asymptomatic viral shedding.<sup>28</sup>

Using PCR assays, viral shedding studies have established AVS rates of 3% to 27% of days, the equivalent of 1 to 8 days per month.<sup>28</sup> AVS is unpredictable, with more than half of AVS episodes occurring more than a week before or after clinical outbreaks.

**Q:** What are the key correlates of asymptomatic viral shedding and what role do these correlates play in the transmission of GH?

**A:** Studies over the past 15 years have substantially increased knowledge about AVS. It is most frequent during the first 12 months after acquiring HSV-2, and in patients with a newly acquired infection, the proportion of days with AVS is twice as great as in patients with an established history of GH (32% vs 14%).<sup>12</sup>

It was previously assumed that AVS was more common among patients with greater numbers of clinical outbreaks. However, studies have demonstrated no significant difference among women with 1 to 12 outbreaks a year, as compared to women with no outbreaks.<sup>28,29</sup>

Although the frequency of clinical outbreaks falls steadily over the first decade after GH diagnosis, AVS patterns are different. The percentage of days with AVS are highest in the first year after GH diagnosis, followed by a plateau at approximately one-third to one-half of the first year's AVS rate.

These rates continue at that level for well over a decade.<sup>30</sup> AVS rates are significantly affected by the use of daily antiviral therapy.

Daily medication reduces asymptomatic and symptomatic viral shedding rates by 70% to 80%.<sup>5,31</sup> This explains the significant reduction in

sexual HSV-2 transmission with daily use of valacyclovir by the infected person. Suppressive therapy for early genital herpes addresses high initial levels of AVS, increased risk of GH transmission, and psychosocial problems associated with frequent clinical outbreaks.<sup>5,32,33</sup> ■

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# FEMALE SEXUAL DYSFUNCTION:

## A vexing problem in women's health

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### Educational Objectives

At the conclusion of this activity, participants should be able to:

- Describe sexual function as it applies to women and define female sexual disorders
- Outline techniques for office evaluation of the woman with sexual complaints
- Discuss management strategies for the initial treatment of female sexual problems

### Credit Designation:

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### Disclosure:

Dr Singer has disclosed affiliation with Procter & Gamble Pharmaceuticals and Sanofi-aventis Pharmaceuticals.

Sexual intimacy is an integral part of life and is closely linked to emotional and physical well-being. Indeed, in a global survey of the importance of sexuality and intimacy in 27,000 men and women aged 40 to 80 years, 83% of men and 63% of women rated sex as extremely important, very important, or moderately important in their lives.<sup>1</sup> Sex also appears to remain an important aspect of life as one ages. In a survey of 1,300 adults over age 60 in the United States, approximately half reported being sexually active, and of those, 79% of men and 66% of women said that sex was an important component of their relationship with their partners.<sup>2</sup> Despite the importance of a healthy sex life to most people, research suggests that sexual dysfunction is common. It is estimated that 43% of women and 31% of men have some sexual complaint,<sup>3</sup> and these numbers may be even higher in the older population.<sup>4</sup>

Sexual complaints in women take many forms and the etiology is often complex. Diagnosis of female sexual dysfunction (FSD) is based on a comprehensive history, psychosocial assessment, and physical examination. Treatment is often multidimensional and may encompass several different disciplines. This article discusses the etiology and diagnosis of FSD and offers basic therapeutic approaches to the management of sexual complaints.

## Sexual Response Cycle

Based on their landmark research in the 1960s, Masters and Johnson developed a linear, 4-stage model of sexual response,

**TABLE 1** Medical and surgical causes of female sexual dysfunction

<b>Cardiovascular</b> <ul style="list-style-type: none"><li>• Hypertension</li><li>• Coronary artery disease</li><li>• Angina</li><li>• Previous myocardial infarction</li></ul> <b>Endocrine</b> <ul style="list-style-type: none"><li>• Diabetes</li><li>• Thyroid disorders</li><li>• Hyperprolactinemia</li><li>• Adrenal disorders</li><li>• Pituitary disorders</li></ul> <b>Neurologic</b> <ul style="list-style-type: none"><li>• Multiple sclerosis</li><li>• Spinal cord damage</li><li>• Parkinson's disease</li><li>• Peripheral neuropathies</li><li>• Cerebrovascular events</li><li>• Dementia</li></ul>	<b>Renal</b> <ul style="list-style-type: none"><li>• Chronic renal disease</li><li>• Renal failure</li><li>• Dialysis</li></ul> <b>Musculoskeletal</b> <ul style="list-style-type: none"><li>• Arthritis</li><li>• Sjögren's syndrome</li><li>• Autoimmune diseases</li></ul> <b>Urinary</b> <ul style="list-style-type: none"><li>• Incontinence</li></ul> <b>Other</b> <ul style="list-style-type: none"><li>• Breast cancer/mastectomy</li><li>• Colostomy</li><li>• Urostomy</li><li>• Skin disorders</li><li>• Alcohol and substance abuse</li><li>• Tobacco abuse</li></ul>
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Figure adapted from various resources by Andrea J. Singer, MD

**TABLE 2** Gynecologic causes of sexual dysfunction

- Infections (Bartholin's or Skene's gland infections, cystitis, focal vulvitis)
- Intact hymen or thick hymeneal tags
- Vulvar dystrophy, dermatitis
- Vaginal atrophy
- Scarring (from episiotomy, vaginal surgery, or radiation)
- Vulvar vestibulitis
- Vaginismus
- Pelvic infection (pelvic inflammatory disease, endometritis)
- Pelvic masses (including fibroids)
- Endometriosis
- Interstitial cystitis
- Cystocele, rectocele, uterine prolapse
- Oophorectomy
- Gynecologic malignancies and treatment

Figure adapted from various resources by Andrea J. Singer, MD

which included the phases of excitement, plateau, orgasm, and resolution. Kaplan proposed an alternate model in 1979 and introduced the concept of desire as the first stage of the normal sexual response cycle. In this model, desire leads to arousal, then plateau, followed by orgasm and resolution. This model has been widely accepted, and most

definitions view sexual dysfunction as an interruption of 1 or more phases of this response cycle. This model was intended to reflect sexual response for males and females; however, researchers have recognized that some women do not experience all 5 phases of the cycle and/or may not do so in the sequential progression described. As such, this model has been criticized since it may not reflect a woman's actual experiences.<sup>6,7</sup>

Basson proposed an alternative model to the traditional linear model to account for the complexity of female sexuality and its core need for closeness and emotional intimacy. This cyclic model is based on intimacy and incorporates integral sexual stimuli, which can be influenced by biological and psychological factors. Spontaneous desire, such as sexual thoughts and conscious wanting and fantasizing, can augment the cycle as well. This model reflects the dependency on the interaction of mind and body of sexual functioning in women.<sup>8</sup> Spontaneous sexual drive may or may not be present, especially as a woman ages.<sup>5</sup> For many women, the goal of sexual activity is intimacy, and they may seek out sexual encounters for this purpose. In response to sexual stimuli, arousal may ensue and desire may then follow. The peak emotional experience and emotional and physical satisfaction may or may not coincide with the physiological release that occurs during orgasm. Indeed, there may be an infinite variety of sexual responses for women.

### Predisposing factors

The vast majority of sexual problems are caused by a variety of factors, often a combination of biological, psychological, and relationship issues. Some medical and surgical conditions can cause or contribute to sexual difficulties (TABLE 1) as can gynecologic causes (TABLE 2). Conditions that affect energy and overall well-being may indirectly affect sexual desire and response as well. Also, conditions that alter the hormonal milieu can impede the sexual response. Neoplastic disease and its treatment, including chemotherapy, radiation, and surgery, can present mortality concerns, alter or remove physical and psychological symbols of femininity, and affect

self-esteem, all of which may result in feelings of decreased sexuality. Treatment of non-neoplastic diseases or their treatment can change body image and self-esteem and can affect sexuality.

In addition, specific medications are known or believed to affect female sexual functioning (TABLE 3). Essentially, any medication that alters blood flow, affects the central nervous system, causes dryness of the skin and mucous membranes, or adversely affects the levels of bioavailable androgens can potentially interfere with normal sexual function.

## Screening for sexual disorders

Although sexual dysfunction is common, it is a topic that many people—patient and physician alike—are hesitant to discuss. Although it is the responsibility of health care professionals to inquire about sexual function, data suggest that very few physicians bring up the topic with patients. In one study, only 14% of adults in the United States aged 40 to 80 reported that a physician had asked about their sexual concerns within the past 3 years.<sup>1</sup> In data obtained from the National Social Life, Health, and Aging Project (NSHAP), only 38% of men and 22% of women aged 57 to 85 reported having discussed sex with a physician since the age of 50, despite the high prevalence (>50%) of sexual problems.<sup>4</sup> Physician-initiated questioning about sexuality has been shown to significantly increase patient reporting of sexual dysfunction<sup>9</sup> and should, therefore, be incorporated into regular practice.

All patients should be screened for sexual dysfunction, and perhaps the most natural time to do so is at the annual or periodic health visit. In addition, particular events are associated with an increased risk of sexual disorders and provide opportunities for screening. These include visits prior to gynecologic or other surgery, menopause-related visits, prenatal and postnatal visits, and visits for infertility, chronic illnesses, and depression.<sup>10</sup> In terms of screening, a brief sexual status history can be covered with 4 basic questions:

1. Are you sexually active?
2. Is your sex life satisfying to you?
3. Is your sexual activity satisfying for your partner?

**TABLE 3** Effects of some medications on sexual function

Medication	Disorder
<b>Antihypertensives</b>	
• Beta blockers	Desire, arousal
• Thiazide diuretics	Arousal
• Other diuretics (spironolactone, acetazolamide)	Desire, arousal
• Centrally acting agents	Arousal
• Lipid medications	Desire, arousal
<b>Psychoactive medications</b>	
• Selective serotonin reuptake inhibitors	Desire, arousal, orgasmic
• Tricyclic antidepressants	Desire, arousal, orgasmic
• Benzodiazepines	Desire, arousal, orgasmic
• Antipsychotics	Desire, orgasmic
• Lithium	Desire, arousal
• Monoamine oxidase inhibitors	Arousal
<b>Hormonal agents</b>	
• GnRh agonists	Desire, arousal
• Oral and non-oral contraceptives	Desire
• Progestins	Desire
• SERMS	Vaginal dryness, dyspareunia
• Danazol	Desire
<b>Anticholinergics</b>	Arousal
<b>Antihistamines (H1 and H2 blockers)</b>	Desire, arousal
<b>Amphetamines and related drugs</b>	Arousal, orgasmic
<b>Narcotics</b>	Desire, arousal, orgasmic
<b>Sedatives (including alcohol)</b>	Desire, arousal, orgasmic

Adapted from Drugs that cause sexual dysfunction: an update. Med Lett Drugs Ther. 1992;34:73-78.

4. Do you have any concerns about your sex life or functioning?

A questionnaire can also be incorporated into a patient intake form and used as a preconsultation screening tool if desired.

The evaluation of a patient complaining of sexual dysfunction should include a detailed medical and sexual history, a complete physical examination, and laboratory tests, if indicated. Areas that may be assessed during a complete sexual history include details about any pain or discomfort, any previous treatment, first sexual experience, early teaching regarding sexuality, sexually transmitted infections,

pregnancies, and history of sexual problems. Psychological, social, and relationship histories are also needed. The patient should be evaluated for anxiety and depression because of their potential effect on intimacy and desire. Life stressors including—but not limited to—financial pressures, employment situations, and family and social responsibilities, should be identified, as these can affect interest in sex. Questions regarding domestic and sexual abuse as well as substance abuse must also be raised.

The partner can often be an important source of information. Therefore, it may be beneficial to have the partner present at some point during the office encounter and during the education process.

### Classification and treatment of sexual disorders

*The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* conceptualizes sexual disorders as “disturbances in the processes that characterize the sexual response cycle or by pain associated with sexual intercourse” and includes: (1) sexual desire disorders, (2) sexual arousal disorders, (3) orgasmic disorders, and (4) sexual pain disorders, which include dyspareunia, vaginismus, and noncoital sexual pain.<sup>11</sup> All classifications are further specified as lifelong or acquired, generalized or situational, and due to psychological or combined factors. In addition, the psychological distress and interpersonal difficulty caused by the sexual disorder is included in the definition.<sup>11</sup>

In 1998, The American Foundation for Urological Disease (AFUD) convened an interdisciplinary panel to develop a classification system that would encompass both the psychological and biological factors involved in female sexual dysfunction. The categories outlined in DSM-IV were retained and expanded to include organic causes.<sup>12</sup> The AFUD system includes personal distress as a critical component in the diagnostic criterion, one which must be present in order for dysfunction to be diagnosed. These definitions continue to distinguish between dysfunctions that are lifelong and those that are acquired.<sup>12</sup> More than one dysfunction may be present, and there may be interdependence among

the disorders. These classification systems have been criticized because they are generally based on the traditional linear model of sexual response. In fact, subsequent publications have recommended changes, suggesting that these categories and their definitions will continue to evolve and take contextual factors into consideration.<sup>12</sup>

### General approaches to treatment

Patients should be educated about normal anatomy, the female sexual response cycle, and normal changes in sexual functioning that may occur throughout the life cycle. Special attention to the effects of aging and menopause may be important as well. In addition to education offered directly by the health care provider, patients can obtain valuable information in the form of books, pamphlets, videos, and reputable web sites. Education can inform the patient and “normalize” her experiences.

Recommendations to enhance communication and improve relationships may be offered. Communicating sexual likes and dislikes, in a nonjudgmental manner, can reinvent novelty and improve satisfaction. It is often necessary to help a couple reestablish intimacy. One such approach includes the use of behavior therapy in the form of sensate-focus exercises or sensual massage, where one partner provides the massage and the other partner provides feedback. There is initially no involvement of sexual areas. The idea is to enhance comfort and communication between partners, eliminate performance expectations, augment awareness of bodily sensations, remove the genital focus, and broaden the sexual repertoire.<sup>13</sup>

Basic treatment strategies may also include ways to increase stimulation, encourage creativity, and eliminate routine. This may begin with lifestyle changes, including rest, minimizing fatigue and stress, and aerobic and strength-training exercises. Viewing erotic materials and fantasizing can be used to enhance libido and arousal. Suggestions for varying the time of day or place in which sexual activity occurs, or varying positions or types of sexual activity, can be offered. Self-pleasure and the use of vibrators can increase stimulation and may also help to maximize familiarity with pleasurable sensations.



## Desire disorders

Hypoactive sexual desire disorder (HSDD) is defined as the persistent or recurrent deficiency or absence of sexual fantasies, thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress.<sup>12</sup> Diagnosis of HSDD requires that the loss of sexual desire causes personal distress (or is an issue) for the patient and/or her partner and therefore requires treatment. HSDD is the most common of the female sexual disorders and has been shown to have a strong positive correlation with low feelings of physical and emotional satisfaction as well as low levels of overall happiness.<sup>3</sup>

Though common, desire disorders are often difficult to diagnose in women because there are no reliable physical markers of sexual desire. In addition, women will often engage in sexual activity despite a lack of innate or spontaneous desire and/or they may fail to initiate sexual encounters when they do experience desire. Therefore, objective measures of sexual desire, such as frequency of intercourse, may not be reliable indicators and may not reflect the true presence or absence of desire.

Desire may readily be diminished or destroyed by interpersonal or relationship difficulties, psychological issues and stressors, medical problems, including estrogen-deficient dyspareunia, and medications, and these underlying causes must be fully evaluated. HSDD may also be a result of coexisting arousal disorder. Postmenopausal women are often thought to be at an increased risk of experiencing HSDD as a result of decreasing androgen levels, although the role of testosterone in sexual desire remains somewhat controversial.

Androgen is important in the regulation of sexual response. Because the ovaries are one of the major producers of androgens in women, a decline in androgen synthesis often occurs with aging. Women in their forties have been shown to have approximately half the level of testosterone of women in their twenties.<sup>14</sup> This age-related decline in androgen synthesis and circulating levels has been thought to lead to a decrease in sexual desire and well-being. Indeed, a syndrome of female androgen insufficiency was proposed by the Princeton Consensus Panel in 2002, in which a pattern of clinical symptoms was described, including a diminished

sense of well-being or dysphoric mood; persistent, unexplained fatigue; and sexual function changes such as decreased libido, sexual receptivity, and pleasure, in the presence of decreased bioavailable testosterone and normal estrogen status.<sup>15</sup> Other potential signs of female androgen insufficiency the panel noted were bone loss, decreased muscle strength, and decreased cognitive function.<sup>15</sup> Based on this pattern, an algorithm of care was developed in which a trial of testosterone therapy could be considered if the patient was adequately estrogenized and was not found to have any other cause(s) for her persistent symptoms.

Despite this international consensus panel statement, the classification of androgen insufficiency as a medical syndrome and the use of androgen therapy in women are controversial and not universally accepted. Accumulating data, primarily in women who have undergone oophorectomy, indicate that testosterone therapy with concomitant estrogen therapy improves sexual function—specifically sexual desire—in postmenopausal women.<sup>16-19</sup>

The North American Menopause Society (NAMS) position statement on the role of testosterone therapy in postmenopausal women concludes that there is consistent evidence that in postmenopausal women with sexual complaints, adding either oral testosterone or testosterone given by other routes of administration (eg, transdermal patch, implants, injections) to estrogen therapy results in positive effects on sexual function, primarily an increase in sexual desire.<sup>20</sup> NAMS further states that such therapy can be considered in postmenopausal women if they present with decreased sexual desire associated with personal distress and no other identifiable cause for their sexual complaint. Finally, NAMS states that laboratory testing of testosterone levels should not be used to diagnose testosterone insufficiency. Laboratory assays are not accurate for detecting testosterone concentrations at the low values typically found in postmenopausal women.<sup>20</sup>

A task force of the Endocrine Society, however, recommended against establishing a diagnosis of androgen insufficiency in women because of the lack of a well-defined clinical syndrome and reliable data on testosterone levels that could be used to define the disorder.<sup>21</sup> Furthermore, the task force

recommended against the widespread use of testosterone in women because of the lack of clear indications as well as concerns over long-term safety.<sup>21</sup>

In the US, no testosterone product is approved by the US Food and Drug Administration (FDA) for the treatment of sexual dysfunction in women. A few testosterone-containing products are FDA-approved for use in women, but would be used off-label to treat sexual desire disorders. Compounded preparations of testosterone are also available by prescription, but they are not subject to the same quality control as FDA-approved products and may result in inconsistent dosing. Attempts to use testosterone products approved for use in men by modifying the dose or amount applied is difficult and could result in delivery of excessive doses. All of these off-label uses lack efficacy, and, perhaps more importantly, safety data. Potential side effects include acne, hirsutism, voice deepening, alopecia, liver toxicity, and adverse effects on lipoproteins. Concerns about the consequences of long-term androgen use focus on possible cardiovascular disease, development or worsening of the metabolic syndrome, thromboembolic disease, and malignancies involving the breast and uterus,<sup>22</sup> although there are few controlled long-term data to definitively support or negate these concerns. DHEA dietary supplements have not been studied in large, well-designed clinical trials. Therefore, there is a lack of efficacy data for such use in treating female sexual dysfunction. Possible androgen therapy includes oral, topical, injection, and implant options.

Understanding the connection between sexuality and physical, psychological, relationship, and sociocultural factors is essential for treating all types of FSD, but especially HSDD. Key components of treatment include recommendations for reestablishing intimacy, changing sexual routines, sensate focus exercises, use of female-centered erotica, and the development of sexual fantasies.

### Arousal disorders

AFUD defines Female Sexual Arousal Disorder (FSAD) as the persistent or recurrent inability to attain or maintain sufficient sexual excitement, causing personal distress. This may be expressed as a lack of subjective excitement, genital response (eg,

lubrication, swelling), or other somatic responses.<sup>12</sup> To understand the etiology of the arousal disorders and to implement appropriate treatment, one must distinguish between the subtypes of FSAD. Generalized arousal disorder includes lack of mental excitement as well as lack of genital engorgement or congestion.<sup>8,10</sup> Genital arousal disorder implies that mental excitement is present, but genital engorgement is absent or minimal.<sup>8,10</sup> In “missed arousal,” genital engorgement occurs, but the woman does not attend to it, and in “dysphoric arousal,” genital engorgement is felt to be unpleasant.<sup>8,10</sup>

The psychological aspects of FSAD should be addressed with psychosocial counseling. For women with missed arousal, it is especially important to consider past negative experiences, distractions, expectations of negative outcome, problematic stimuli or context of sexual activity, and depression.<sup>10</sup> Similarly, for those with dysphoric arousal, past negative experiences should be reviewed, including abuse, negative messages from childhood regarding sex, and guilt about sexuality.<sup>10</sup>

Medical factors are frequently implicated in the development of arousal disorders and should be addressed and treated as indicated. Such factors include vascular diseases (eg, atherosclerotic disease, coronary artery disease, diabetes), tobacco abuse, medication effects, postsurgical changes, and menopause.

Urogenital atrophy is perhaps the most common cause of arousal disorders in postmenopausal women. Treatment of atrophy with a local vaginal estrogen cream, ring, or tablet can be effective. Systemic estrogen therapy can be considered if there are no contraindications to its use and may be superior to local therapy alone when there is coexisting HSDD. The transdermal route of administration may be preferred to oral estrogen supplementation to avoid an increase in sex hormone-binding globulin levels and a subsequent decrease in bioavailable testosterone.<sup>10</sup>

Nonpharmacologic approaches to the treatment of FSAD usually focus on erotica and over-the-counter lubricants, vitamin E oil, and mineral oil, which should be used on a regular basis rather than solely with intercourse. Decreased vasocongestion during arousal can create the need for

increased tactile stimulation to achieve adequate clitoral, labial, and vaginal response. Providing an explanation of the need for more stimulation, whether manual, oral, or with the use of vibrators, and encouraging extended foreplay, especially in older women, can have a positive effect on their sexual response and relationship.

### **Vasocative medications and devices**

Use of vasoactive medications, either systemically or locally, for patients with genital arousal disorder seems to make sense theoretically. Treatment with phosphodiesterase (PDE5) inhibitors, such as sildenafil (Viagra), however, has generally not been shown to be effective in larger, randomized, placebo-controlled trials of women with FSD. Lack of focused, patient-selection criteria may have limited potential demonstration of efficacy, as these trials involved women in whom arousal and desire disorders rather than genital arousal disorder were diagnosed.<sup>13,23</sup>

Though some smaller studies of women with genital arousal disorder seem to show favorable results, further studies of PDE5 inhibitors in treating FSAD have been discontinued and there is no ongoing effort to seek FDA approval for use of these agents in FSD.<sup>10,13,23</sup> Use of PDE5 inhibitors in women, even on a case-by-case basis, is off-label. Two formulations of the topical vasodilator alprostadil are under investigation.

A vacuum device, EROS-CTD (clitoral therapy device), is FDA-approved for the treatment of FSAD and orgasmic disorder. It works by improving blood flow to the clitoris and external genitalia. A small, multicenter prospective cohort study suggests that the device is associated with increased vaginal lubrication, genital sensation, orgasm frequency, and overall sexual satisfaction.<sup>24</sup> A follow-up study of 19 women showed significant changes in women with FSD as well as women without complaints of sexual dysfunction.<sup>25</sup> The device is relatively expensive and may or may not be reimbursed by insurance.

### **Orgasmic disorder**

Female orgasmic disorder is the persistent or recurrent difficulty, delay in, or absence of attaining orgasm following sufficient sexual stimulation. In general, desire and arousal must be present in order

for a woman to reach orgasm. Most women seeking care for orgasmic disorder also have low arousal. Orgasmic disorders may be primary (lifelong) or secondary (acquired). Etiologies associated with lifelong female orgasmic disorder include fear of losing control or being vulnerable, prior deliberate curtailing of high arousal (eg, for religious or moral reasons), lack of trust of others, or fear of intimacy.<sup>10</sup> Contributing factors to acquired orgasmic disorder include medication-associated orgasmic disorder, especially with use of selective serotonin reuptake inhibitors (SSRIs) and sedatives; use of alcohol; neurologic diseases or autonomic nerve damage; testosterone insufficiency (although this is more often associated with low desire and arousal); and control issues.<sup>10</sup>

Orgasmic disorders are quite responsive to therapy. Among women for whom sexual inexperience and insufficient stimulation play a role, minimizing inhibition and maximizing stimulation are important. The patient should be encouraged to explore and practice self-stimulation as well as assert her preferences for stimulation with her partner. Vibrators may be helpful, and the use of vaginal weights may strengthen pelvic floor muscles and improve awareness of sexual response. Referral to a sex therapist is often necessary and success rates are high. A multidisciplinary approach, including counseling, behavior therapy, and pelvic floor physical therapy or rehabilitation should be considered.

### **Sexual pain disorders**

Female sexual pain disorders include dyspareunia, vaginismus, and noncoital sexual pain. Dyspareunia is recurrent or persistent genital pain associated with sexual intercourse. Penile-vaginal penetration may be impossible because of the pain caused by partial or complete penile entry. A complete history and careful physical examination are of paramount importance in determining possible causes, which include estrogen deficiency, genitourinary atrophy, infection, vulvar vestibulitis, interstitial cystitis, vulvar dystrophies, endometriosis, and anatomic changes following surgery, radiation, trauma, or childbirth.

Vaginismus is the recurrent or persistent involuntary spasm of the musculature of the outer third of the vagina that interferes with vaginal

penetration. Physical causes and gynecologic disease are absent, and this condition generally has a significant psychological component.

A discussion of the detailed evaluation and management of dyspareunia and vaginismus is beyond the scope of this article; however, diagnosis of an underlying etiology for the pain should be sought. Both disorders can benefit from education, pelvic floor physical therapy (including biofeedback and massage), and psychological counseling. Couples may need encouragement to engage in sexual activities that exclude intercourse, at least in the initial stages of treatment. In postmenopausal women, administration of vaginal or systemic estrogen can decrease pain on insertion, improve lubrication, and decrease vaginal burning. Women with vaginismus often respond very well to treatment with the daily use of dilators in graduated sizes.

## Referral for sex therapy

There are several situations in which referral to a sex therapist can be helpful in treating female sexual dysfunction. Long-standing or lifelong sexual dysfunction is often associated with anger, performance anxiety, and sex-avoidance behaviors and may require counseling. If a patient presents with more than one dysfunction, it may be difficult to identify the initial cause of the sexual problems.

Psychological problems such as depression, anxiety, interpersonal difficulties, current or past sexual abuse, and substance abuse have a negative impact on sexual function and complicate treatment strategies. Finally, lack of response to behavioral and pharmacologic interventions may necessitate psychological evaluation to identify additional contributing factors.

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# PELVIC ADHESIONS:

## Prevention through adjunctive therapies

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### Educational Objectives

At the conclusion of this activity, participants should be able:

- To discuss the use of barriers and preventative measures to lessen the incidence of pelvic adhesions

### Credit Designation:

Omnia Education, Inc. designates this educational activity for a maximum of 1 AMA PRA Category 1 Credit(s)<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

### Disclosures:

Dr Silverberg has disclosed affiliation with Genzyme Corp., Merck Serono and Duramed Pharmaceuticals, Inc.

Pelvic adhesions are a significant problem following gynecologic and obstetric surgery. More than 400,000 surgical procedures are performed annually for lysis of adhesions, with the resulting economic impact exceeding \$1.3 billion.<sup>1,2</sup> Approximately 40,000 of these operations are performed for tubal and/or ovarian adhesions. In addition, 30% to 35% of bowel obstructions are thought to result from these adhesions.

This article will review the adjunctive therapies designed to reduce the incidence of postoperative adhesion formation.

## Incidence

Many gynecologic and obstetric procedures are associated with an increased risk of development of pelvic adhesions. These include:

- Myomectomy
- Hysterectomy
- Resection/ablation of endometriosis
- Lysis of adhesions
- Tuboplasty
- Cesarean section

In 1999, Tulandi reported the incidence of pelvic adhesions at second-look laparoscopy ranging from 55% to 100% following exploratory laparotomy.<sup>3</sup> Specifically, following myomectomy, de novo adnexal adhesions developed in 94% of patients who had posterior uterine incisions compared to 56% of patients who had anterior or fundal uterine incisions.

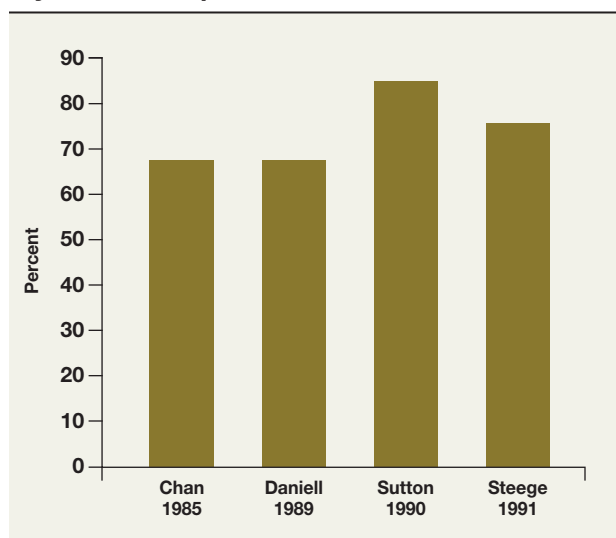
**FIGURE 1** Pain relief following adhesiolysis: 1-year follow-up

Figure adapted from various resources by Kaylen M. Silverberg, MD

=Although current thinking suggests that pelvic adhesions are more common following gynecologic surgery, they are also a significant problem following cesarean section. Such adhesions make subsequent cesarean delivery more difficult and result in a delay in delivery, with concomitant prolonged anesthetic exposure to both the baby and the mother. In addition, the risk of intraoperative injury increases significantly in the presence of adhesions.<sup>4-5</sup>

## Peritoneal adhesions and chronic pelvic pain

It is now well recognized that sensory neural fibers are present in human peritoneal adhesions. Sulaiman demonstrated that not only were neural fibers present in all peritoneal adhesions examined, but neural fibers expressing substance P were also present in all adhesions irrespective of whether or not the patient complained of chronic pelvic pain.<sup>6</sup> A review of the literature suggests that adhesiolysis in chronic pelvic patients provides limited relief, with 70% to 90% of patients experiencing relief within 1 year of surgery (FIGURE 1).

## Surgical adjuncts

### Crystalloid solutions

Crystalloid solutions are used almost universally as intraoperative surgical irrigants. By facilitating the removal of blood from the pelvis, they aid in the maintenance of a clear surgical field and may enhance tissue dissection. Many surgeons prefer to leave some crystalloid in the pelvis upon completion of a procedure, believing that this will allow the tissues to float away from each other and minimize adhesion formation. This concept, known as “hydroflotation,” is logical; however, the intraperitoneal residence time for crystalloid is less than 20 hours, ie, far less than the requisite 5 to 7 days necessary to have a significant effect.<sup>7</sup> Multiple studies have demonstrated that hydroflotation employing crystalloid has no adhesion prevention activity.<sup>7</sup> In fact, Wiseman’s meta-analysis of 259 total reports from 1966 to 1996 demonstrated that the adhesion-free outcome was enhanced when crystalloid was not left in the pelvis following procedures performed via either laparoscopy or laparotomy.<sup>7</sup> The study’s conclusion was that crystalloid “does not reduce adhesion formation [and] its use is not warranted.”

### Heparin

Some surgeons add heparin to the crystalloid solutions used for irrigation. Heparin prevents blood clotting and, when used in combination with crystalloid as an irrigant, facilitates the removal of blood from the cul de sac during surgery. It also prevents fibrin deposition, which can interrupt the adhesion formation process. Although animal studies are favorable, data on the efficacy of heparin when used as an adjunct in human pelvic surgery are limited. A randomized, placebo-controlled trial of 92 patients—the largest to date—demonstrated no difference in adhesion formation between the study and control groups.<sup>8</sup> As a result, many surgeons today use heparin in their irrigant (2,000-5,000 units per 1,000 cc crystalloid) intraoperatively, but remove the fluid at the completion of the procedure.

### Hyskon

Another product proposed to achieve hydroflotation is hyskon. This solution, comprised of 32%

dextran 70 in dextrose, is not approved by the US Food and Drug Administration (FDA) for adhesion prevention. It is highly viscous and has an intraperitoneal residence time longer than that of crystalloid. Part of its effect results from its extraordinary osmotic capability: every cc of hyskon that is left in the pelvis following surgery can pull 9 cc of fluid from the intravascular compartment to the extracellular compartment. When used in excess, this can create significant fluid shifts and result in profound physiologic derangements. Since hyskon cannot be removed by dialysis, these fluid shifts and concomitant metabolic changes can be long lasting and cause severe morbidity and mortality. There are several prospective, randomized trials comparing hyskon to crystalloid, with conflicting results.<sup>9</sup>

### NSAIDs

Several other adjuncts, including nonsteroidal anti-inflammatory drugs (NSAIDs), have also been proposed to prevent postoperative pelvic adhesions. NSAIDs block the production of thromboxane, thereby interrupting one of the adhesion formation pathways. As a result, they have been proposed as a postoperative surgical adjunct. These compounds—especially the newer versions—have not been adequately studied, so no definitive conclusions can be drawn regarding their use. In addition, appropriate concerns about the risk of postoperative bleeding may limit the widespread use of these agents in certain clinical circumstances.

### Adhesion barriers

Due to the magnitude of the problem of pelvic adhesions as well as the limited efficacy of the methods described above, the medical technology companies have developed a variety of barriers that can be used intraoperatively to minimize adhesion formation. Over the past 20 years, many such devices have been proposed, scientifically evaluated, and clinically validated. Several have gone through the regulatory process and have obtained FDA approval, and they are now available for use.

The typical study design used to clinically evaluate new adhesion barriers is a prospective, randomized trial, approved by an institutional

### The perfect adhesion barrier

If one were to design the perfect adhesion barrier, it would possess many characteristics that would maximize efficacy and minimize the potential for adverse effects. It would be nonreactive, reducing the risk of inducing adhesion formation, and would be supplied in an easily administered formulation, such as a liquid, gel, spray, or solid material. Perhaps most important, it would have adequate residence time. As discussed previously, to maximize effectiveness, an ideal barrier would keep tissues separated for at least 5 to 7 days. Following that time, the barrier would be absorbed or metabolized without initiating a tissue response, and the metabolic products would be inert and easily excreted. Finally, it could be used either at laparoscopy or laparotomy.

review board (IRB). At the time of the initial surgical procedure, all existing adhesions are noted and scored. Any sites that undergo a surgical procedure (incision, repair, laser vaporization, cautery, etc) are also noted. Although many different scoring systems have been proposed, most of the more recent trials evaluate approximately 20 different sites in the pelvis and abdomen. Adhesions are classified based on:

- The organs involved
- The extent of involvement
  - Less than 1/3 of the organ involved
  - 1/3 to 2/3 of the organ involved
  - Greater than 2/3 of the organ involved
- The nature of the adhesion
  - Thin, filmy
  - Dense, vascular
  - Cohesive
- The area of the adhesion

Patients typically undergo a second-look laparoscopy 4 to 8 weeks after their first procedure, at which time any adhesions are again scored to assess both de novo adhesion formation as well as adhesion reformation. All procedures are recorded on DVD, and the discs are reviewed by the investigator and a blinded, independent reviewer. Statistical analysis is then performed to determine the efficacy of the new product.

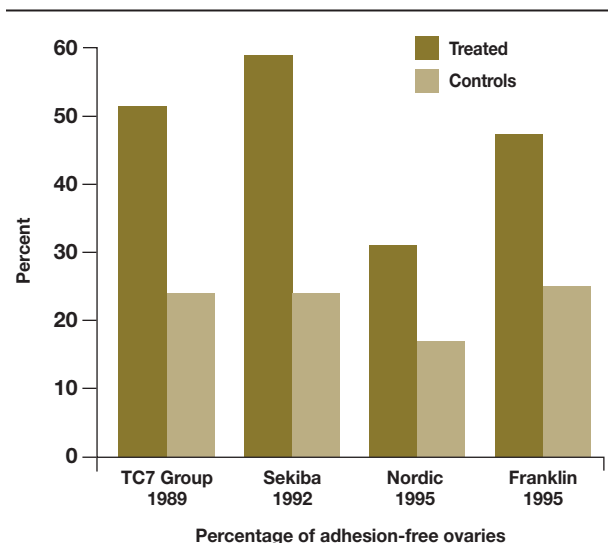
**FIGURE 2 Interceed Trials**

Figure adapted from various resources by Kaylen M. Silverberg, MD

## Available barriers

### Oxidized regenerated cellulose

Oxidized regenerated cellulose (Gynecare Interceed (TC7) Absorbable Adhesion Barrier) was one of the first commercially developed adhesion barriers. Initially called TC7, Interceed is made of oxidized regenerated cellulose<sup>10</sup> and comes packaged in a single 3- × 4-inch sheet approved by the FDA for use at laparotomy. The Interceed sheet can be cut to obtain the desired size and can then be placed onto the tissue surface, where it adheres without suturing. The sheet turns into a gel within 8 hours and then forms a gelatinous “cocoon” overlying the tissue within approximately 20 hours. Within 3 days, Interceed degrades into glucose and glucuronic acid, and it is completely excreted within 10 days of application.

Although easy to apply at laparotomy, Interceed is somewhat more challenging to use through the laparoscope. The sheet can technically be rolled and passed through a 5-mm trocar, where it can then be placed using 2 surgical instruments. It is important to note that even though laparoscopic use is feasible, the FDA issued a black box warning regarding the laparoscopic use of Interceed, indicating that neither safety nor efficacy have been demonstrated.

Since the first published study on Interceed in

1989, multiple surgical trials have demonstrated clinically significant efficacy of Interceed (**FIGURE 2**). Most early trials used each patient as her own control, placing Interceed on one sidewall following an initial lysis of adhesion procedure. Sidewalls were then scored at the time of second-look laparoscopy, and the results of both de novo and adhesion reformation were determined and compared. Despite consistent reports of efficacy, other surgical trials and communications began to suggest that, in the absence of absolute hemostasis, Interceed was less effective at best, and potentially adhesiogenic at worst.<sup>11,12</sup> It was noted that upon contact with blood, Interceed would often turn black. This led to the recommendation that black Interceed should be removed and, after achieving better hemostasis, a new sheet should be placed.

With the hope of extracting more significant data from many small series, Wiseman and colleagues published a meta-analysis in 1999 evaluating 10 published randomized studies of 560 patients.<sup>12</sup> This analysis demonstrated a 24.2% reduction in adhesions on the side treated with Interceed, compared with the control side ( $P < .001$ ). Based on their statistical analysis, the authors concluded that the barrier was 1.5 to 2.5 times more effective at preventing pelvic adhesions than good surgical technique alone. The authors corroborated several earlier reports, suggesting that Interceed might be ineffective in the presence of bleeding, and expressed concern that Interceed might not remain intact at the application site for a sufficient length of time to optimally prevent adhesion formation.

### Expanded polytetrafluorethylene

At about the same time that Interceed was being evaluated, another adhesion preventative, expanded polytetrafluorethylene (Gore-Tex), was introduced to the market. Gore-Tex has a micropore structure that prevents cellular ingrowth.<sup>13</sup> It is noninflammatory and nonabsorbable, which led to the recommendation that it be removed at second-look laparoscopy. Unlike Interceed, Gore-Tex does not adhere to the tissue and has to be sutured in place. The few trials that have been published suggest clinical efficacy. One of the largest trials ( $n=27$ ), published by the Myomectomy Adhesion Multicenter Group, demonstrated that



55% of study patients had no adhesions on the uterine surface, compared with 7.4% of controls.<sup>14</sup> A subsequent, comparative trial by Haney and colleagues demonstrated an 85% reduction in the mean area of adhesions with Gore-Tex compared to 65% with Interceed in 32 patients.<sup>15</sup>

A single long-term study evaluated the safety of Gore-Tex (n=146) in a prospective, multicenter, observational manner.<sup>16</sup> In this trial, 58 patients had Gore-Tex placed laparoscopically, while 88 underwent exploratory laparotomy. Although this trial was designed to evaluate long-term safety, 24 patients underwent second-look laparoscopy. There was a single postoperative infection that did not necessitate removal of the membrane. All other patients did well, indicating that the membrane can remain in place indefinitely. Although the trial was not designed to assess efficacy, of the 24 patients who did undergo second-look laparoscopy, adhesions were present at 8 of the 21 sites where the membrane was placed, whereas adhesions were present at 17 of those 21 sites at the first surgery ( $P = .005$ ). Despite reporting this second-look laparoscopy data, the authors recognized that it was inappropriate to draw efficacy conclusions from this uncontrolled trial.

#### **Sodium hyaluronate and carboxymethylcellulose**

In contrast to the fabric-like structure of Interceed and the nonabsorbable structure of Gore-Tex, is a firm sheet of sodium hyaluronate and carboxymethylcellulose (Seprafilm). Hyaluronic acid is a ubiquitous substance found naturally in cartilage, skin, and extracellular fluid. It is also present in many cosmetic preparations. Carboxymethylcellulose is a starch that extends the product's residence time.

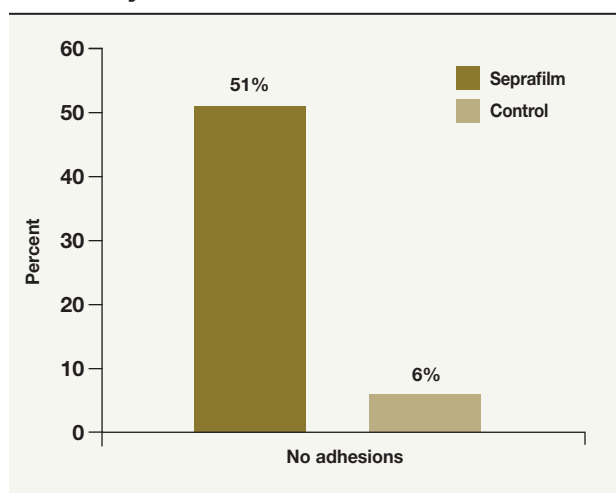
In preclinical studies, Seprafilm did not demonstrate toxicity when administered either via the intracutaneous or intraperitoneal route.<sup>17</sup> It is also nonantigenic, biocompatible, and nonhemolytic. Seprafilm does not promote bacterial growth, even in the presence of an infected bowel, and several studies have demonstrated no inhibition of wound healing.

Like Interceed, Seprafilm adheres to tissue without suturing. When applied intra-abdominally, it turns to a gel within 24 to 48 hours and remains at the site of application for up to 7 days. It is cleared

completely from the body in less than 28 days. To date, there is no evidence that Seprafilm is adhesiogenic in the presence of blood, although tissues should be dry prior to application so that the film will lay flat and adhere to tissue.

The 2 most commonly cited concerns regarding Seprafilm include the learning curve required to place it adequately and the fact that it cannot be applied laparoscopically. Seprafilm comes packaged in a Tyvek pouch, which can facilitate its application. When the product is opened and trimmed to the appropriate size, one side of the pouch should be discarded. The product and remaining Tyvek should then be grasped with forceps and placed on the tissue without contacting the surgeon's gloves or other surgical instruments. The Tyvek can then be used to gently rub over the film to ensure even application to the tissue. Concerning laparoscopic use, the brittle nature of the film makes it nearly impossible to deliver through a 5-mm trocar into the peritoneal cavity. Although anecdotal reports suggest alternatives, such as making a slurry out of small pieces of film, no significant data validate this approach.

Seprafilm is perhaps the most widely studied adhesion barrier, with more than 20 published studies demonstrating efficacy in more than 4,600 patients. In one of the largest trials, Becker et al placed 2 sheets of Seprafilm under a midline abdominal incision prior to closure in patients undergoing colectomy for ulcerative colitis.<sup>18</sup> Adhesion formation was assessed several weeks later at the time of ileostomy closure. Of the study patients, 51% were adhesion-free, compared to 6% of control patients (**FIGURE 3**). Data suggest that Seprafilm should not be wrapped around bowel anastomotic sites, because an increase in both leakage and fistula formation has been reported.<sup>19</sup> A recent multinational, prospective, randomized study by Fazio et al demonstrated that not only did Seprafilm reduce the formation of postoperative adhesions, it also reduced the incidence of subsequent small bowel obstruction.<sup>20</sup> In a prospective, randomized gynecologic trial, Diamond et al demonstrated that Seprafilm significantly reduced the incidence of postoperative adhesion formation regardless of whether myomectomy incisions were

**FIGURE 3** Incidence of adhesions following colectomy

Becker JM, Dayton MT, Fazio VW, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg*. 1996;183:297-306.

made on the anterior uterine surface, the posterior uterine surface, or both.<sup>21</sup>

Despite the demonstrated efficacy of adhesion barriers, many surgeons are reluctant to use these products because of cost concerns. In an attempt to address this issue, Bristow et al recently published a cost effectiveness study using Seprafilm in a radical hysterectomy model.<sup>22</sup> Assumptions were identical between the 2 groups concerning the incidence of factors such as postoperative radiation, length of hospital stay, and surgical complications. Based on their analysis, the authors concluded that the routine use of Seprafilm was associated with significant cost savings for both the insurers and society.

### Adept Adhesion Reduction Solution

(4% icodextrin solution)

Due partly to concerns about the delivery of solid barriers into the peritoneal cavity, many companies have been exploring liquid and/or gel alternatives for easier delivery both at laparoscopy and laparotomy. One such product that has recently gained FDA approval is Adept, a 4% icodextrin solution made of an alpha (1-4)-linked glucose polymer. It is dissolved in a buffered, isotonic electrolyte solution and is non-viscous, colorless, and odorless. Once delivered into the peritoneal cavity, it is metabolized by amylase to maltose and glucose. The relative absence of amy-

lase in peritoneal fluid affords the product increased residence time. Adept is eventually absorbed by the lymphatics and metabolized. Published data suggest that icodextrin provides prolonged hydroflotation, as approximately 60% of Adept was still present in the abdomen 4 days after instillation.<sup>23</sup>

To date, the only published data for Adept has been from its pivotal trial.<sup>24</sup> This double-blind, randomized, controlled study used lactated ringers as the control. To qualify for inclusion, patients had to have at least 3 adherent sites, which were lysed at the time of laparoscopy. Adept, 100 mL, was applied as an irrigant every 30 minutes, and 1 L was left in the pelvis at the completion of the procedure. A second-look laparoscopy was performed 4 to 8 weeks later, and both de novo adhesion formation and adhesion reformation were evaluated at that time. Although 777 patients consented to participate in the study, only 449 qualified intraoperatively. There were no differences in baseline measurements between the 2 groups. Three primary end points were designed for the pivotal trial:

- A decrease in adhesions at second-look laparoscopy of at least 3 sites or 30% of the sites where adhesions were initially lysed
- Fewer sites with adhesions at second-look laparoscopy compared to the initial surgery in study patients
- A greater number of study patients with a lesser number of sites with dense adhesions at second-look laparoscopy compared to controls

Data analysis demonstrated that significantly more study patients achieved the first primary end point than did controls ( $P < 0.05$ ). In addition, study patients demonstrated a 23% reduction in the number of sites with adhesions at second-look laparoscopy compared to the first surgery ( $P < .001$ ). There was no difference in the incidence of dense adhesions between the 2 groups at the time of the second-look laparoscopy.

## Summary

These studies suggest that, despite tremendous recent advances in adhesion prevention, the most

important factor in the treatment of postoperative adhesion formation may be to minimize the formation of adhesions from the beginning. This starts with surgical technique, including the minimization of tissue manipulation, the use of continuous irrigation and nonreactive small-gauge suture, meticulous hemostasis, and peritoneal closure.

Crystalloid has several advantages: it is inexpensive, it can be instilled both at laparoscopy and laparotomy, and its use facilitates the removal of blood from the posterior cul de sac. However, as an adhesion preventative, its use is limited by an ultrashort intraperitoneal residence time. Furthermore, a meta-analysis suggested that the incidence of postoperative adhesion formation is actually greater when crystalloid is left in the pelvis following surgery than when it is not.

Interceed is effective and easy to apply at laparotomy. Although more technically challenging, it can be applied at laparoscopy. Potential disadvantages of using Interceed include: a residence time that may be too short, according to one meta-analysis; it is contraindicated in the presence of infection; and it is possibly adhesiogenic in the presence of blood. Therefore, in order to take maximum advantage of its demonstrated efficacy, it is important to strive for absolute hemostasis prior to placing Interceed.

The most widely studied adhesion-prevention product to date is Seprafilm, with published data on more than 4,600 patients. This product appears to have an adequate intraperitoneal residence time, and its efficacy is unaffected by either blood or inflammation. It is the only product proven to not only reduce adhesion formation but also to reduce the incidence of subsequent bowel obstruction. Disadvantages of Seprafilm include the learning curve necessary to apply the product correctly and the

absence of a readily available and approved means of using the product at laparoscopy.

The liquid formulation of Adept makes it easy to use both at laparotomy and laparoscopy, although it is currently contraindicated for use at laparotomy. It is not miscible with blood; therefore, it can be effectively used instead of crystalloid as an intraoperative irrigant. In the only published trial to date, Adept reduced adhesion formation more significantly than lactated Ringer's solution. The exact intraperitoneal residence time of Adept is not well described, although more than 60% remained in the peritoneal cavity 4 days after instillation. Adept is contraindicated for bowel procedures, including appendectomy, and in the presence of intra-abdominal infection.

## Conclusion

Pelvic adhesions represent a significant cause of both morbidity and mortality following intra-abdominal and/or pelvic surgery. Surgical procedures associated with a significant incidence of pelvic adhesions include myomectomy, resection/vaporization of endometriosis, lysis of adhesions, tuboplasty, ovarian cystectomy, and hysterectomy. Recent data also suggest that cesarean section causes significant adhesion formation. In order to minimize the potential morbidity and mortality associated with adhesion formation following these procedures, it is incumbent on the surgeon to take all possible measures to lessen the likelihood of inducing the formation of adhesions. Such measures include optimizing surgical technique to decrease the occurrence of tissue damage and considering the use of intraoperative barriers. ■

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# THE OMNIA CME JOURNAL:

## A CME Self-Study Activity

Please complete the self-evaluations for each article you read and complete the activity evaluation. 1 CME credit is designated per article. Please check only one box for each question. Complete the request for certificate on page 27 and fax or mail completed evaluations to the information provided.

### SELF-EVALUATIONS

#### GENITAL HERPES: Common questions about diagnosis and transmission

- Compared to viral culture, use of polymerase chain reaction (PCR) to detect herpesvirus (HSV) in genital lesions:**
  - ☐ Is more dependent on careful sampling and transport
  - ☐ Has higher sensitivity
  - ☐ Requires more time for results to be available
  - ☐ Is less expensive
- Which one of the following statements is correct regarding interpretation of type-specific serology results in nonpregnant women who are culture- or PCR-negative?**
  - ☐ Results indicating seropositivity for HSV-1 indicate a definite genital HSV-1 infection
  - ☐ Results indicating seropositivity for HSV-2 indicate a definite genital HSV-2 infection
  - ☐ Results indicating seropositivity for HSV-2 indicate that the infection is orolabial, not genital
  - ☐ Results indicating seropositivity for HSV-2 indicate that there is no need to swab subsequent lesions
- How confident do you feel counseling patients with genital herpes on strategies that can reduce their risk of sexually transmitting HSV to their partners?**  
(5 = Extremely confident, 1 = Not at all confident, N = Not applicable)  
5   4   3   2   1   N
- Patients presenting with recurrent lower genital-tract inflammations in the absence of ulcerative GH lesions are rarely considered by the physician or the patient to have GH.**
  - ☐ True
  - ☐ False
- The Centers for Disease Control (CDC) and the American College of Obstetricians and Gynecologists (ACOG) recommend type-specific serologic testing to diagnose unrecognized GH infection. Practice situations in which serologic testing is essential in making a GH diagnosis can be:**
  - ☐ To confirm a visual diagnosis especially with a negative GH culture
  - ☐ To diagnose patients with recurrent lower genital-tract clinical symptoms suggestive of GH but without lesions
  - ☐ To determine whether current or previous sex partners of a GH patient also have GH
  - ☐ If an STD patient has an increased risk of also having GH that warrants STD screening
  - ☐ To include as part of STD screening when a patient has another form of STD infection that suggests a risk of also having GH
  - ☐ If a patient requests his or her GH infection status
  - ☐ All of the above
- Based on this article, what 2 new patient care strategies do you plan to use that you have not used before?**  

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- What challenges or barriers might you face as you work to implement these strategies?**  

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## FEMALE SEXUAL DYSFUNCTION: A vexing problem in women's health

- Which of the following approaches is NOT emphasized in the Biopsychosocial Model of Sexual Functioning:
  - ☐ Sexual arousal
  - ☐ Sexual stimuli
  - ☐ Orgasm
  - ☐ Emotional intimacy
  - ☐ Emotional and physical satisfaction
- Hypoactive sexual desire disorder is the most common female sexual disorder and is often associated with:
  - ☐ Low levels of physical and emotional satisfaction
  - ☐ Sexual activity despite lack of desire
  - ☐ Failure to initiate sexual encounters when desire is experienced
  - ☐ Diminished desire due to relationship difficulties and/or psychological issues
  - ☐ All of the above
- Laboratory testing of serum testosterone levels in postmenopausal women is indicated for which of the following?
  - ☐ To confirm the diagnosis of hypoactive sexual desire disorder
  - ☐ To identify supraphysiologic levels of testosterone in women receiving androgen therapy
  - ☐ To diagnose women with testosterone insufficiency
  - ☐ As a measure of efficacy in women receiving androgen therapy
- Exercises designed to enhance comfort and communication between partners and reduce a patient's anxiety about various aspects of sexual function are called:
  - ☐ Cognitive restructuring
  - ☐ Reframing
  - ☐ Sensate focus
  - ☐ Kegel exercises
- The experience of sexual arousal is primarily modulated by the woman's:
  - ☐ Degree of genital congestion
  - ☐ Degree of vaginal lubrication
  - ☐ Age
  - ☐ Partner's sexual drive
  - ☐ Emotional response
- Based on this article what 2 new patient care strategies do you plan to use that you have not used before?  

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- What challenges or barriers might you face as you work to implement these strategies?  

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## PELVIC ADHESIONS: Prevention through adjunctive therapies

- Pelvic adhesions are more likely to occur following a myomectomy when the incisions are made on the anterior aspect of the uterus.
  - ☐ True    ☐ False
- The intraperitoneal residence time for crystalloid solutions is:
  - ☐ <20 hours      ☐ 2 to 3 days
  - ☐ 48 hours        ☐ 7 days
- After a pelvic adhesion barrier is used, in how many days will a confluent layer of mesothelial cells provide a natural, adhesion-resistant surface to prevent the formation of new adhesions?
  - ☐ 3 days    ☐ 5 days    ☐ 7 days
- Approximately how many surgical procedures are performed each year for lysis of adhesions?
  - ☐ 200,000      ☐ 400,000
  - ☐ 300,000      ☐ 500,000
- How many weeks following their first procedure do patients typically undergo a second-look laparoscopy?
  - ☐ 2 to 3 weeks
  - ☐ 3 to 5 weeks
  - ☐ 5 to 7 weeks
  - ☐ 4 to 8 weeks
- Based on this article, what 2 new patient care strategies do you plan to use that you have not used before?  

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- What challenges or barriers might you face as you work to implement these strategies?  

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## ACTIVITY EVALUATION

Answer questions 1 and 2 using a scale of 1 to 5 in which 5 = Strongly Agree, 3 = Agree, and 1 = Strongly Disagree

	HERPES	FSD	PELVIC ADHESIONS
1. Article met the stated objectives.	5 4 3 2 1	5 4 3 2 1	5 4 3 2 1
2. Article is relevant to my current clinical practice needs.	5 4 3 2 1	5 4 3 2 1	5 4 3 2 1
3. Disclosure of faculty relationships with commercial organizations was made available to me before the articles.	<input type="checkbox"/> True <input type="checkbox"/> False	<input type="checkbox"/> True <input type="checkbox"/> False	<input type="checkbox"/> True <input type="checkbox"/> False
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7. Any off-label drug use and/or investigational drug use not yet approved by the FDA was disclosed before or during the activity.	<input type="checkbox"/> True <input type="checkbox"/> False	<input type="checkbox"/> True <input type="checkbox"/> False	<input type="checkbox"/> True <input type="checkbox"/> False

8. If you answered "false" to any of the above questions, please provide details in the comments section below.

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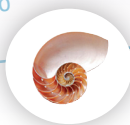
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