Virtual Well Woman Visit
Innovations in routine gynecologic care

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Julia Cron, MD &
Shefali R. Pathy, MD, MPH

ContemporaryOBGYN.net
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS
Few cases (0.36%) of adverse reactions of cystitis, pyelonephritis and other upper urinary tract infection (UTI) have been reported in Phexxi™ clinical studies. Of these, one case of pyelonephritis was considered serious and required hospitalization. Avoid use of Phexxi™ in females of reproductive potential with history of recurrent urinary tract infection or urinary tract abnormalities.

ADVERSE REACTIONS
Most common adverse reactions were vulvovaginal burning sensation, vulvovaginal pruritus, vulvovaginal mycotic infection, urinary tract infection, vulvovaginal discomfort, bacterial vaginosis, vaginal discharge, genital discomfort, dysuria, and vulvovaginal pain.

Patients should be counseled on the following:
- To contact and consult with their healthcare provider for severe or prolonged genital irritation or experiencing urinary tract symptoms.
- To discontinue Phexxi™ if they develop a local hypersensitivity reaction.
- That Phexxi™ does not protect against HIV infection or other sexually transmitted infections.

To report SUSPECTED ADVERSE REACTIONS, contact Evofem at toll-free phone 1-833-EVFMBIO or you may contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
IMPORTANT SAFETY INFORMATION

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INDICATIONS AND USAGE

Phexxi™ is indicated for the prevention of pregnancy in females of reproductive potential for use as an on-demand method of contraception.

LIMITATIONS OF USE

Phexxi™ is not effective for the prevention of pregnancy when administered after intercourse.

Please see full Prescribing Information for Phexxi™.

Please see Brief Summary on the following page.

REFERENCES:


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ADVERSE REACTIONS

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

The safety of PHEXXI (pre-filled applicator with 5-gram dose) has been evaluated in two clinical trials (Study 1 and Study 2) in 2804 subjects (over 19,000 cycles of exposure). The racial/ethnic distribution was 66% White, 27% Black or African American, 2% Asian, 1% American Indian or Alaska Native, 0.5% Native Hawaiian or Pacific Islander, and 5% other; 32% of the study population was Hispanic. Study 1 included a one-year extension phase where 342 U.S. subjects were exposed to PHEXXI for 13 cycles.

The most common adverse reactions (≥10%) in the U.S. population in Study 1 were: vulvovaginal pruritus (14.5%), vulvovaginal pain (10%), and urinary tract infection (9.1%). The most common adverse reactions (≥10%) in Study 2 were: vulvovaginal pruritus (14.5%), vulvovaginal pain (10%), urinary tract infection (9.1%), and UTI (9.0%). The majority of these adverse reactions were considered serious and required hospitalization. Avoid use of PHEXXI in females of reproductive potential with a history of recurrent urinary tract infection or urinary tract abnormaties.

ADVERSE REACTIONS

ADVERSE REACTIONS

Table 1. Adverse Reactions that Occurred in ≥2% of Subjects Who Used PHEXXI to Prevent Pregnancy (Studies 1 and 2 – U.S. population only)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PHEXXI (N=2480) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal Burning Sensation</td>
<td>18.0</td>
</tr>
<tr>
<td>Vulvovaginal Pruritus</td>
<td>14.5</td>
</tr>
<tr>
<td>Vulvovaginal Mycotic Infection*</td>
<td>9.1</td>
</tr>
<tr>
<td>Urinary Tract Infection†</td>
<td>9.0</td>
</tr>
<tr>
<td>Vulvovaginal Discomfort</td>
<td>9.0</td>
</tr>
<tr>
<td>Bacterial Vaginosis</td>
<td>8.4</td>
</tr>
<tr>
<td>Vaginal Discharge</td>
<td>5.5</td>
</tr>
<tr>
<td>Genital Discomfort</td>
<td>4.1</td>
</tr>
<tr>
<td>Dysuria</td>
<td>3.1</td>
</tr>
<tr>
<td>Vulvovaginal pain</td>
<td>2.1</td>
</tr>
</tbody>
</table>

‡Does not include PTs cystitis, kidney infection, and pyelonephritis [see Warnings and Precautions (5.1) of PHEXXI Full Prescribing Information].

Among subjects who used PHEXXI in Studies 1 and 2, 1.6% discontinued from the clinical trials due to an adverse reaction. The most common adverse reactions leading to study discontinuation were vulvovaginal burning sensation (0.7%); and vulvovaginal pruritus and vulvovaginal discomfort (0.1% each).

Adverse Reactions in Male Partners:
Among male partners of subjects who used PHEXXI for contraception in Study 2, 9.8% (151 of 1330) reported symptoms of local discomfort (burning, itching, pain, and “other”). Of these local discomfort symptoms, 74.7% were mild, 21.4% were moderate, and 3.9% were severe. Two subjects discontinued participation in the study due to male partner symptoms.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There is no use for PHEXXI in pregnancy; therefore, discontinue PHEXXI during pregnancy. There are no data with the use of PHEXXI in pregnant women or animals. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

Lactation
Risk Summary
There are no data on the presence of lactic acid, citric acid, and potassium bitartrate or their metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.

Pediatric Use
The safety and effectiveness of PHEXXI have been established in females of reproductive potential.

Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users 17 years and older. The use of PHEXXI before menarche is not indicated.

PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling.

Advise the patient to read the Patient Information and FDA-approved patient labeling (Instructions for Use).

Advise the patient:
• To intravaginally administer the contents of one pre-filled single-dose applicator of PHEXXI before each episode of vaginal intercourse and to administer an additional dose if intercourse does not occur within one hour of administration [see Dosage and Administration (2.1) of PHEXXI Full Prescribing Information].
• To consult their healthcare provider for severe or prolonged genital irritation [see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information].
• To discontinue PHEXXI if they develop a local hypersensitivity reaction [see Adverse Reactions (6.1) of PHEXXI Full Prescribing Information].
• To contact their health care provider if experiencing urinary tract symptoms [see Warnings and Precautions (5.1) of PHEXXI Full Prescribing Information].
• That PHEXXI does not protect against HIV infection and other sexually transmitted infections.

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CHAIRMAN’S LETTER

Quality content is our commitment

With this issue we welcome three members to the distinguished editorial board that has guided Contemporary OB/GYN since its inception. Yalda Afshar, MD, PhD; Christine Isaacs, MD; and Laura Riley, MD, begin their time in lending expertise to our content. Read more about each remarkable scientist on Page 7. We hope you also will find the articles in this issue timely and informative. The Society for Maternal-Fetal Medicine (SMFM) shares its Consult Series #50 on Activity Restriction in obstetric management. Editor-in-Chief Catherine Y. Spong, MD, dedicates her editorial to the topic with an endorsement to put activity restriction to bed—her pun fully intended.

Practitioners continue to navigate health care in a pandemic, conducting much patient communication virtually. Four doctors from Yale—Linda L. Fan, MD, FACOG; Shefali R. Pathy, MD, MPH; Julia Cron, MD; and Sangini S. Sheth, MD, MPH—offer their guidance on managing the Well Woman visit via telehealth.

In the first of a two-part series, Amanda Kallen, MD, FACOG, and Sandra Ann Carson, MD, FACOG, offer a thorough guide to diagnosing an infertile couple. Watch for next month’s article as well, where they provide a guide for treatment.

Beginning on Page 31, Ronald J. Wapner, MD, makes a case for improved carrier screening as historical screening has limitations.

Please let us know what you think of this content; reader feedback is invited by emailing Senior Editor Angie DeRosa at aderosa@mjhlifesciences.com.

Mike Hennessy, Sr.
Chairman and Founder, MJH Life Sciences
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WELL WOMAN
Virtual Well Woman Visit
Innovations in routine gynecologic care
Linda L. Fan, MD, Sangini S. Sheth, MD, MPH, Julia Cron, MD, & Shefali R. Pathy, MD, MPH

THE EDITORS ARE PLEASED TO ANNOUNCE the availability of our parent company’s continuing education activities. We’ve picked this one especially for our readers - http://bit.ly/BreastCancerCME
In a world that has often misunderstood women's health, Hologic has always put women first. Our mission to help you provide the highest quality of personalized care to women has never wavered, and we’re committed to partnering with you to advance women's health through truth, expertise and scientific understanding.

At Hologic, we develop leading-edge technology based on a deep understanding of women's needs. We offer a broad range of solutions for screening, detecting and treating health challenges throughout a woman's life – from breast and cervical cancer to osteoporosis, preterm birth and heavy periods. For you, that means greater certainty and confidence in the diagnoses, decisions and treatments you provide to the women in your care.

Hologic.com/womenstories.
Putting activity restriction in pregnancy to rest

Many obstetric and gynecologic practices are not based on strong evidence, despite the great strides that we’ve made in the last several decades in identifying therapies and providing data to support existing practice recommendations. We rely on expert opinion and common-sense management strategies for many conditions - in part, due to limited research for pregnant and lactating women. We are always in search of a new therapy, a new intervention, and data to support the therapies we provide. Often we adopt practices that seem intuitive; however, once evaluated, we find that what seemed to make complete sense at the time is not actually supported by evidence.

As detailed in this issue, the Society for Maternal-Fetal Medicine (SMFM) is highlighting one of these situations: the role of activity restriction in obstetric management. For decades, activity restriction – from bedrest to reducing daily activities, exercise, and/or work – was recommended with the intent to improve pregnancy outcomes. With the concern that activity may increase uterine activity, rest was felt to be important in women with preterm labor and preterm rupture of membranes to reduce the risk of preterm birth (PTB). In the setting of premature cervical dilation, in addition to reducing uterine activity, rest – specifically bed rest or lying down – was used to reduce the “pull of gravity.” Finally, the concept that rest might improve placental perfusion underlies recommendations in the setting of fetal growth restriction and hypertension.

Given the widespread implementation of activity restriction, evidence for or against this recommendation has been difficult to obtain. As outlined in the article, research is now available to provide guidance for our practitioners recommending against routine use of activity restriction. Furthermore, the data demonstrating risk of activity restriction – both physiologic and psychologic - are outlined.

The translation of research findings, especially when they go against common opinion, takes decades. The initial randomized controlled trials of activity restriction for PTB – demonstrating no benefit – were published 15 and 26 years ago. I am hopeful that this expert guidance from SMFM will provide the final impetus to put this advice “to rest” – pun intended.

The longer the practice had been recommended the more likely it was to be administered. In addition, the setting was important, as the intervention in the outpatient setting (progesterone) was the least administered. Interestingly, over 90% of providers were satisfied with their knowledge and stated they used all three interventions, yet when eligible patients were identified, 93% were offered antenatal steroids, 71% magnesium sulfate, and 39% progesterone.

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is pleased to announce the addition of new members to its distinguished editorial board.

YALDA AFSHAR, MD, PHD
Dr. Afshar is an assistant professor in the division of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, at the University of California, Los Angeles.

“It is such an honor to join a team working tirelessly to disseminate information about evidence-based best practices to a diverse readership with a simple goal: taking excellent care of the patients in front of us!”

CHRISTINE ISAACS, MD
Dr. Isaacs is a general ob/gyn, professor, and Academic Specialist Division Chief at the Virginia Commonwealth University School of Medicine in Richmond, VA. She also is the medical director of Midwifery Services.

“I’m excited for the opportunity to reflect on the many advancements in our field, to learn from the wisdom of inspirational colleagues, and to contribute to the well-vetted and practical guidance that supports us as busy clinicians!”

LAURA RILEY, MD
Dr. Riley is chair of Obstetrics and Gynecology at Weill Cornell Medicine and Obstetrician and Gynecologist-in-Chief at New York Presbyterian Hospital in New York City.

“I am excited to join the editorial board because I have always found the articles in Contemporary OB/GYN to be timely, accurate, and relevant to current practice—always a great resource.”
Physician burnout was recognized as a growing problem in the medical field well before the start of the COVID-19 pandemic. Burnout is characterized by exhaustion, reduced professional efficacy, and a feeling of negativity or cynicism towards work. It occurs in response to chronic work stress in which one’s perceived needs outweigh the perceived resources available. Prior to the pandemic, studies demonstrated that 35% to 54% of US nurses and physicians had symptoms of burnout.

Any professional who is exposed to high levels of stress is at risk. Physicians are especially vulnerable. The characteristics that are emphasized and rewarded during medical training are the same ones that make a physician vulnerable to burnout. They include dedication, compassion, altruism, being detail-oriented, and putting others above self. Although these traits are important for the day-to-day work of the physician, they also have the potential to exacerbate burnout when taken to the extreme. Over a prolonged period, burnout erodes our humanity and our ability to connect in a meaningful way with ourselves, our loved ones, and our patients. The consequences are far-reaching and can have implications on a personal and institutional level. Physicians who are suffering from burnout can have decreased career satisfaction, strained personal relationships, abuse substances, and be at higher risk of suicide. Physicians with burnout have lower patient satisfaction scores. From an institutional perspective, burnout decreases physician retention, leading to higher faculty turnover and lower productivity.

In times of crisis, as the medical community is now experiencing with COVID-19, chaos and trauma can stress an already fragile community. During the pandemic, physician self-care and organizational efforts to protect physician well-being are vital to maintaining a healthy and able workforce, which in turn enables a strong response to the ongoing health crisis. Many health organizations and institutions have created programs to address this and have made strides to remedy it. In this article, we will review how individual physicians can recognize and prevent burnout, as well as how to use an institution’s position to mitigate physician burnout and deal with traumatic events.

Self-care
The first step to addressing burnout on an individual level is recognizing the symptoms. It can manifest both emotionally and physically and can present in varying degrees of severity. Physicians can feel a range of emotions, including sadness, fear, or apathy. They can feel easily frustrated, irritable, or anxious, which can affect work and personal relationships. Physical symptoms can include weight gain or loss, palpitations, fatigue, and poor sleep, which can have long-term health consequences. Physicians who suffer from burnout may also distance themselves from colleagues and family. Social distancing, whether forced or as a result of burnout, can lead to feelings of isolation and disruptive behaviors, which in turn lead to further isolation. In certain vulnerable individuals, isolation can contribute to depression and create barriers to seeking professional help.

Physician burnout and self-care
by DEEPIKA SAGARAM, MD, AND FRANCINE HUGHES, MD

“Unfortunately, medicine has always prided itself on this toxic culture of invincibility: the imperturbable physician, one who rises above daunting circumstance ever calm and collected. We idealize ourselves as superhuman, yet in reality we are so plainly human.”

– Atul Nakhasi, MD
help. Several tools have been developed to identify physicians with burnout, including prominent ones such as the Maslach Burnout Inventory® and Mini-Z Burnout Assessment, which is adapted from the work of Mark Linzer, MD.7

From early in training, physicians are taught and valued for their ability to “power through,” whether it be the long hours, difficult rotations or deprivations of food, sleep or bathroom breaks. The ability to persevere is important for withstanding short-term challenges but is not sustainable in the long term. Practicing self-care can help individuals withstand longer periods of hardship.

“The most important patient we have to take care of is the one in the mirror.”

– Robert Wah, MD, Former AMA president

A core principle of self-care is prioritizing one’s own needs in some way that is valuable to the individual. Therefore, self-care is different for everyone. Carving out time and energy to do something that is important to you is the key. Self-care is a practice that is rarely taught during medical training but is essential to prevent or mitigate burnout. The well-known phrase, borrowed from the airline industry, illustrates this concept: One must secure her own mask before helping others. By caring for themselves first, physicians are in a better position to give quality care to patients, leading to both patient and physician satisfaction. Methods to prevent and combat burnout can be addressed at the personal and institutional levels.

Fundamental to self-care is ensuring that basic needs are met. This includes obtaining adequate sleep, eating regular meals, and taking adequate breaks as needed throughout the day. Fatigue is a common cause and symptom of burnout, leading to difficulty in concentrating, poor communication, and emotional lability. To combat fatigue, prioritizing sleep and creating a regular pre-bedtime routine can aid in restful sleep. Strategically timed naps can also be helpful in combating fatigue, particularly during night shift work. Nutrition is another important factor in maintaining well-being and can also play a role in fatigue. Alcohol and caffeine should be consumed judiciously.

The practice of medicine and medical culture can be isolating. As such, it is important to remain connected to loved ones. In the time of social distancing, this can be done through regular communication via phone calls or video chats. Table 1 lists several options for remaining connected to loved ones. Taking regular breaks throughout the day can also provide respite from stressful work. Breathing exercises can be done during these breaks or during high stress situations to ground oneself. Practices such as mindful meditation and yoga can be helpful in creating a calm and balanced mind.8,9 Meditation has recently gained attention as an effective method for alleviating stress. Several applications exist that can be downloaded to a phone for use. For example, Headspace has been used by surgeons prior to an operation to improve focus and relaxation.10 Exercise, especially if done outdoors, can be invigorating and can boost mood. Checking one’s emotional “temperature” is imperative to recognizing the early signs of burnout, and if necessary, obtaining professional help. Seeking professional help is encouraged, and these days, there are many options, including teletherapy, group therapy, and group webinars.

Physician resilience is not only key in preventing and combating burnout, but can lead to improved work satisfaction, workplace retention, and patient outcomes and satisfaction. Resiliency training can be done at any stage of a career but is best initiated during medical training. It involves self-reflection and self-awareness to identify negative deep thoughts and emotions that are ingrained as a result of medical culture. Rephrasing these negative thoughts and developing healthy patterns of thought can go far in creating and maintaining a healthy engagement with the practice of medicine.4

**Going beyond self-care**

Institutions play a significant role in creating an environment that fosters physician well-being. Studies have shown that institutions can promote well-being by first creating a positive work environment and a positive learning environment.7 These two factors create an en-

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**IDEAS FOR STAYING CONNECTED**

- Scheduled phone or video calls
- Scheduled family/friends get-togethers:
  - Board game night*
  - Movie night*
  - Group dinner*
  - Bowling with friends and family
- Email chain
- Book club*
- Vacation with family/friends
- Group fitness class*
- Group paint night or hobby
- Cooking*

*Can be modified for online connection during social isolation
vironment of support and growth that can improve the education and health of physicians and trainees. Studies have also shown that providing support to clinicians and learners can improve the environment and ultimately lead to better care. Many hospitals offer workplace wellness programs that address stress management in addition to routine physical health. For example, many hospitals use the annual National Hospital Week to recognize employees for their contributions and to bring awareness to employee health and wellness.

The role of institutions and leadership becomes more important during times of crisis. The chaos and confusion can lead to additional stress. Institutions can help by creating methods for communicating transparently and effectively as well as avenues for feedback. This helps to create an environment of collaboration and camaraderie. Leadership can also provide for the physical needs of employees, including ensuring access to meals, access to break rooms for adequate rest, time off, and lodging as needed. They should provide resources for emotional support and schedule regular check-ins to address concerns.

**Traumatic events**

During times of crisis, resources may be scarce and the demands and rules governing the practice of medicine may change on a near daily basis. In addition, physicians bear witness to unprecedented suffering and death of the patients under their care. At the same time, physicians have been asked to put their own lives and the health of their families at risk. The stress and anxiety of this time is unparalleled. As a result, the risk of developing burnout as a physician is high. Furthermore, such unpredictable conditions and stressful situations can lead to post-traumatic stress disorder (PTSD).

PTSD in healthcare workers has not been well-studied, but the few studies done during infectious outbreaks or in traumatic environments have demonstrated a prevalence ranging from 10% to 33% and a strong correlation between burnout and development of PTSD. Second victim syndrome can also be a consequence of a traumatic event or crisis. In these instances, the physician who is involved in the care of patients feels personally responsible for the outcome. A physician experiencing this may feel guilt, shame, and remorse. For fear of repercussions or demonstrating weakness, the second victim can often suffer in silence, leading to further isolation and depression.

The recent pandemic is an example of a healthcare crisis that is affecting physicians and putting them at risk for burnout, depression, and PTSD. Physicians are being asked to work in unfamiliar environments and specialties, and to care for extraordinarily ill patients battling a virus with unpredictable outcomes. They are experiencing trauma daily as they care for an increasing surge of sick patients, many of whom cannot be saved. Healthcare workers witness their colleagues becoming ill, as they work in a setting of equipment and personal protective equipment shortages. Recognizing the effect of this unique circumstance is important because burnout can be an avenue to PTSD and serious long-term physical comorbidities.

During the pandemic and resultant social distancing, standard practices for self-care may not be possible. Because the risk of isolation is especially high, it is important to create and maintain connections with family and colleagues. These connections can create an environment of support and camaraderie, while fostering creativity and novel ideas. During times of crisis and isolation, connections with loved ones are key to maintaining emotional health. While it is important to stay abreast of news and new developments, setting limits on media exposure may be necessary to preserve well-being. Performing regular self-check-ins or check-ins with a colleague may be a way of recognizing the early signs of burnout so they can be addressed in a timely manner.

**Conclusion**

Physician burnout remains a serious and pervasive problem. Medicine has created a culture that values dedication, independence, and excellence, often to the detriment of the physician. This can then have consequences that jeopardize patient care and the life of the physician.

As a community, we can alter our culture to support self-care and a safe environment that fosters healthy lifestyles in physicians.
FOR THE TREATMENT OF WOMEN WITH MODERATE TO SEVERE DYSPAREUNIA, A SYMPTOM OF VULVAR AND VAGINAL ATROPHY, DUE TO MENOPAUSE

DISCOVER A TREATMENT EXPERIENCE WITH SIMPLICITY AT ITS CORE

THE ONLY ULTRA-LOW-DOSE VAGINAL ESTRADIOL AVAILABLE IN BOTH 4-MCG AND 10-MCG DOSES

PROVEN EFFICACY AT WEEK 12 AND BEGINNING AS EARLY AS WEEK 2 (A SECONDARY ENDPOINT)

MESS-FREE ADMINISTRATION WITH NO APPLICATOR, DOSE PREPARATION, OR CLEANUP NEEDED

INDICATION

IMVEXXY (estradiol vaginal inserts) is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

IMPORTANT SAFETY INFORMATION

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

• There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens
• Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia
• The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT)
• The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

Estrogen Plus Progestin Therapy

• Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia
• The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI)
• The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer
• The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older

CONTRAINDICATIONS

• IMVEXXY is contraindicated in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease or a history of these conditions; known anaphylactic reaction or angioedema to IMVEXXY; known liver impairment or disease; known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

WARNINGS AND PRECAUTIONS

• IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY.
• The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.
• The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.
• Other warnings include: gallbladder disease; severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice.
• Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
• Women on thyroid replacement therapy should have their thyroid function monitored.

ADVERSE REACTIONS

• The most common adverse reaction with IMVEXXY (incidence ≥3 percent) and greater than placebo was headache.

Please see Brief Summary of the Full Prescribing Information, including BOXED WARNING, on the following page.


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IMVEXXY® (estradiol vaginal inserts)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use IMVEXXY safely and effectively. Please visit www.IMVEXXYHCP.com for Full Prescribing Information.

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

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see Warnings and Precautions (5.3) and Clinical Studies (14.2)] in full prescribing information].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].

The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (0.625 mg)-alone, relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHI Memory Study (WHMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)] in full prescribing information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3) in full prescribing information].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke, and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg) relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)] in full prescribing information].

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see Warnings and Precautions (5.3), and Clinical Studies (14.2)] in full prescribing information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins. Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin [see Warnings and Precautions (5.3, 5.15)] in full prescribing information].

Use of estrogen-alone, or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

CONTRAINDICATIONS

Undiagnosed abnormal genital bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active DVT, PE, or history of these conditions; active arterial thromboembolic disease (e.g., stroke and myocardial infarction (MI)) or a history of these conditions; known anaphylactic reaction or angioedema with IMVEXXY; known liver impairment or disease; known hypertriglyceridemia; hepatic impairment and/or past history of cholestati jaundice; hypothyroidism (women on thyroid replacement therapy may require higher doses of thyroid hormone); fluid retention; hypocalcemia; exacerbation of endometriosis; hereditary angioedema; exacerbation of other conditions (asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomata).

ADVERSE REACTIONS

Clinical Trials Experience: In a single, prospective, randomized, placebo-controlled, double-blind trial, the most common adverse reaction with IMVEXXY (incidence ≥ 3 percent) and greater than placebo was headache.

Post-Marketing Experience: The following adverse reactions have been identified during post-approval use of IMVEXXY 4 and 10 mcg. Genitourinary-System: vaginal discharge.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration.

USE IN SPECIFIC POPULATIONS

IMVEXXY is not indicated for use in pregnancy, in females of reproductive potential, or in children.

Geriatric Use

An increased risk of probable dementia in women over 65 years of age was reported in the Women’s Health Initiative Memory ancillary studies of the Women’s Health Initiative.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

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

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

Breast Cancer

In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.83] [see Clinical Studies (14.3)] in full prescribing information].

Use of estrogen plus progestin plus progesterin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer.

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer.

Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [see Use in Specific Populations (8.5), and Clinical Studies (14.5) in full prescribing information].

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

Other Warnings and Precautions include:

- Gallbladder disease; severe hypercalcemia; visual abnormalities; elevated blood pressure; hypertrophic cardiomyopathy; hepatic impairment and/or past history of cholestati jaundice; hyperthyroidism (women on thyroid replacement therapy may require higher doses of thyroid hormone); fluid retention; hypocalcemia; exacerbation of endometriosis; hereditary angioedema; exacerbation of other conditions (asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomata).

Based on IVXY-LAB-20004.2

REV 04/2019

IMVEXXY 4/10 mcg | 09/2019

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Since the 1900s, based on the belief that activity restriction results in uterine quiescence and increased blood flow to the uterus, obstetrical care providers have recommended activity restriction to prevent preterm birth (PTB), and it remains a common intervention for PTB prevention in multiple clinical settings (Table 1). Restriction of activity is also used in management of pregnancy complications such as preterm premature rupture of membranes (PPROM), gestational hypertension, preeclampsia, fetal growth restriction (FGR), placenta previa, threatened miscarriage, and complications of multiple gestations. Activity restriction has been prescribed in nearly 20% of all pregnancies at risk for PTB. Survey data from 2009 demonstrated that over 80% of maternal-fetal medicine subspecialists recommended activity restriction in women with cervical dilation, threatened preterm labor, and PPROM.

A growing body of literature suggests that activity restriction fails to provide benefit, and in fact, confers significant physical and psychosocial risks for pregnant women, including deconditioning, inadequate maternal weight gain and lower infant birth weight, bone loss, increased risk of thromboembolic events, and significant financial costs and maternal stress. The American College of Obstetricians and Gynecologists (ACOG) and other obstetric experts do not recommend the prescription of activity restriction and specifically “bed rest” for the prevention or treatment of preterm labor. Nevertheless, activity restriction continues to be commonly recommended by obstetricians and maternal-fetal medicine subspecialists.

Q | What is the definition of activity restriction in pregnancy?

One of the difficulties in determining the benefits and harms associated with activity restriction is that no standard definition exists for this term. The terms “bed rest” and “activity restriction” are often used synonymously but may denote significantly different levels and intensity of activity. “Activity restriction” is typically used as a general term to describe some form of reduction in normal activity, while “bed rest” is usually considered the most restricted form of activity restriction. Bed rest has been variously defined in research studies as limited ambulation of not more than 1 to 2 hours per day with bathroom use and bathing permitted; confinement to bed with bathroom use permitted; or resting three times a day for 1 hour. Additional restrictions of activity may include pelvic rest and cessation from exercise, heavy lifting, and employment. Pelvic rest has been variously defined as refraining from placement of anything in the vagina, with or without cessation of sexual intercourse and other sexual activities (such as orgasm).

In addition to the lack of a standard definition, there are no universally accepted objective measurements for activity restriction. Measures of activity restriction used in most studies are based on patient report in which subjects may be asked to keep a diary of their activity to quantify data. The lack of objective measurements, such as heart rate or electronic activity monitoring, complicates the interpretation of research data and further limits the quality of available evidence.
Q What is the evidence regarding the benefits of activity restriction to prevent PTB in women with singleton pregnancies?

Two randomized clinical trials (RCTs) conducted by Elliott et al. and Hobel et al. found no differences in the rates of PTB in women who were prescribed activity restriction during pregnancy and those who were not prescribed this intervention. In addition to the lack of defined objective measurement of activity restriction, these two trials are limited by additional factors, including insufficient detail about methodology, absence of baseline characteristics of some of the study participants, and inclusion of both singleton and multiple gestations. Some evidence suggests harm resulting from activity restriction. A secondary analysis of the Maternal–Fetal Medicine Unit (MFMU) Preterm Prediction Study found that women who were assessed as being at increased risk of PTB at 23 to 24 weeks of gestation and who were prescribed activity restriction were twice as likely to have a preterm delivery than those who were not prescribed activity restriction. Study limitations included a lack of a consistent definition of activity restriction, absence of information regarding patient compliance with activity restriction, and the possibility that it was primarily the women at the highest risk for PTB who were prescribed activity restriction.

In a secondary analysis of a trial of multiparous women with singleton gestations and cervical length less than 30 mm who were randomized to treatment with 17α-hydroxyprogesterone caproate or placebo, Grobman and colleagues found that PTB at less than 37 and less than 34 weeks of gestation was more common when women were placed on any type of activity restriction, whether inpatient or outpatient. After controlling for potential confounders, they found an increase in the risk of delivery at less than 37 weeks of gestation and at less than 34 weeks of gestation (aOR 2.28, 95% CI 1.36–3.80) in women placed on activity restriction.10

A small pilot study used quantitative methods to study the effect of maternal activity on the rate of PTB. In this study, 49 pregnant women assessed as high risk for PTB wore a smart band activity tracker continuously for a week between 24 and 32 weeks of gestation. The primary outcome was the rate of PTB at less than 37 weeks of gestation, and a secondary outcome was the rate of PTB at less than 34 weeks of gestation. In all, 37 of the participants delivered preterm, and 12 delivered at 37 weeks of gestation or later. The median number of steps per day was significantly lower in participants who delivered preterm. In addition, regression analyses found an inverse association between the number of median steps per day and PTB.

In summary, although the evidence is limited and the quality generally low, available data do not demonstrate a benefit of activity restriction in women at risk for PTB, and some data suggest that this approach increases the risk of PTB. We recommend against the routine use of activity restriction in pregnant women at risk for PTB based on preterm labor symptoms, arrested preterm labor, or shortened cervix. (GRADE 1B)

Q What is the evidence regarding the benefits of activity restriction in women with hypertension, PPROM, multiple gestations, and FGR?

In addition to prevention of PTB, management of hypertensive disorders in pregnancy, PPROM, multiple gestation, and FGR are common reasons for antepartum hospital admission and frequently lead to a recommendation for activity restriction. With regard to hypertensive disorders, it has been hypothesized that activity restriction might result in a decrease in systolic blood pressure and an improvement in placental perfusion. At present, the evidence regarding use of activity restriction for the prevention or management of hypertensive disorders in pregnancy is too limited to inform recommendations.

Women with PPROM are typically managed with inpatient admission and are also placed on activity restriction or bed rest in an attempt to prolong gestation and prevent umbilical cord prolapse. However, we identified no studies examining the effects of this practice on pregnancy outcomes.

Inpatient bed rest in mid- to late gestation was once recommended routinely for women with multiple gestations. A 2010 Cochrane review identified 7 RCTs that included 713

<table>
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What is the evidence regarding the benefits of activity restriction in women with hypertension, PPROM, multiple gestations, and FGR? In addition to prevention of PTB, management of hypertensive disorders in pregnancy, PPROM, multiple gestation, and FGR are common reasons for antepartum hospital admission and frequently lead to a recommendation for activity restriction. With regard to hypertensive disorders, it has been hypothesized that activity restriction might result in a decrease in systolic blood pressure and an improvement in placental perfusion. At present, the evidence regarding use of activity restriction for the prevention or management of hypertensive disorders in pregnancy is too limited to inform recommendations.

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In summary, although the evidence is limited and the quality generally low, available data do not demonstrate a benefit of activity restriction in women at risk for PTB, and some data suggest that this approach increases the risk of PTB. We recommend against the routine use of activity restriction in pregnant women at risk for PTB based on preterm labor symptoms, arrested preterm labor, or shortened cervix. (GRADE 1B)
women assigned to routine inpatient bed rest versus hospitalization only if complications developed. These trials did not demonstrate any difference in the rates of PTB or perinatal mortality. The only detectable benefit of hospital bed rest was a decrease in the number of neonates born weighing less than 2500 g. A later Cochrane review in 2017 investigated the effect of strict bed rest (defined as resting in bed as much as possible with minimal physical activity) or partial bed rest (defined as rest for a few hours during the day with no other physical activity restrictions) in the hospital versus routine care on perinatal outcomes in women with a multiple gestation and found no differences in the risk of very PTB, perinatal mortality, low birth weight, small-for-gestational-age (SGA) infants, or PPROM. Similar findings were noted for partial bed rest. While strict bed rest was associated with a higher mean birth weight, it was not associated with a decrease in SGA infants.

A few studies have examined maternal outcomes in women with multiple gestations on activity restriction, such as weight gain and indicators of mental health status. Maloni and colleagues found that maternal stressors, symptomatic side effects, and depressive symptoms were all increased, and maternal weight gain was suboptimal in patients placed on hospital bed rest. We recommend against the use of routine inpatient hospitalization and activity restriction for the prevention of PTB in women with multiple gestations. (GRADE 1A)

FGR is often attributed to placental insufficiency, and activity restriction or bed rest is often prescribed to improve placental perfusion. However, a Cochrane review found only a single RCT that allocated women with growth-restricted fetuses to either bed rest in the hospital or work restriction at home (no subjects were allocated to normal activity). No differences were found in infant birth weight, Apgar scores, cord pH, or operative delivery rate. Given the lack of data definitively demonstrating that activity restriction improves perinatal outcome in pregnancies complicated by FGR, PPROM, or hypertensive disease of pregnancy, coupled with evidence of adverse effects of activity restriction, we suggest that activity restriction not be prescribed for treatment of pregnancies complicated by FGR, PPROM, or hypertensive disease. (GRADE 2B)

<table>
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<tr>
<th>TABLE 2</th>
<th>Physiologic and psychological effects of bed rest in pregnancy</th>
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</thead>
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| **PHYSIOLOGIC EFFECTS** | • Loss of muscle tone  
| | • Decreased lung volume  
| | • Constipation  
| | • Increased risk of thromboembolism  
| | • Increased risk of infection  
| | • Insulin resistance  
| | • Muscle soreness  
| | • Insomnia, fatigue  
| | • Increased bone resorption  
| | • Shortness of breath |
| **PSYCHOSOCIAL EFFECTS** | • Boredom  
| | • Difficulty concentrating  
| | • Increased family stress  
| | • Depression  
| | • Loss of income |
the extent to which bed rest, underlying maternal-fetal disease, or both contribute to inadequate maternal weight gain and poor intrauterine growth.

As in nonpregnant adults, prolonged inactivity in pregnant women is associated with negative effects on bone health. Studies of pregnant women treated with strict bed rest found an increased rate of trabecular bone loss and an increase in bone resorption markers, one of which continued to increase gradually over time and persisted into the postpartum period.

Evidence suggests that inpatient activity restriction is associated with higher rates of gestational diabetes mellitus (GDM) among women admitted to the hospital for antepartum management of pregnancy-related complications. One retrospective study found that the risk of GDM increased by 4% for every day a pregnant woman remained on the inpatient unit. While data in pregnancy are limited, elevated blood glucose levels have been well documented in nonpregnant patients placed on activity restriction.

Another serious concern with prolonged bed rest is the potential increased risk of thromboembolic events. In general, inactivity increases the risk for venous thromboembolism (VTE), which is compounded by the hypercoagulable state of pregnancy. In one study, Kovacevich et al found a significant increase in the risk of thromboembolic events in pregnant women treated with bed rest lasting 3 days or more compared with those not on bed rest (15.6 cases per 1000 women vs 0.8 cases per 1000 women; \( P < .0015 \)).

What are the psychosocial effects of activity restriction?

Activity restriction in pregnancy can also cause significant emotional and psychological distress. Compared with women with uncomplicated pregnancies, high-risk women on bed rest have more anxiety and depression. The negative psychosocial effects of bed rest are apparent with both inpatient and outpatient management, although hospitalized patients are known to have more sources of stress.

In particular, the extended time in bed can result in negative feelings, perseveration, and excessive worrying that can manifest as somatic symptoms. Women reported anxiety about the threat of losing their unborn child, guilt about separation from other children and loved ones, and concern for loss of employment or financial stability. The loss of wages can lead to significant financial concerns and is often a major source of stress for women.

Many women who are placed on hospitalized bed rest express frustration and anger resulting from a lack of control or the perception that hospitalization confers minimal clinical benefit. Bed rest can also be associated with family disruption, leading to emotional stress for the spouse and other children. Separation from one’s family has been shown to be the most significant stressor for some women. Social support from family, friends, and professionals is an important mediator of stress and depressive symptoms. Strain on these relationships compromises an important coping mechanism.

Summary

Little evidence supports the routine use of activity restriction for preterm birth and other obstetric conditions, and some data indicate adverse impact on obstetric outcomes. In addition, prolonged inactivity is associated with a variety of negative physiological and psychological effects (Table 3). Given the lack of data definitively demonstrating that activity restriction improves perinatal outcome, coupled with evidence of adverse effects, we suggest that activity restriction should not routinely be prescribed.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Summary of recommendations</th>
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<tbody>
<tr>
<td>Number</td>
<td>Recommendations</td>
</tr>
<tr>
<td>1</td>
<td>We recommend against the routine use of any type of activity restriction in pregnant women at risk for PTB based on preterm labor symptoms, arrested preterm labor, or shortened cervix.</td>
</tr>
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Abbreviations: PTB = preterm birth; PROM = premature rupture of membranes; PPROM = preterm premature rupture of membranes; FGR = fetal growth restriction.
Why I started a women’s health pharmaceutical company

By Brian A. Bernick, MD, FACOG

Many people ask me how and why I started TherapeuticsMD. The simple answer to why is that, like many of my colleagues, I was frustrated by current therapies in women’s health that were antiquated and by the lack of innovation in commonplace treatments for contraception and menopause. Having spent the last 25 years focused on women’s health, I used my personal experience as an obstetrician-gynecologist, along with the collective feedback of my fellow healthcare providers and our patients, to create and bring to market new products like Bijuva (estradiol and progesterone) capsules, Imvexxy (estradiol vaginal inserts), Annovera (segesterone acetate and ethinyl estradiol vaginal system), and our vitaMedMD prenatal vitamins with the goal of answering the needs of our patients with modern solutions that fit their lifestyles.

Practicing in South Florida, I had the opportunity to take care of many menopausal women. Then, in 2002, the initial news from the landmark Women’s Health Initiative (WHI) study suggested that synthetic hormones increased the risk of breast cancer, stroke, heart attack, and blood clots.1 This finding was in contrast to what many healthcare providers were recommending to women based on the general belief that hormones were good for their heart, brain, and bones, and that they should stay on them indefinitely. Unfortunately, all US Food and Drug Administration (FDA)-approved combination hormone products for postmenopausal conditions contained a synthetic progestin.

After WHI, I observed that most women and healthcare providers shifted to hormone therapy containing bioidentical estradiol and bioidentical...
progesterone because they believed this was a better alternative.² The lone FDA-approved progesterone, however, was only studied and approved as 200 mg for 12 nights sequentially in combination with 0.625 mg of conjugated estrogen, yet many healthcare providers began prescribing it as 100 mg daily with any amount or form of estrogen.³ As an evidence-based practitioner, I was concerned about endometrial safety with this approach, based on the results of small studies that showed endometrial hyperplasia. I struggled with the reality that no combination of estradiol and progesterone, whether oral or transdermal, had been studied in a randomized, placebo-controlled trial and FDA approved to be used together.

I struggled with the reality that no combination of estradiol and progesterone, whether oral or transdermal, had been studied in a randomized, placebo-controlled trial and FDA approved to be used together.

The importance of this is significant because the risk to the endometrium represents the greatest risk to a woman when using hormone therapy. The background incidence of endometrial hyperplasia in a non-hormone user is 1% (1/100), which increases significantly when estrogen therapy is not adequately opposed by a progestogen.⁴

Like many of my colleagues, I had a preference for transdermal estrogen because it conveys a small reduction in the venous thromboembolism (VTE) risk from oral estradiol and micronized progesterone (1.5 vs 1.2–3 per 1000 woman-years).⁵⁻⁷ That, however, was trading a lower risk of VTE for a 10-fold higher risk of endometrial hyperplasia/cancer without robust data for the unapproved regimen of transdermal estradiol with progesterone in women with a uterus.³ Moreover, I was frustrated by the confusion among my colleagues and our patients regarding the risks of hormone therapy as these particularly relate to breast cancer and cardiovascular disease, especially after the reanalysis of WHI and subsequent studies. As such, I set out to address these concerns and develop the first and only FDA-approved hormone therapy combination of estradiol and micronized progesterone that would be rigorously studied in a large phase 3, randomized, placebo-controlled trial.⁴

Further, I was troubled by the fact that many of my menopausal patients suffered from symptoms of vulvar and vaginal atrophy, yet too few of them would try or stay on treatment. It is estimated that vulvar and vaginal atrophy occurs in more than 1 out of 2 menopausal women, but only 7% of women are treated with prescription hormone therapy.⁸ I recognized that my patients and fellow healthcare providers were looking for treatments that were easy to use and not messy to administer, and worked quickly in low doses with limited systemic exposure. I then set out to address these concerns and develop an applicator-free, rapidly dissolving softgel vaginal insert containing ultra-low doses of 17β-estradiol.

I also partnered with the Population Council, a not-for-profit organization founded by John D. Rockefeller, III, with a focus on reproductive health. The Population Council was the initial developer of the world’s long-acting reversible contraceptives, including the 10-year copper intrauterine device (IUD), the original 5-year levonorgestrel IUD, and the contraceptive implant. More than 170 million women worldwide use contraceptive technologies developed by the Population Council. The Population Council recognized, however, that despite the importance of long-acting reversible contraception, all too often women declined the
options because these required a procedure for insertion and removal. Accordingly, they developed a contraceptive that does not require a procedure for insertion or removal and provides women with long-lasting efficacy for 1 year (13 cycles). This contraceptive is now part of the TherapeuticsMD product portfolio and supports our commitment to deliver a selection of modern products for women throughout the different stages of their lives. Likewise, to complement these products, I created a line of prescription prenatal vitamins with options for all types of women’s preferences.

Finally, as a community healthcare provider for many years, I understand that affordability is one of the most important considerations for our patients. Starting a pharmaceutical company is not easy. It takes many years of experimentation and development, millions if not billions of dollars, and a lot of luck. Several clinical trials were conducted all over the United States and throughout the world to support our products. I am fortunate to have had people believe in these opportunities and be willing to invest their money and experience in helping me along the way. I truly feel that what we have accomplished is the result of the collective input and experience of my fellow healthcare providers and the women we treat. I am humbled to have played a role in helping to bring more attention and treatment options to women’s health.

For product information and Full Prescribing Information, including BOXED WARNINGS, visit TherapeuticsMD.com/products.

References

Author Biography

Brian A. Bernick, MD, FACOG, is a board-certified obstetrician-gynecologist and co-founder and chief scientific officer of TherapeuticsMD, Inc. He is also a clinical affiliate associate professor at Florida Atlantic University Charles E. Schmidt College of Medicine in Boca Raton.
Low BMD linked to periodontitis in perimenopause

by BOB KRONEMEYER

A prospective study of generally healthy perimenopausal women has concluded that low bone mineral density (BMD) is significantly linked with periodontal disease in women over 58 years old, and independent of tobacco consumption or oral hygiene.

The study in the *Journal of Periodontology* recruited 173 women aged 45 to 72 (mean age 57.8 years) with good oral hygiene and a mean of 23 functional teeth from the Departments of Rheumatology and Endocrinology at Jaen General Hospital in southern Spain between 2016 and 2018.

Of the 173 women, 70 were healthy with normal BMD, whereas the remaining 103 women had decreased BMD (61 with osteoporosis and 42 with osteopenia). In addition, 22 women reported smoking between 1 and 20 cigarettes per day, of whom 12 had osteoporosis/osteopenia.

More than 90% of women with osteoporosis/osteopenia were postmenopausal, which was the most frequent cause of low BMD.

Moderate or severe periodontitis was present in 52.6% of the study population. This prevalence is comparable to that in oral health surveys conducted in Spain.

“Theoretically, the general bone loss derived from osteoporosis would also involve jawbones, favoring the bone loss observed in periodontitis and increasing the risk of tooth loss,” wrote the authors.

The authors also noted that osteoporosis and periodontitis have common risk factors, including age, genetics, hormonal changes, smoking habits, corticosteroid treatment, and low serum calcium and vitamin D levels.

To assess the severity of periodontal disease, the percentage of sites with a clinical attachment level (CAL ≥ 4 mm and ≥6 mm) was recorded.

Age was a modifiable variable for the association between osteoporosis and periodontitis: women older than 58 years with low BMD had a higher mean percentage of sites with CAL ≥ 4 mm, as well as more severe cases (CAL ≥ 6 mm), compared with controls. These findings were independent of tobacco consumption, oral hygiene or serum levels of 25-OH vitamin D or calcium.

For CAL ≥ 4 mm, the probability of having osteopenia/osteoporosis was 27.40% more likely (95% confidence interval [CI]: 12.19 to 42.61) for each unit of increase (mm) in clinical attachment loss.

In cases of CAL ≥ 6 mm, the probability increased by 13.62% (CI 95%: 1.49 to 25.75) for each unit of increase.

These associations were detected when osteoporosis and osteopenia were analyzed independently, although a significant connection was not seen between osteopenia and severe cases of periodontitis.

Significant differences in study results were not found in women under age 58 years.

“Findings such as ours imply that postmenopausal women, facing estrogen-related loss of bone density, may challenge clinicians to properly diagnose and correctly assess the risk for periodontitis,” wrote the authors. “It is of vital importance that physicians and nurses caring for women with decreased BMD refer their patients to dentists for appropriate diagnosis and treatment. This multidisciplinary approach will further unite the medical and dental efforts to achieve overall patient wellness.”

The authors said longitudinal studies, larger sample sizes, and trials evaluating the effect of medication for osteoporosis on CAL would lend scientific credence to the findings of the current study.

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

SOURCE INFORMATION: contemporaryobgyn.net/BMD
Training in cytoreduction yields better outcomes

by BOB KRONEMYER

Training gynecologic oncologists to perform cytoreduction for advanced ovarian cancer can result in better outcomes for patients, according to results of a new study. It also may enable more patients to have primary surgery, reduce the burden on the surgical team to schedule more complex procedures, and help eliminate the need to involve other specialties in the procedures.

The findings are from a prospective United Kingdom study in the journal Minerva Ginecologica. “The aim of surgery for patients with advanced ovarian cancer is to remove all visible disease in the pelvis and abdomen,” said co-author Nikos Akrivos, MD, PhD, a consultant gynecological oncologist and head of the 3rd Department of Gynecologic Oncology at Hygeia Hospital in Athens, Greece. “However, there is significant variation in surgical technique among gynecological oncologists. Also, marked differences in the presence of disease in the upper abdomen remain one of the main reasons for not achieving the desired surgical outcome.”

The aim of the study was to present the experience of Dr. Akrivos and his surgical colleagues in developing surgical skills required to resect metastatic ovarian cancer in the upper abdomen. The study comprised 126 patients undergoing cytoreductive surgery at Norfolk and Norwich University Hospital, United Kingdom, for stage IIIIC and IV epithelial ovarian cancer that required at least one surgical procedure in the upper abdomen. At the time the research was done, Dr. Akrivos was a subspecialty fellow in gynecologic oncology at that hospital.

Patients were divided into three groups: Group 1 had surgery from December 2012 to July 2014; Group 2 from August 2014 to March 2016; and Group 3 from April 2016 to March 2018.

The percentage of patients undergoing primary surgery in groups 1, 2 and 3 was 47.6%, 50.0% and 73.8%, respectively ($P = 0.02$). In comparison to Groups 1 and 2, Group 3 had a significant increase in the percentage of patients undergoing cholecystectomy ($P = 0.02$); resection of disease from porta hepatitis ($P = 0.008$); liver capsulectomy ($P < 0.001$); lesser omentectomy ($P < 0.001$); and celiac trunk lymphadenectomy ($P < 0.001$). But among the three groups, there was no difference in the percentage of patients undergoing splenectomy, diaphragmatic peritoneectomy/resection and gastrectomy.

Complete cytoreduction was achieved in 54.8%, 35.7%, and 64.3% of patients in Groups 1, 2 and 3, respectively ($P = 0.028$). There was also no significant difference in the occurrence of grades 3 to 5 complications among the three groups. However, a liver surgeon was required in 9.1%, 5.6%, and 0% of cases in groups 1, 2 and 3, respectively.

“We found that aggressiveness of cytoreductive surgery increased with time, as reflected in the percentage of patients that had optimal surgical outcome,” Dr. Akrivos told Contemporary OB/GYN. “We observed no increase in the rate of complications, despite an increase in surgically complex cases. This likely is due to our multidisciplinary approach to perioperative care management.”

The study underscores the need to train and educate gynecological oncologists in acquiring skills for performing surgery on the upper abdomen. “Collaboration with colleagues from other disciplines such as hepatobiliary or upper gastrointestinal tract surgeons is required to develop or improve surgical skills,” Dr. Akrivos said. “Cadaveric training is also necessary to improve understanding of the relevant surgical anatomy.”

Furthermore, collaborating with multiple gynecological oncology surgeons on complex upper abdominal procedures can facilitate learning, according to Dr. Akrivos, whereas monitoring of surgical morbidity is of greatest importance. “In short, surgical management of metastatic ovarian cancer can be safely assigned to gynecological oncologist surgeons,” Dr. Akrivos said.

DISCLOSURES Dr. Akrivos reports no relevant financial disclosures.

SOURCE INFORMATION contemporaryobgyn.net/cytoreduction
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During the COVID-19 pandemic, collaboration of insurance carriers, physicians, and healthcare systems and use of technology have allowed for accelerated uptake of telehealth. These innovations have been leveraged to respond to the changing needs of patients in an unpredictable landscape. Because this pandemic is not transient, ob/gyn practices may need to further evolve to provide full-spectrum care for women remotely. Virtual Well Woman visits should be offered as a safe approach to timely care. The decision to offer these virtual visits is patient-specific and may serve a purpose, depending on time and geography, particularly as some locations brace for the possibility of a second wave of the SARs-CoV-2 virus. Some practices may decide to incorporate this type of visit as an option for patients as a convenience or to maintain appropriate social distancing. Others may use it as a structured triaging tool to balance the urgency of in-person visits.

Because of their seemingly non-urgent nature, well-woman visits are prone to rescheduling or cancellation, by both patients and practices. However, preventive measures addressed during these visits are crucial to maintaining positive health outcomes. Deferring screening for too long can result in avoidable urgent and emergent scenarios. Women who often face primary childcare responsibilities will be further challenged by distance learning, and social isolation may open the door for worse domestic violence and mental health concerns. Given the uncertain duration of the pandemic, the need to advocate for routine women’s health services in a patient-centered manner is essential.

Using screening guidelines to streamline your practice

Periodic screening guidelines for female patients are continually reassessed by multiple professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), the United States Preventive Services Task Force, and the American Cancer Society. These guidelines have been updated to reflect the evolving health landscape and to ensure that women can access critical preventive care despite the pandemic.

Guide to effective virtual visits during COVID-19

As the pandemic forces health care to adapt, virtual Well Woman visits can be offered as a safe approach to timely care.

by LINDA L. FAN, MD, SANGINI S. SHETH, MD, MPH, JULIA CRON, MD, AND SHEFALI R. PATHY, MD, MPH
Force (USPSTF), and the American Society for Colposcopy and Cervical Pathology (ASCCP) for evidence regarding efficacy, optimal frequency, and potential for harm. Because the current guidelines for well-woman care have moved away from the obligatory yearly pelvic exam, there is an opportunity to offer remote well-care visits. Becoming familiar with these guidelines and incorporating them into ambulatory practice can enhance efficient patient care. A checklist or template that reflects the latest guidelines can streamline workflows and allow for a fluid virtual well woman visit. Screening during this visit can then guide subsequent care while minimizing unnecessary visits experienced by patients.

Table 1 is a comprehensive list of health maintenance issues that are ideal for an initial virtual assessment. Because essential elements of the traditional well-woman visit include screening, it can be used to provide guidance in follow-up visits. For example, a 62-year-old with COVID-19 risk factors who presents for a virtual annual visit would benefit from a full clinical assessment of her health maintenance needs. In providing the necessary care, if the patient is asymptomatic and up to date on her mammography and Pap test, she may not require an in-office breast and pelvic examination. However, the patient may benefit from counseling about cardiovascular risks, lifestyle modifications, psychosocial stressors, and sexual well-being—all topics suitable for a virtual visit. If the patient’s history reveals abnormal cervical cancer screening, the clinician may be compelled to consider the risks and benefits of scheduling the necessary in-office visit (repeat Pap test vs colposcopy).

**Human touch in telehealth**
A well-designed approach to the virtual well-woman visit should preserve the essence and breadth of care provided at a traditional health maintenance visit. Press-Ganey scores have indicated that positive patient experience and loyalty are driven by indicators that can be implemented virtually: coordination of care, confidence in the care provider, responsiveness to patient concerns.

**Figure 1 What patients need to know about Virtual Well-Woman visits**

**Why should I consider telehealth?**
Depending on the need for social distancing, the majority of important screening performed in a well-woman visit can be done through a video conversation. This may allow you to do this in the comfort of your home in a more convenient timeframe.

**When should I be seen in the office?**
By using screening video visits, we ensure that only the patients who need to come to the office should come in. In the screening, we identify a reason for you to come to the office, we will weigh the need for social distancing with the urgency of your visit.

**But how can it be an annual well-woman visit without a Pap test and an exam?**
In the patients without symptoms, the benefits to performing certain elements of the physical exam (clinical breast exam, speculum exam, and bimanual exam) is not clear and need to be discussed in the context of fear, anxiety, and discomfort. The decision to perform exam should be made after a discussion with your physician.

Based on your prior Pap smear history, and risk factors, you may not need the Pap test (cervical cancer screening) this year, and it may be spaced out as far as 5 years. These guidelines ensure that you get the fewest number of pap tests and unnecessary procedures, while receiving the appropriate screening.

**Figure 2 Because telehealth communication may be unfamiliar and distracting, consider these strategies to improve the patient experience:**

**SETTING**
- Ensure that you are providing telehealth from a private and quiet environment
- If you are new to telehealth or in a new setting, you may wish to view yourself with the video function of the device to ensure that the lighting and backdrop are optimized.
- Practice with your technology if it is your first time.

**GREETING**
- Introduce yourself and your role.
- Check-in with the patient and ensure that both parties can hear and be heard.
- Consider asking them how they are doing during the pandemic.

**COMMUNICATION**
- Maintain “eye-contact” and practice active listening.
- Increase the frequency of empathic statements and use a warm tone of voice.
- If you look away, let the patient know why. For example: “When I look away, I am typing.”
- Summarize your visit and utilize teach-back methods to ensure patient understanding of explanations or plans.

**FOLLOW-UP**
- Because the patient’s will be checked-out virtually, let them know what to expect with respect to follow-up visits. For example: “My office will call you within 24 hours to arrange your next visit and ultrasound.”
listening, and courtesy. Patients may also find personal protective equipment intimidating, particularly if they are already anxious and afraid about the pandemic. An inability to read faces and emotional response, as well as muffled voices, may impede clear communication. A face-to-face interaction between patient and provider, in the comfort of their own home, can help re-engage individuals in their healthcare. Telehealth has been shown to provide comparable health outcomes without compromising the patient-physician relationship and in fact, has been shown to enhance patient satisfaction and engagement.

Enhanced communication via telehealth can be achieved through a multifaceted strategy. First, the patient must be engaged in understanding the rationale and safety of virtual well-woman visits. Figure 1 demonstrates examples of scripted explanations.
nations providers can share with patients. Second, physician practices and hospital systems need to reassess resources to ease a patient’s transition into telehealth.

A three-stage approach is effective in achieving this transition:
1. Use of patient portal electronic messaging with instructions for accessing and using the telehealth platform;
2. Review of the telehealth platform by the staff scheduling the visits; and
3. A process for virtual rooming of the patient the day of the visit. Other simple steps that can optimize the patient experience and facilitate an environment conducive to open communication are summarized in Figure 2. Because this is, by and large, a new approach to patient care, practices should consider adopting such a workflow to standardize the virtual visit.

“But don’t I need a pelvic exam every year?”
The changing landscape of preventive medicine, including the need for routine pelvic and breast exams and breast and cervical cancer screening, can often cause confusion for patients. Certainly, for patients who are symptomatic, ob/gyns should continue to perform exams as indicated. However, the necessity of certain portions of the gynecologic exam in asymptomatic patients has been called into question. While the sensitivity of the bimanual exam in screening for ovarian cancer is low, 82% of patients believe that the exam provides reassurances of their gynecologic health. It is ingrained in patients that the well-woman exam is synonymous with the pelvic exam and Pap test. However, cervical cancer screening guidelines have progressively shifted over the last two decades toward the goal of reducing the number of unnecessary tests women receive over their lifetime “to better ensure that they receive the benefits of testing while minimizing the harms.” Because there is potential for patient anxiety and discomfort with pelvic exams, and the benefits of the pelvic exam in an asymptomatic patient are unclear, the well-woman task force states “the need for a pelvic exam for screening should be determined through shared decision making.” Consequently, telehealth visits are ideal for this shared discussion between patient and clinician, and allow for the determination of subsequent office visits for an examination.

The pandemic is not over…
Reimbursement for well-care visits is dependent on payer and individual states. Some states have mandated payment parity for telehealth well-care visits in their Medicaid or private health care plans. As the COVID-19 crisis continues, states should continue to advocate for appropriate payment of this safe, patient-centered approach. This includes ensuring parity in reimbursement. During this pandemic, ob/gyns must be allowed to offer all options. Innovation is vital to ensure exceptional and timely care of women.

The virtual well-woman exam is an ideal opportunity to promote healthy lifestyles, ensure appropriate screening for various conditions, and counsel patients on risk-reducing behavior. Successful adoption and uptake of telehealth may allow for interventions and care of patients at an unprecedented rate. While some healthcare disparities have surfaced related to technology barriers to telehealth, in many ways, virtual visits may improve access to routine healthcare for women who have been encumbered by social distancing, work challenges, lack of transportation, and childcare. Women’s healthcare faces innumerable challenges, from access to family planning to shifting insurance coverage, emphasizing the need to reassure patients that all aspects of their health are important, even during the COVID-19 pandemic.

**DISCLOSURES** The authors report no conflicts of interest.

**FOR REFERENCES VISIT** contemporaryobgyn.net/virtualWW
Considerable heterogeneity exists in reported outcomes and measures used in clinical trials of treatments for genitourinary syndrome of menopause (GSM), which impacts between 40% and 60% of postmenopausal women, according to a systematic review in the journal *Menopause*.

However, there is uncertainty over which outcomes best represent patient priorities and symptoms. The authors searched PubMed, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) through December 2018 for randomized controlled trials in English language with a primary or secondary outcome of genitourinary symptoms associated with menopause.

The 109 studies that met inclusion criteria were from 1979 to 2018, with data from 30,792 women and 34 countries. Overall, 48 different outcomes were reported, with “atrophy” as the most prevalent (51% of studies), followed by measures of sexual function (17%). In total, the studies used 21 patient-reported and 22 clinician-reported measurement tools for these symptoms. All but one study included patient-reported symptoms, “suggesting that the patient experience is considered an essential component of treatment efficacy,” wrote the authors.

However, patient-reported symptoms consisted of 21 different measures and 39 symptom combinations, which “prevents aggregation and direct comparisons between treatments, limiting understanding about which treatments are most beneficial for patients,” wrote the authors.

Clinician-reported scales of vulvovaginal appearance were used in 33% of trials, with extensive variation in what was measured and reported. Cytological measures from the vaginal epithelium were the most commonly used objective tools, reported in 70% of the studies. In fact, vaginal epithelial cytology is required for FDA approval of new treatments for GSM.

One of the challenges of the studies was use of varied terminology to describe similar symptoms, such as “vaginal atrophy” and “vulvovaginal atrophy” or “urogenital atrophy” and “urogenital aging.” But there was no consistency in defining these terms.

While most studies defined atrophy as vaginal dryness, itching, and dyspareunia, other studies included symptoms of both vaginal and vulvar itching/irritation/soreness. Some studies also included urinary symptoms and pain or bleeding associated with intercourse to define atrophy.

“Our findings are consistent with previous systematic reviews comparing the efficacy of interventions for genitourinary symptoms in postmenopausal women, which concluded that meaningful comparisons between treatments for symptoms were limited by inconsistency in outcome measures,” wrote the authors.

Introduction of the term GSM by the North American Menopause Society (NAMS) in 2014 has improved consistency in reporting; however, specific tools to measure the condition are still in development. The FDA recommends three primary endpoints for clinical trials of treatment for GSM: mean change from baseline to week 12 of the most bothersome symptom and the clinician-obtained measures of vaginal pH and vaginal maturation index. But whether these measures reflect clinical outcomes or patient priorities is unclear, according to the authors.

Review findings have been shared with an international survey of stakeholders to determine priorities for outcome selection and reporting. The survey will then inform the development of a Core Outcome Set for use in future clinical trials by the COMMA (Core Outcome Set in Menopause) consortium.

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

FOR REFERENCES VISIT contemporaryobgyn.net/GSM
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The diagnosis of the infertile couple

Myriad factors influence fertility in reproductive physiology; when it comes to determining infertility, a thorough approach is necessary.

by AMANDA KALLEN, MD, AND SANDRA ANN CARSON, MD

Introduction

Many couples choose to be childless; no one chooses to be infertile. In a classic 1956 study by Alan Guttmacher examining conception rates among 5,574 women attempting pregnancy, 85% conceived within 12 months. However, it has also become increasingly clear that time to conception is strongly influenced by age-related factors, including declining oocyte quantity and quality over time. Indeed, Guttmacher also reported a doubling of median conception time from age 24 to 44. Thus, while infertility is more the lack of a “normal” physiological outcome than a disease per se, a thorough workup for infertility is essential to identify underlying disease. In addition, lifestyle issues and environmental factors can adversely affect infertility. Importantly, infertility may be a marker of non-reproductive disease and often portends serious health issues. This discussion will highlight how each of these factors affect normal physiology, their diagnosis, and the treatment designed to achieve the delivery of a healthy term baby.

Assessment & Diagnosis

The breathtaking physiology of reproduction may go astray in any facet and result in infertility. Evaluation for that aberration, followed by diagnosis-specific treatment, is perhaps the most cost-effective way to help a couple conceive. This is an opportune time to add antenatal screening to the basic diagnostic evaluation of the infertile couple (Table 1).

TUBAL & PERITONEAL INFERTILITY

Tubal disease is a common cause of infertility, with reported rates between 25-35% of infertility diagnoses though these numbers can vary widely depending on the population being tested. Tubal obstruction is suspected in women with a history of sexually transmitted infection, cervical dysplasia, abdominal surgery or previous intra-abdominal infection (e.g., ruptured...
appendix). While laparoscopy with chromotubation is often considered the “gold standard” for evaluation of tubal disease, hysterosalpingography (HSG), with a sensitivity and specificity of 65% and 83%, respectively, is considered the first line diagnostic tool. Radiopaque dye is injected into the uterus and followed through the Fallopian tubes under fluoroscopy. A similar procedure utilizing ultrasound instead of fluoroscopy, sonohysterography (SHG), is less reliable in determining tubal patency although more accurate for uterine evaluation with a sensitivity and specificity of 76% and 67%. Treatment options for tubal infertility include tubal cannulation (for proximal tubal obstruction), surgery for tubal reanastomosis, or in vitro fertilization (IVF), which bypasses tubal blockage, with IVF being frequently employed due to success rates and comparable costs with surgery.

Endometriosis is a complex condition characterized by the presence of endometrial tissue in sites outside the uterine cavity. Endometriosis frequently presents with pain and affects 25-40% of women with infertility. Posited mechanisms for the relationship between endometriosis and infertility include distortion of pelvic anatomy, tubal obstruction, impaired oocyte quality, release and pickup, and altered endometrial receptivity, although a definite cause-effect relationship between any of these pathologies and endometriosis-related infertility is controversial. While excisional surgery has been shown to improve spontaneous pregnancy rates in women with endometriosis, surgery is not recommended for the routine evaluation of infertility in women without other symptoms of endometriosis.

**UTERINE FACTOR**
Endometrial polyps, intracavity leiomyomas, intrauterine synechiae and Mullerian anomalies with associated distortion of the endometrial cavity may be associated with infertility. Superior to the HSG in detecting uterine anomalies, sonohysterography detects intruterine polyps or leiomyomas with a sensitivity and specificity of 91% and 84%, respectively. Direct visualization via hysteroscopy may be used to confirm the diagnosis (Figure 1). Treatment to remove the distorting mass is surgical.

**CERVICAL FACTOR**
The cervix is the entry to the upper reproductive tract. Its alkaline mucus protects sperm from the acidity of the vagina and guides sperm into the upper reproductive tract. Structural alterations of the cervix, either congenital or post-surgical (for example, after loop electrosurgical excision procedure (LEEP) or large cervical cone biopsy) can cause cervical stenosis and prevent sperm entry. Post-operative stenosis is diagnosed by the failure to pass a 1 mm probe into the uterine cavity. The post-coital test, performed after intercourse to assess the viability of sperm in mucus, has been used to evaluate cervical function; however, the limited predictive value of this test has relegated it to history (Table 2). In
the absence of mucus and in the presence of cervical stenosis, intrauterine insemination is a successful therapy, assuming all other factors are normal.

**OVULATORY DYSFUNCTION AND ANOVULATION**

Failure to ovulate results from a variety of non-reproductive influences including thyroid disease, pituitary disease, elevated androgens from adrenal hyperplasia, obesity, and stress. Anovulation is diagnosed by a mid-luteal serum progesterone concentration <3 ng/ml, although mid luteal serum progesterone levels are usually higher than 7 ng/mL, and should be suspected when cycles are irregular and occur more often than every 21 days and less often than every 36 days. The most common cause of anovulation is a metabolic disease, polycystic ovarian syndrome (PCOS) in which multiple follicles exist in various stages of development and are simultaneously a result of and caused by an altered hormonal milieu including insulin resistance, elevated LH, and elevated androgens. Women who do not ovulate do not produce progesterone and thus are at risk for the consequences of unopposed estrogen: endometrial hyperplasia and cancer. Similarly, women with PCOS may experience non-reproductive disorders, particularly, acne, hirsutism and hyperinsulinemia. The metabolic consequences of PCOS increase a woman’s risk of diabetes mellitus, hyperlipidemia, gestational hypertension and gestational diabetes. Correcting thyroid deficiency, lowering elevated prolactin, blocking elevated adrenal androgen production often stimulates ovulation. Weight loss of 15% of body weight often prompts ovulation to resume. Infertility associated with an-

### Table 1: Basic Infertility Evaluation

<table>
<thead>
<tr>
<th>Historical Highlights (in addition to standard ROS, Medicines, Allergies, PMH &amp; PSH)</th>
<th>Couple</th>
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<td>Coital frequency and timing</td>
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<td>Occupational exposures</td>
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<td>Erectile or ejaculatory dysfunction</td>
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<td>Anabolic steroid use</td>
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<td>Previous abdominal or scrotal surgery</td>
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<td>Sexually transmitted disease</td>
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<th>Female Physical Examination Highlights</th>
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<td>Breast secretions</td>
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<td>Acne</td>
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<td>Hirsutism</td>
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<td>Pelvic abnormalities including</td>
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<td>Cervical stenosis</td>
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<td>Enlarged uterus,</td>
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<td>Adnexal masses</td>
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<td>Genetic Screening based on ethnicity</td>
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<td>Infectious Disease screening</td>
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<td>Gonorrhea</td>
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<td>Screening for needed immunizations</td>
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| Ovarian Reserve | FSH, E2 on Day 3 of cycle; AMH, Ultrasound Antral Follicle Count on |
| Uterine Evaluation | Sonohysterogram OR Hysteroscopy |
| Tubal Evaluation | Hysterosalpingogram |
| Male Evaluation | Semen analysis |
ovulation is best treated with ovulation induction unless other factors such as diminished ovarian reserve and male factors are present. (see “Treatment” section below)

**OVARIAN AGING (DIMINISHED OVARIAN RESERVE)**

Female fecundity (the ability to conceive and carry a pregnancy to term) declines with increasing age, decreasing more rapidly after age 35,18,19 reflecting, in part, the progressive loss of oocytes (the “ovarian reserve”) that occurs with age. Aging oocytes also accumulate meiotic defects and DNA damage, causing deterioration of gamete quality and increasing the risk of aneuploid embryos and miscarriage.20,21 Therefore, women over 35 who have failed to conceive for six months should be offered expedited evaluation and treatment; for women over 40, immediate evaluation is warranted.19

Ovarian reserve refers to the number of oocytes available for stimulation and ovulation. It can be evaluated using serum FSH and estradiol concentrations on days 3-5 of a menstrual cycle, serum anti-Müllerian hormone (AMH), and/or ultrasound imaging of the ovaries for antral follicle count and ovarian volume determination (Table 3).22-26 Notably, these tests may be predictive of response to exogenous ovarian stimulation and are not predictive of live birth or even natural fertility.

Accelerated oocyte loss can result in loss of fertility and early menopause (prior to age 40). While the majority of these cases are idiopathic,27 ovarian reserve should be monitored in women with a history of prior ovarian surgery, chemotherapy, radiation therapy, or with a family history of premature menopause. These women may be at risk for carrying the fragile X (FMR1) pre-mutation and also the consequences of estrogen deprivation.

**MALE FACTOR**

Disorders of male physiology occur in 35% of infertile couples and are the sole factor in 17% of couples.28 Similar to the female, in the male, FSH and LH stimulate the testes to produce testosterone and develop the immature gametes. Unlike the oocytes, sperm mature for three months in the male reproductive tract before being ejaculated.

**Hormonal dysfunction** of the male may arise from all areas of male reproductive physiology. When testosterone is low but not absent, erectile dysfunction and decreased libido commonly accompany altered semen parameters resulting in infertility. **Testicular fail-**
ure also results in azoospermia. In addition, the concomitant lack of testosterone results in decreased libido and erectile dysfunction. As testosterone concentrations drop in the male, risk for heart disease, hyperlipidemia, osteopenia, and muscular mass loss increases. Testosterone failure is diagnosed by a low serum testosterone and elevated LH and FSH. Of course, correcting any hormonal abnormality and screening for related disorders should precede treatment.

Diagnosis of male factor infertility begins with a well collected, comprehensive semen analysis performed in a certified andrology laboratory (Table 4). The semen sample is best collected at the laboratory, but when it must be collected at home, it should be delivered to the laboratory at body temperature within 30 to 60 minutes after ejaculation. A diagnosis of an “abnormal” semen analysis should only be made after a confirmatory semen analysis has been performed, and must be interpreted in the context of the couple’s overall fertility evaluation. Other tests of sperm function are available, but their practical diagnostic value is subject to interpretation and are clinically not as useful.

**Azoospermia** is the absence of sperm in the ejaculate, not necessarily indicating an absence of sperm in the upper reproductive tract or the testes. When the vas is patent, retrograde ejaculation may be diagnosed by retrieving sperm from the urine after orgasm and may be washed and used for intrauterine insemination. If the vas is blocked, sperm may be aspirated from the epididymis (MESA) or surgically extracted from the testes (TESA) and used for intracytoplasmic sperm injection (ICSI) at IVF. In cases of azoospermia in which the sperm must be retrieved from the testes, testing for a mutation in the DAZ (Deleted in Azoospermia) gene can be a useful predictor of testicular sperm presence, as presence of the DAZ-c mutation predicts an almost 0% likelihood of finding sperm in the testes.30 These genes may also be passed on to offspring; affected male patients may opt to use a donor sperm to prevent this outcome. Similarly, men with an absent vas deferens may have a mutated allele for cystic fibrosis or a 5-T variant and if sperm is aspirated from the epididymis or testes for use in IVF, the resultant child may inherit cystic fibrosis.31 Thus, screening for the mutations is recommended when an absent vas deferens is detected.

**Oligozoospermia**, or less than 15 million sperm/ml, and may signal partial retrograde ejaculation, hormonal disturbance or genetic conditions. If the testosterone levels are normal or low and the LH and FSH are normal, an empirical treatment with clomiphene citrate for 6 to 12 months may increase the sperm count.32 Monitoring testosterone and the semen analysis after three months is recommended.

**Asthenozoospermia** is diagnosed when motility is < 40%, while **teratozoospermia** refers to the presence of < 4% normally formed sperm.

Male factor infertility may be treated by intrauterine insemination, possibly combined with ovulation induction of the female (COH-IUI) as discussed below. However, success rates with ICSI at IVF far exceed those with COH-IUI, especially when the normal morphology is <4% or the count is < 2 million sperm/cc.

FOR REFERENCES VISIT contemporaryobgyn.net/infDiagnosis

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**Table 4 World Health Organization Lower Limits of Normal Semen Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.2 - 7.8</td>
</tr>
<tr>
<td>Volume</td>
<td>1.5 cc</td>
</tr>
<tr>
<td>Total Sperm Count</td>
<td>39 million</td>
</tr>
<tr>
<td>Concentration</td>
<td>≥15 million sperm/ml</td>
</tr>
<tr>
<td>Motility</td>
<td>≥40% forward progression</td>
</tr>
<tr>
<td>Morphology</td>
<td>≥4% normal forms (By Kruger criteria)</td>
</tr>
<tr>
<td>White Blood Cells</td>
<td>≤1 million/microliter</td>
</tr>
</tbody>
</table>

*Samples from men who had fathered a pregnancy in the previous year and taken after 2-7 days of ejaculation abstinence. Values represent the 5thile
A case for improved carrier screening

Expanded carrier screening addresses limitations in historical ethnic-based screenings, including potential racial and ethnic bias

by RONALD J. WAPNER, MD

Introduction
Driven by the cost effective introduction of next generation sequencing, prenatal screening for fetal genetic disease has dramatically expanded. Although noninvasive prenatal testing (NIPT) for the common aneuploides (trisomy 21, 18 and 13) has had the greatest uptake and gained the most attention, fetal Mendelian disorders actually affect more pregnancies. For example, trisomy 21 occurs in approximately 1 in 750 livebirths, trisomy 18 in 1 in 5500, and trisomy 13 even less frequently. Alternatively, autosomal recessive and X linked disorders are each individually rare but collectively occur in up to 1/175 pregnancies.1 Severe or profound Mendelian disease is predicted to occur in 1 in 545 pregnancies.2 These disorders also have public health importance as they account for 20% of pediatric hospitalizations and 18% of pediatric deaths.3

Until recently, screening approaches to identify pregnancies at risk for Mendelian disorders was based on parental race or ethnicity. Notable examples of this are Tay Sachs disease in the Ashkenazy Jewish community, Sickle Cell Disease in the African American Population, and beta thalassemia in the Mediterranean population.

This approach underwent expansion in 2001, when both the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics (ACMG) recommended that cystic fibrosis carrier screening be “offered” to non-Hispanic European Americans, for whom the carrier rate was approximately 1 in 25 and the detection rate was greater than 85%. This approach proved to be difficult to implement in busy obstetric practices and in 2005 the guidelines were updated suggesting that all couples, regardless of race or ethnicity, underwent screening for cystic fibrosis even though the carrier risk and detection rate in some populations may be lower.4 Carrier screening for spinal muscular atrophy, which occurs in 1 in 10,000 pregnancies and has a carrier rate of 1 in 50, was recommended in 2009 by ACMG for all racial and ethnic groups owing to the severe characteristics of the disease and the advocacy of affected families.5

Introduction of Expanded Carrier Screening (ECS) Panels
Simultaneously, the practical and ethical limitations of ethnicity-driven carrier screening were being challenged. Demographic data from the United States Census found increasing populations of multiracial children and couples. Similarly, many individuals have limited or incorrect knowledge of their ethnic ancestry.6 For example, 40% of US individuals age 18-64 are unable to indicate the ethnicity of their four grandparents.

These limitations of ethnic-based screening were confirmed in 2013, when a large scale study evaluating the feasibility of screening for a large number of genetic variants and genes without consideration of the patient’s ethnicity or race (pan ethnic ECS) found that up to one in four individuals were carriers for at least one of approximately 100 recessive diseases. Most importantly, approximately three-fourths of these carriers would not have been detected by the suggested ACOG or ACMG guidelines.7 It was also of concern that the existing guidelines...
Introduction of ECS into clinical practice

With the development of cost-effective genomic technologies and spurred by recognition that expanding carrier screening could identify more carriers and narrow the equity gap inherent in ethnic-based screening, pan-ethnic ECS began to be offered to clinicians. Initially, genotyping techniques were used in which a select number of known variants were analyzed. Although much improved over ethnic-based screening in which only a few genes were tested, genotyping was limited at both the individual and population level, i.e. when only looking at a limited list of targeted variants, diseases with multiple disease-causing variants such as cystic fibrosis are detected with variable success in different ancestries.

Next-generation high-throughput sequencing solves this problem and has now replaced genotyping in most labs and has significantly expanded detection of disease variants. For example, full-exon sequencing of 50 of the most common variants yields a 1.5- to 2-fold increase in detection rates over simple genotyping.2

Initially ECS was introduced into practice by industry as a lab developed test that did not require extensive FDA scrutiny, premarket review or oversite. At the time there were no guidelines by academic thought leaders, consensus with practitioners, nor patient and community engagement. In an attempt to have the clinical community “catch up”, in March of 2015 a Joint Statement of the Perinatal Quality Foundation, ACMG, ACOG, the Society for Maternal-Fetal Medicine (SMFM), and the National Society of Genetic Counselors published “points to consider” when performing ECS in reproductive medicine.4 These points are summarized in Box 1.

Most recently in 2017, ACOG issued a committee opinion4, which for the first time suggested that ECS was an appropriate alternative to standard ethnic-based screening and suggested that each individual practice should choose either standard screening based on ethnicity plus cystic fibrosis and spinal muscular atrophy or expanded screening for all of their patients. In comparing the two acceptable approaches, a practice should consider that the present ethnic-based approach will identify only approximately 30% of the disorders identified on an extended carrier panel of approximately 100 disorders. In addition, an ethnic-based approach has an inherent racial and ethnic bias in carrier identification.

Pre-test counseling

It is not possible or necessary to counsel every patient about the individual disorders included on an expanded screen but they should be provided with pre-test education that describes the screening process and gives them an overview of the severity of the disorders. The major points to be considered in pretest counseling and education are outlined in Box 1.10 This information may be provided by the clinician, their trained staff, or by informational resources recommended by their provider.
in offering pan-ethnic expanded carrier testing.8, 10

Major points and basic concepts to be considered

BOX 1: Major points and basic concepts to be considered in offering pan-ethnic expanded carrier testing8, 10

1. All individuals, regardless of race or ethnicity, should be offered screening for the same set of conditions.
2. Carrier screening of any nature is voluntary, and it is reasonable to accept or decline.
3. Results of genetic testing are confidential and protected in health insurance and employment by the Genetic Information Non-Discrimination Act of 2008.14
4. The majority of conditions on current expanded panels are autosomal-recessive. However, some may be X-linked or autosomal-dominant single gene conditions.
5. Expanded carrier screening panels can include more than 400 genetic conditions; many of which are rare. Conditions included on expanded carrier screening panels vary in severity. Many are associated with significant adverse outcomes such as cognitive impairment, decreased life expectancy, and need for medical or surgical intervention.
6. Before testing, it is not practical or necessary to fully explain all of the clinical and test characteristics of each condition. Pretest education and consent should broadly describe the types of conditions being screened for and their common features as well as the limitations of screening. Educating patients before testing may be done verbally or by using other informational approaches such as pamphlets, videos, or online resources.
   a. General concepts to be included in pretest counseling should include:
      i. Some conditions screened have less well defined phenotypes.
      ii. Because many conditions being screened are rare, disease prevalence, mutation frequencies, and detection rates may be imprecise and residual risk estimations may not be reliable.
      iii. Screen-negative results reduce the likelihood of the carrier state for the conditions, but a residual risk of being a carrier always remain i.e. A negative screen does not eliminate risk to offspring
7. Screening panels may change over time, and there may be differences in the conditions screened between laboratories. Despite this, rescreening with each pregnancy should not be offered or recommended.
8. Pregnancy risk assessment depends on accurate knowledge of paternity. If the biologic father is not available for carrier screening, accurate risk assessment for recessive conditions is not possible.
9. Because expanded carrier screening includes a large number of disorders, it is common to identify carriers for one or more conditions. In most cases, being a carrier of an autosomal recessive condition has no clinical consequences for the individual carrier. If each partner is identified as a carrier of a different autosomal recessive condition, offspring are not likely to be affected.
10. In some instances, an individual may learn that they have two pathogenic variants for a condition (homozygous or compound heterozygous) and thus learn through carrier screening that they have an autosomal-recessive condition that could affect their personal health.

Unfortunately, a survey of ob/gyns revealed that only one-third felt comfortable providing pre-test counseling and fewer felt comfortable explaining the results of expanded panels.11

Patient education should include a discussion of residual risk i.e. a negative screening test significantly decreases, but does not completely rule out, the possibility of an affected child with a specific disorder since the test may only evaluate known variants of a particular gene. Although sequencing has decreased the residual risk, it is still not 100%. Likewise, screening does not evaluate all disease-causing genes. For example, if a patient of Ashkenazy Jewish descent with a pretest carrier risk of 1 in 25 undergoes cystic fibrosis screening with a detection rate of 94%, her carrier risk after a negative screen is reduced to 1 in 380. Additional details and examples of residual risk are discussed in the ACOG Committee Opinion No. 691.12

Laboratories will report the residual risk for genes on their panels and if not known, this will be indicated. The residual risk may vary by ethnic groups since the frequency of known variants and their detection rates will vary. Panels testing for a large number of disorders will invariably include some that are extremely rare in which knowledge of disease-causing variants is limited and hence calculation of the residual risk less precise.

Patients should be informed that more than 1 in 4 individuals will be a carrier of at least one disorder included on the ECS and that the carrier state almost never poses health risks. Exceptions to this are carriers for Gaucher disease who have an increased risk of Parkinson disease and pre-mutation carriers of the Fragile X Syndrome. For some X linked disorders, such as Duchenne Muscular Dystrophy, some female carriers will have mild symptoms of the disease because of skewed X inactivation.

Selection of conditions for inclusion on ECS panels

Despite the increasing use of ECS over the last 5 years no general consensus exists on which and how many conditions to include nor on appropriate clinical implementation. That carrier screening should focus on diseases of significant clinical impact such
as those that cause pediatric mortality and/or intellectual disability is generally accepted. Similarly, disorders in which immediate neonatal care may be altered by the diagnosis should be included. Severity-related criteria for inclusion of other conditions should maximize the clinical utility of ECS and include disease characteristics that at-risk couples would reasonably act to avoid in their offspring. For example, ACOG cites cognitive and physical impairment, detrimental effect on quality of life, an onset early in life, and a requirement for surgical or medical intervention as characteristics that describe a severe phenotype.9

Contemporary guidelines do not recommend specific conditions to be included in ECS (beyond recommending pan-ethnic cystic fibrosis and spinal muscular atrophy screening), instead suggesting general principles for ECS panel design (see Table 1). This has led to ECS offerings being widely variable in number and scope among laboratories, ranging in size from dozens to hundreds of conditions. A 2018 study comparing panels offered at 16 laboratories found that panels ranged from 41 to 1,792 conditions, with only three conditions in common among all panels analyzed.13 In addition, some of the more frequent diseases with non-conventional molecular findings such as spinal muscular atrophy, fragile X syndrome, and congenital adrenal hyperplasia, are not routinely included in all panels.14

The use of population carrier frequency as a criteria for inclusion on a panel has been suggested to provide a balance between identifying a large proportion of at-risk couples without identifying a large number of carriers for ultra-rare conditions in which partners are extremely unlikely to be carriers. ACOG has recommended that a disorder should “have a carrier frequency of 1 in 100 or greater.” It is unclear, how-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>ECS panel design criteria by medical professional societies</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>ACOG9</td>
</tr>
<tr>
<td>Carrier frequency</td>
<td>Disorders should have a carrier frequency of 1 in 100 or greater.</td>
</tr>
<tr>
<td>Disease severity</td>
<td>Disorders should have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life.</td>
</tr>
<tr>
<td>Genotype-phenotype association</td>
<td>Have a well-defined phenotype.</td>
</tr>
<tr>
<td>Variant pathogenicity</td>
<td>There must be validated clinical association between the mutation(s) detected and the severity of the disorder.</td>
</tr>
<tr>
<td>Residual risk</td>
<td>For each disorder, the causative gene(s), mutations, and mutation frequencies should be known in the population being tested, so that meaningful residual risk in individuals who test negative can be assessed.</td>
</tr>
<tr>
<td>Prenatal diagnosis available</td>
<td>Condition can be diagnosed prenatally.</td>
</tr>
</tbody>
</table>
ever, whether that includes conditions with a 1 in 100 carrier frequency in any ethnicity, in a US-weighted population, or in all ethnicities. This differentiator is important since it requires a 1 in 100 carrier frequency in all ethnicities, a compliant panel would include only three conditions and overall identify only approximately 45% carrier couples relative to a 176-condition panel. Alternatively, a 1 in 100 carrier frequency in any ethnicity, would include 38 conditions and identify approximately 89% of at-risk couples. Although ACOG does not explicitly state it, it seems likely that it intended for the criterion to be in any ethnicity, since some of the example conditions cited as reasonable to consider for ECS have carrier frequencies greater than 1 in 100 in some ethnicities, but less than 1 in 100 in others.

There is a common misconception that as panels become larger the number of patients screening positive will linearly increase increasing a burden on genetic counseling and the health care system. However, this is not the case. A disorder with a lower carrier frequency will result in a smaller number of positive results so that as rarer conditions are added to panels the increase in the number of positive results will begin to plateau. For example, a panel with the 18 most prevalent conditions typically screened for would identify about 84% of at-risk couples, and the addition of the 73 next most-prevalent conditions would increase identification of at-risk couples by only another 11%, to approximately 95%.

Despite cautious selection of genes for screening panels, on occasion the phenotype for a variant identified on screening will be uncertain; especially for a rare variant or one in an ethnic or racial group in which the variant is rarely seen. As opposed to diagnostic molecular testing in which a fetus has already demonstrated anomalies, carrier screening is designed to identify potential disorders in those that appear unaffected.

Although the criteria set forth by ACOG, ACMG, and other professional societies provide guidance on panel design, they are broad and leave room for interpretation by laboratories designing ECS panels. Laboratories should be encouraged to publish their criteria for choosing the conditions offered on their ECS panels. Likewise, clinicians should use these criteria in choosing the panel appropriate for their patients.

**Post-test counseling of pregnant carrier couples**

In approximately 1.7% to 2.5% of screened couples both members will be identified as carrying a pathogenic variant in the same gene giving them a 1 in 4 chance of having an affected pregnancy. In such cases, referral to a trained genetic counselor or clinical geneticist familiar with prenatal diagnosis is strongly recommended. The counseling session should include a detailed discussion of the fetal, infant, child and adult phenotype including the impact of incomplete penetrance and variable expressivity. The medical and psychosocial implications of having an affected child should be frankly discussed. Reading material designed for parents should be provided and the significance of this information for other family members (e.g., parents or siblings) should be mentioned and family counseling at a later date offered.

Prenatal management, delivery planning and coordination of care for the child as well as pregnancy termination or adoption planning should be discussed. When appropriate, the session should also include a discussion of the availability, safety, and techniques involved in pregnancy termination. If the genetic practitioner is uncomfortable discussing pregnancy termination, the patient should be referred.

**Ideally, women of reproductive age would be offered carrier screening before conception to maximize the subsequent reproductive options for carrier couples.**

The methods and risks involved in prenatal diagnosis should be outlined. If the patient is in the first trimester and pregnancy termination is an option for the couple, first trimester CVS is the diagnostic procedure of choice because of the high a-priori risk of an affected pregnancy. Although previous concerns existed for using chorionic villi for specific inherited disorders this is no longer the case. It’s important to note that not all labs perform prenatal testing for all disorders on expanded carrier tests requiring the clinical team to identify an appropriate laboratory prior to the procedure. The specific variant must be submitted to the lab and most labs will request a sample of blood from each parent to serve as a positive control. Present data suggests that if performed by an experienced physician, the risk of either a transabdominal or transcervical CVS leading to miscarriage is less than 1 in 600 to 1000 pregnancies. For patients requiring prenatal diagnosis in the second trimester, amniocentesis can be performed. Pregnancy loss rates from amniocentesis are similar to those with CVS; approximately 1:1000. As with CVS, pre-procedure communication with the molecular lab is important.
PVR found effective and safe for lactating women

by BOB KRONEMYER

Among lactating women during the first postpartum year, the contraceptive efficacy and safety of the 3-month progesterone vaginal ring (PVR) is comparable to the Copper-T380A intrauterine device (IUD), which lasts up to 12 years, according to a multicenter study in India.

The open-label study enrolled 789 healthy, married lactating women (aged 20 to 35 years; mean age 24) at 20 centers in India. All the women were 6 to 9 weeks postpartum following the birth of a normal, healthy infant, exclusively breastfeeding and willing to continue breastfeeding at least four times daily for 1 year. Participants also had not used any contraceptives since delivery, but were at risk for pregnancy.

Of the women, 459 used the PVR and 330 the IUD. No significant difference was seen between the two groups in 1-year pregnancy rates using either the Pearl Index (PI) for incidence of pregnancy per 100 women-years nor Kaplan-Meier (K-M) life tables. (PI: 0.62 for PVR and 0.35 for IUD vs. for K-M: 0.7 for PVR and 0.4 for IUD ($P = 0.58$).

Overall, 99.3% of PVR users and 99.6% of IUD users avoided pregnancy. But contraceptive continuation rates at 12 months were 78.5% for IUD compared to only 56.9% for the PVR ($P < 0.001$).

“...This outcome was due primarily to expulsions that occurred during toileting and other squatting activities within the first three months and non-replacement of lost rings consistent with the protocol, a stipulation that limited comparisons and comparability of the two study arms,” the authors wrote.

Ring expulsions and menorrhagia were the two most common reasons for discontinuation among PVR and IUD users, respectively. However, few women (4 PVR users and 0 IUD users) reported weaning as a reason for discontinuation.

Median duration of amenorrhea among PVR users was 405 days versus 120 days for IUD users ($P < 0.001$). Infants from both groups were fed seven to 12 times daily and grew at expected rates. The study underscores the value of PVR as a method that promotes breastfeeding as being beneficial to infant health.

Both groups reported similar treatment-emergent adverse events (TEAEs): 24.2% of PVR users and 23.0% of IUD users. Five PVR users experienced severe TEAEs: three cases of menorrhagia and one case each of dizziness and vaginal ulceration. This compared to three IUD users with severe TEAEs: one each of extremity pain, seizure and menometrorrhagia/menorrhagia.

Ensuring access to safe and effective contraception for postpartum women is an important national goal for India because only one-quarter of the country’s postpartum population is using contraception. In addition, short pregnancy intervals increase the risks of adverse maternal and infant outcomes.

In 2015, the World Health Organization (WHO) said that women who breastfeed and are 4 or more weeks postpartum can use the PVR without restriction. “The authors concluded that a user-controlled device like the PVR ‘offers an additional contraceptive choice for lactating women for one-year postpartum use and can help to address the unmet need for contraception among postpartum women while encouraging breastfeeding to enhance infant growth and well-being.’”

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

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Major vascular injury incurred at laparoscopy

An LVAH case underscores the importance of continuing education.

A 39-year-old G2P1102 presented to her gynecologist with a complaint of pelvic pressure. She had regular menses and no loss of urine. Her history was significant only for a postpartum bilateral tubal ligation 2 years earlier.

The woman’s examination revealed prolapse of the uterus, with the cervix visible at the introitus. An ultrasound performed by the physician 1 week after her initial presentation revealed a 4.8 x 4.5 x 6.8-cm left ovarian cyst. The physician recommended a laparoscopically assisted vaginal hysterectomy (LAVH) and left salpingo-oophorectomy (SP). The woman was presented with several options for management, including a total abdominal hysterectomy and left SP. The gynecologist reviewed the risks of surgery and potential complications. All the patient’s questions were answered and operative permissions were signed. The surgery was scheduled for 1 week later.

During surgery, insertion of the Veress needle was without incident. However, upon insertion of the umbilical trocar, profuse bleeding was noted and the patient became bradycardic and hypotensive and experienced cardiac arrest. She was resuscitated, following which, the gynecologist made a midline vertical incision and noted a laceration in the area of the aorta. A general surgeon was consulted, who could not fully control the bleeding. Thus, pressure was applied to the aorta and the patient was transferred to a tertiary hospital 40 minutes away that had a vascular surgeon.

Upon arrival at the tertiary hospital, the patient was taken immediately to surgery. The vascular surgeon noted transaction of the anterior wall of the common iliac artery encompassing almost half the diameter of the artery. Also noted was a duodenal serosal tear, presumably from the pressure held during transport. The vascular surgeon also noted thrombi of the common iliac artery, and the right and left iliac arteries. The surgeon repaired the vascular injury with an end-to-end anastomosis, and performed right and left iliofemoral thrombectomies, as well as from the common iliac artery, restoring flow to the right and left common iliac arteries. He then noted that both the patient’s feet had good capillary refill. The duodenal laceration was repaired without consequence. The patient had a relatively uncomplicated recovery, with the exception of residual neuropathy in her right leg and hip, with foot drop that persisted despite months of occupational and physical therapy.

Approximately 9 months after the attempted LAVH, the patient sought care of another gynecologist, who noted that her uterus was protruding to the introitus with Valsalva.

**Dr. Shwayder** is Professor of Obstetrics and Gynecology and former Chair at the University of Mississippi Medical Center. He is a graduate of the University of Denver College of Law and is a nationally and internationally recognized expert in gynecology ultrasound and minimally invasive surgery. He actively consults on legal matters in medicine, including liability in ultrasound and gynecologic surgery, as well as issues surrounding privileging and insurance fraud.
the care of another gynecologist, who noted that her uterus was protruding to the introitus with valsalva. An ultrasound was obtained, which was interpreted as normal, with no pelvic or ovarian masses or cysts. The physician recommended a total vaginal hysterectomy. Despite being “scared to death,” the patient elected to go forward with the procedure, which was performed without incident. Surgical findings stated that “both tubes and ovaries appeared normal.”

Ultimately, the patient filed suit against the original gynecologist, alleging inadequate and inappropriate preoperative evaluation, improperly performed surgery, with resultant complications, long-term physical deficits, pain and suffering, and loss of life’s enjoyment.

Deposition of the defendant gynecologist revealed several potential concerns. When questioned if it would be an option to wait and see if the cyst would go away on its own, the gynecologist stated, “I would not consider that to be an option in this case. I was trained that anything over 5 cm is a problem.”

During questioning about the performance of the surgery, the gynecologist described a closed-entry technique, using a Veress needle. A saline-drop test was used to confirm intraperitoneal placement of the Veress needle. The opening pressure was 7 mmHg. To establish the pneumoperitoneum, the abdomen was elevated with the surgeon’s hand, and the trocar was inserted at a 45º angle into the pelvis. The gynecologist suspected that the vascular injury occurred with insertion of the trocar.

In reviewing the gynecologist’s surgical experience, he stated that he had performed thousands of laparoscopies and had assisted on or performed LAVHs since 1990. It was noted that the physician had completed his residency in 1984. Unfortunately, he could not document any formal continuing education courses, nor additional training or education in ultrasound or more advanced laparoscopy since that time. The physician was board-certified and was current with his maintenance of certification.

The plaintiff’s ultrasound expert reviewed the original ultrasound images and noted a 6.80 x 4.86 x 4.49-cm simple, unilocular cyst, consistent with a persistent follicular cyst or a serous cyst. This expert opined that the current recommendation for follow-up of such a cyst in reproductive-aged women is a repeat ultrasound in 2 to 6 months. Thus, immediate intervention was not indicated. Subsequently, prior to the TVH, an ultrasound revealed that the cyst had completely resolved, confirming that surgical intervention for the ovarian cyst was not required. Thus, one could have avoided the risk of laparoscopy altogether, particularly with the primary surgical indication of uterine prolapse.

The plaintiff’s laparoscopy expert noted several breeches in the standard of care. Although a closed-entry technique, and even a direct-insertion technique without a pneumoperitoneum, is an acceptable alternative, the method the defendant described was not within the standard of care. Insufflating a specific amount of CO₂, for example 2 L, is not adequate. Contrary to the defendant’s statement, patients are paralyzed for the procedure, and thus, they are totally relaxed. One cannot assume that 2 L of CO₂ provides an adequate pneumoperitoneum in all patients. Thus, current practice is to infuse enough CO₂ to establish an intraperitoneal pressure of 12 to 15 mmHg prior to insertion of the primary trocar. In fact, many surgeons insufflate to a pressure of 20 mmHg for initial trocar insertion, reducing this pressure to 12 to 15 mmHg for placement of the secondary trocars. Inadequate intraperitoneal distension subjects the patient to a greater risk of vascular injury, as occurred in this case. The placement of a patient in Trendelenburg for insertion of the umbilical trocar is not currently recommended. The Trendelenburg position places the aorta and the common iliac vessels in direct line with insertion of a trocar at

THIS CASE HIGHLIGHTS THE IMPORTANCE OF REMAINING COGNIZANT OF CURRENT LITERATURE AND SURGICAL PRACTICES.
a 45° angle. Although this was common practice in the past, current recommendations, literally for several decades, are to maintain the patient in a supine position, with the abdominal wall elevated, for insertion of the umbilical trocar, only changing to the Trendelenburg position for insertion of the secondary trocars. The plaintiff’s expert opined that placing the patient in the Trendelenburg position for insertion of the umbilical trocar was a breach of the standard of care. Doing so places the patient at risk for the exact vascular injury encountered in this case. No criticisms were levied against the care of the general surgeon, the vascular surgeon, or the subsequent postoperative care and rehabilitative services. Thus, the defense focused on the criticisms levied against the preoperative evaluation and the surgical technique.

In evaluating the defensibility of the case, the identified lack of documented continuing education and additional surgical training placed the case defense at risk. Unfortunately, proceeding to trial posed a significant risk of losing the case, with subsequent exorbitant damages. It was elected to settle the case prior to trial for $900,000.

Case analysis
This case highlights the importance of remaining cognizant of current literature and surgical practices. All too often, physicians fail to remain current in the various areas of their practices. One would assume that maintenance of certification would allow physicians to stay current in their practice. However, ongoing education in specific practice areas may be required. Ultrasound, a valuable adjunct to our care of patients, is rapidly changing. The approach to adnexal masses is constantly evolving, with consensus guidance for management available. In this case, the physician’s lack of awareness of these newer guidelines impacted the preferred management option: observation. If there is any question about diagnosis or management, one can always seek a second opinion from a more experienced sonologist. As in this case, this functional cyst resolved, negating the need for an abdominal approach. Thus, the physician could have pursued a vaginal hysterectomy, the preferred route, which was ultimately performed, avoiding the risk of laparoscopy.

The need to adapt one’s surgical techniques is particularly true in the rapidly changing surgical environment of minimally invasive surgery. Changes in accepted techniques were not adopted in the current case. With the physician’s lack of documented continuing education and additional surgical training, this case was at greater risk. The cited breeches rendered the case one with a significant risk of losing at trial. Thus, the best perceived option was settlement.

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CARRiER SCREENING • CONTINUED FROM PAGE 35

Reproductive Options for Carrier Couples Identified Before Pregnancy

When surveyed, the majority of ob/gyn providers believed that expanded panels should be offered pre-conception as part of family planning. It is unfortunate that the majority are not. Screening performed before a couple is pregnant allows prevention of an affected pregnancy. These options include in vitro fertilization (IVF) with preimplantation genetic testing for monogenic conditions (PGT-M), use of a non-carrier donor gamete, adoption, or avoidance of pregnancy. Among couples identified as at-risk before pregnancy, more than three-quarters reported that they had undertaken or planned to undertake one of these options.

Historically, PCR-based methods had been widely used for PGT-M; however, these methods suffered from allele drop out, resulting in misdiagnosis. To avoid this, lineage analysis using polymorphic markers (usually short tandem repeats) close to the gene of interest were required, taking months of work by highly skilled scientists. Most recently, karyo-mapping using a single nucleotide polymorphism array of approximately 300,000 genome-wide SNPs has been developed to facilitate the rapid identification of informative markers. In most instances this approach increases the number of informative markers to an average of approximately 70 SNPs in the window around the gene of interest, significantly shortening pretest preparation to a few weeks.

FOR REFERENCES VISIT contemporaryobgyn.net/carrier
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Even if a patient has had sex in the prior 24 hours:

- A negative result *is* valid
- A positive result may not be valid & should be confirmed > 24 hours

Interference from semen can sometimes cause a false positive due to fibronectin in semen, but a negative fFN result is a valid result.
Riley Maternity and Newborn Health Offers Personalized Collaborative Care

The Riley Children’s Health Fetal Center is Committed to Providing Personalized Care

The Riley Fetal Center provides preeminent management of a broad range of complex and high-risk conditions while supporting families with coordinated care specific to the needs of the patient.

- Houses fetal imaging modalities, such as ultrasound, fetal echocardiography, and fetal MRI.
- Personalized and multidisciplinary care consultations pair families with subspecialists for fetal diagnosis discussions, pregnancy and delivery care planning, and postnatal treatment for the newborn.
- Multidisciplinary Fetal Center conferences bring together more than 40 Riley subspecialists to discuss best practices for complex fetal diagnoses.
- Family support provided before, during and after a Fetal Center visit by a skilled team that includes a fetal care coordinator, family support coordinator, and social worker.

Riley Hospital for Children is a nationally recognized center of excellence in providing care for children. In 2020, 10 of 10 specialties were ranked by U.S. News & World Report, including but not limited to:

- Neonatology (ranked 14th)
- Cardiology & Cardiothoracic Surgery (ranked 5th)
- Neurology & Neurosurgery (ranked 22nd)

Experts in Comprehensive High-Risk Pregnancy Services

Riley Children’s Health Maternal-Fetal Medicine offers pregnancy consultation and services for women with medical and obstetrical conditions, including preexisting diabetes, chronic high blood pressure, preeclampsia, preterm labor, and other complex medical conditions that affect pregnancy. Our maternal-fetal medicine specialists also care for women who experience unexpected problems during pregnancy and provide care for women whose pregnancies are complicated by fetal congenital anomalies or abnormal growth problems.

Specialty Programs
We offer special programs aimed at providing excellent care for specific groups of pregnant women.

- Mood Disorders Program
- Maternal Recovery Program
- Diabetes in Pregnancy Program
- Centering Pregnancy Program
- Cardiac Disease in Pregnancy Program
- Critical Care
- Placenta Accreta Program

Ultrasound examinations interpreted by maternal fetal medicine-physicians, 2018 – 2019:

- 2019: 14,760
- 2018: 12,464

Learn more about the Fetal Center at rileychildrens.org/maternity
Scheduled to open in 2021, the Maternity Tower at Riley Hospital for Children at IU Health will centralize all obstetric and neonatal care in Indianapolis. The facility will feature a new coordinated care model anchored by the long-standing reputation of Riley at IU Health for delivering expert care for complicated pregnancies and at-risk newborns. IU Health offers comprehensive, multidisciplinary services that surround patients experiencing low-risk to high-risk pregnancies with exceptional medical support.

The new tower contains four floors of inpatient hospital services to house a labor and delivery & antepartum unit, including birthing suites.

**On-site level III & Level IV NICUS.**

The Maternity Tower will house a Level III NICU and when combined with the already existing Level IV NICU, Riley Hospital for Children will house the largest NICU in the state.

Riley at IU Health offers one of the most comprehensive obstetrics and maternal-fetal medicine programs in the state. With the new Maternity Tower opening in 2021, the team will be able to deliver fully integrated care. Services will include:

- 105 private NICU rooms
- 68 private postpartum rooms for mother & baby
- Experienced obstetricians and midwifery program
- Dedicated OB ICU

Learn more, visit [rileychildrens.org/maternity](http://rileychildrens.org/maternity)