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Can grit prevent burnout?

Ob/gyns have the mental make-up to thrive in medicine but success requires tenacity

As I approach my ninth year as a medical school dean (can that really be true?) there are many things that keep me up at night. But first and foremost is the fundamental question of how to help my students, residents, fellows, faculty and affiliated community physicians keep up with the accelerating pace of new medical information. Next year it’s estimated that medical knowledge will double every 73 days (it was every 20 years when I was a medical student).¹

Pulitzer Prize-winning author Tom Friedman, has argued that the accelerating rate of technological change has already exceeded the ability of humans to adapt.² Nowhere is the rate of acceleration greater than in medicine. Many factors contribute to physician burnout, including burdensome regulations, arcane billing rules and the insatiable demands of electronic charting, but I think the greatest challenge to our mental wellbeing is keeping up with the thousands of new articles published monthly, the plethora of new drugs being approved every year, and rapid proliferation of new genetic tests.

So how can we keep up? First, we need to learn to be curators of medical information rather than repositories of such knowledge. Medical school curricula are quickly evolving from memorization of “facts” to clinical reasoning using curated up-to-date data. Medical students are also being taught that they must become lifelong learners because much of what they are taught in medical school may be out of date in a few years. The same applies to residents, fellows, faculty and community physicians. What does it take to be a lifelong learner without burning out? I would contend it takes the same personality trait that got you into medicine in the first place: grit.

What is grit?

I was pondering questions about preventing burnout and promoting lifelong learning while attending this fall’s Association of American Medical Colleges’ annual meeting when I serendipitously walked into a lecture by Dr. Angela Duckworth. She is a Professor of Psychology at the University of Pennsylvania and a 2013 MacArthur “Genius” awardee. An expert on the science of achievement, she has focused much of her professional career on studying what makes successful people successful. Dr. Duckworth’s seminal contribution to this question is that they are simply grittier than less successful people. I know that sounds pretty simplistic but there is a compelling body of qualitative and quantitative data to support her thesis. Dr. Duckworth is a very engaging and dynamic speaker, as you can discern from viewing her TED Talk on grit: (https://www.youtube.com/watch?v=H14bBuluwB8).

As I looked about the packed audience, it dawned on me that, by definition, the physicians all around me were gritty or they wouldn’t be there and grit might just be the key to maintaining the discipline of lifelong learning while avoiding burnout.

When I got home, I read Dr. Duckworth’s book, Grit: The Power of Passion and Perseverance, which is part autobiography, part biography, and part an exceedingly readable psychology text.³ She describes various people, from Navy Seals and Olympic swimmers to Spelling Bee champions and kids who survived impoverished neighborhoods and broken families to excel scholastically. They all share one characteristic: grit.

Grit can be defined as passion and perseverance to achieve long-term...
goals. It requires certain building blocks, the first of which is curiosity to explore a variety of interests before settling on the one most compelling. Next comes a desire to master that interest completely. Initial novelty is soon replaced by deep appreciation of the nuances of a given field or discipline but mastery requires deliberate practice. The latter consists of pushing oneself to continuously improve, to overcome weaknesses through intense concentration and honest feedback, and to meet progressive stretch goals. Long periods of effortful, deliberate practice lead to exhilarating moments of effortless flow and peak performance which drive an ever more intense desire for mastery.

Physicians are gritty
Physicians (and especially ob/gyns) should relate to all these characteristics. Think how hard you worked in your pre-med years. First, you discovered you might want to be a physician because you loved science and wanted to help your fellow man. This was followed by intense study, shadowing, summer research projects and the pursuit of perfection on assignments. Think of the elation you felt when you were finally accepted to medical school. Then the process started all over again—mastering fundamental science and the rudiments of physical exams and clinical reasoning, followed by exposure to different clinical disciplines. Next your interest was piqued during your ob/gyn clerkship and after weighing your options, you committed yourself to our wonderful profession. Can you remember the exhilaration of the Match? And then the process started all over yet again. Recall how you learned to perform pelvic exams, ultrasounds, and episiotomies, and then mastered progressively more challenging aspects of surgery. Remember how you constantly sought to perfect your skills and how they progressively improved during your 4 years—with further refinements if you did a fellowship and/or then in practice.

But gritty exemplars exhibit more than interest and practice, they have purpose. It is that higher purpose that builds resilience in the face of adversity and exhaustion. There is abundant data that grittier people are more optimistic than their non-gritty peers. This optimism helps gritty individuals view setbacks as temporary. Gritty individuals exude helpfulness and eschew learned helplessness. In fact, they are statistically happier. While you could debate whether all this is “chicken or egg,” there is evidence that being optimistic and happy allows you to be grittier, but that being gritty makes you more optimistic and happy—in other words, there is a virtuous cyclicity to grit.

Using grit to crush burnout
Gritty individuals tend to seek out and thrive in gritty cultures and follow gritty leaders. These cultures and leaders tend to be both demanding and supportive. If you find yourself being led by someone who is supportive without being demanding, you are in a permissive culture without progress or excellence. Being in a demanding but not supportive setting creates a harsh, relentlessly hostile environment that no one can thrive in or long tolerate. Being in a milieu that is neither supportive nor demanding creates apathy and ennui. But being both demanding and supportive is what sets great parents, teachers, coaches, managers, leaders and physicians apart and it is the ideal setting for gritty individuals! Great mentors know just how far to push trainees; to demand excellence through deliberate practice without intimidation and fear. If we can practice in such an environment, we will thrive. If we can ourselves practice such “wise parenting” with our patients, we can achieve better outcomes. If we practice it with our staff, trainees, and colleagues, we will not only create a culture of excellence, we can combat the insidious ingredients of burnout: emotional exhaustion, doubt, cynicism, and pessimism. More to the point, if we can maintain our grittiness, we will not only pursue lifelong learning, we will take pleasure in the process and it will make us grittier.

Grit can be defined as passion and perseverance to achieve long-term goals.

Grit: The Power of Passion and Perseverance by Dr. Angela Duckworth

CONTINUED ON PAGE 39
Using oral antidiabetic agents to manage Hyperglycemia in GDM

These drugs offer advantages over insulin, but limited data on their long-term effects warrant caution when prescribing.

by DONALD R COUSTAN, MD
address these three medications for GDM: insulin, glyburide and metformin (Table 2).

**Insulin**

Insulin of various types is the long-standing first-line treatment when GDM glycemic goals are not met with lifestyle modification. There is minimal passage of insulin across the placenta, which is the primary reason why it is preferred for GDM. The major drawbacks of the drug include the requirement for subcutaneous injection and risk of hypoglycemia, which is unusual in GDM unless a meal is missed after an insulin injection. In addition, people with diabetes with significant glycosuria may gain weight when insulin treatment prevents loss of calories in urine. A description of various types of insulin and dosing paradigms is beyond the scope of this article and may be found elsewhere.⁹

**Sulfonylureas: Glyburide**

A drug that can be taken orally is preferable to one that must be injected. Glyburide, a sulfonylurea, is commonly used to treat GDM in the United States, as noted above. Sulfonylureas bind to receptors in pancreatic β-cells, stimulating insulin secretion at all blood glucose levels. As with insulin, adverse effects may include hypoglycemia and weight gain. One concern with sulfonylureas is that, should they cross the placenta and reach the fetus, fetal insulin secretion could be augmented, leading to the various problems of “diabetic fetopathy” that are related to fetal hyperinsulinemia. However, a 2000 randomized trial comparing the second-generation sulfonylurea glyburide with insulin reported that both agents were similarly successful in controlling glucose levels with similar rates of fetal macrosomia, cesarean delivery, and neonatal hypoglycemia.¹⁰ Only 4% of patients treated with glyburide required supplemental insulin. No glyburide was detected in cord blood samples despite measurable maternal levels. After publication of this study, glyburide rapidly increased in popularity for treating GDM.

In 2009, the NICHD Fetal Pharmacology Network reported that, using a more sensitive assay, umbilical cord glyburide levels were approximately 70% of simultaneous maternal levels.¹¹ This was confirmed by a second study reporting cord levels at 50% of maternal levels.¹² While most cord levels were subtherapeutic, maternal levels were also quite low; the last dose of glyburide in the latter study was taken, on average, 13 hours prior to delivery. Because glyburide is cleared more rapidly during pregnancy than in the nonpregnant state, returning to baseline levels 8 hours after dosing, fetal levels would likely be higher at the time of peak maternal levels, 2 to 3 hours after dosing.¹³ Concern about the unknown consequences of in utero exposure to glyburide, whether beneficial or harmful, prompted some centers to discontinue use of glyburide as a first-line agent when GDM required medication.

A 2015 systematic review and meta-analysis found that glyburide use for GDM resulted in higher birth weights, more macrosomia (RR 2.62) and more neonatal hypoglycemia (RR 2.04) when compared with insulin.¹⁴ Treatment failure requiring supplemental insulin occurred in 24% of glyburide-treated subjects in the two included studies comparing glyburide and metformin. A second systematic review and meta-analysis reported that glyburide was associated with an odds ratio of 2.29 for large for gestational age (LGA) offspring.¹⁵ These findings, combined with the evidence for transplacental passage of glyburide, supported the downgraded status of glyburide for treatment of GDM by ADA and ACOG.¹⁶

Unlike the above two systematic reviews, a 2017 Cochrane review found no significant difference in outcomes between glyburide-treated and insulin-treated GDM pregnancies, supporting the use of glyburide for GDM.¹⁷ These inconsistent data underscore the lack of consensus regarding glyburide use.

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**TABLE 1  Recommendations from professional organizations for treatment of GDM that requires medication**

<table>
<thead>
<tr>
<th></th>
<th>ACOG¹</th>
<th>ADA²</th>
<th>SMFM³</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin or metformin</td>
</tr>
<tr>
<td>Second line</td>
<td>Metformin</td>
<td>Metformin or glyburide</td>
<td>Glyburide</td>
</tr>
<tr>
<td>Alternative</td>
<td>Glyburide</td>
<td></td>
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</tbody>
</table>

A 2017 survey of MFM specialists reported that 57% use glyburide as their first-line treatment for GDM.
Unlike insulin and glyburide, [metformin] does not produce hypoglycemia or weight gain but can cause nausea or diarrhea.

for GDM. The average failure rate of glyburide was reported as 25%.\textsuperscript{13} Evidence that clearance of glyburide is more rapid during pregnancy, and that higher dosing would be required to reach plasma concentrations similar to those achieved in nonpregnant individuals,\textsuperscript{11} suggests that better glucose control may be achieved by prescribing glyburide 30 to 60 minutes before meals, and prescribing a second dose at dinner to cover the post-dinner glucose excursion.\textsuperscript{16} It is unlikely that predinner or bedtime glyburide will be effective in controlling fasting glucose levels because plasma glyburide levels are dissipated by 8 hours after dosing. These suggestions notwithstanding, the fact that long-term effects on offspring of in utero glyburide exposure are unknown requires caution in prescribing this medication, and thorough counseling of patients who will be taking it.

**Biguanides: Metformin**
Metformin is commonly used to treat type 2 diabetes, insulin resistance syndrome, and polycystic ovary syndrome (PCOS) in nonpregnant individuals. This drug suppresses hepatic insulin production and increases peripheral insulin sensitivity. Unlike insulin and glyburide, it does not produce hypoglycemia or weight gain. It can cause gastrointestinal (GI) upset such as nausea and diarrhea. Metformin crosses the placenta, with average umbilical artery levels approximately twice simultaneously measured maternal vein levels in one study, and cord levels approximately 60% of maternal levels in another.\textsuperscript{17,18}

In 2008, a randomized clinical trial (RCT) (the “MiG trial) compared insulin versus metformin in patients with mild GDM.\textsuperscript{19} There were no differences between the two treatment arms in a composite outcome as well as individual outcomes such as LGA, small for gestational age (SGA), cesarean deliveries, hypertensive disorders and neonatal hypoglycemia. Patients in the metformin group had higher rates of preterm birth before 37 weeks (12.1% vs. 7.6%, \(P = 0.04\)) but a 60% decrease in neonatal hypoglycemia (any blood glucose < 28.8 mg/dL), however, there were no differences in sustained neonatal hypoglycemia in the metformin-treated group. Most patients in the metformin arm (77%) would prefer the same treatment in a subsequent pregnancy while only 28% in the insulin arm would prefer insulin to metformin. GI side effects requiring limitation or cessation of dosing occurred in 11% of the metformin group and none of the insulin group. Weight gain during treatment was significantly lower in the metformin-treated group.

Of the subjects randomized to metformin treatment, 46% required supplemental insulin.

The MiG Trial was soon followed by increasing use of metformin for GDM. One systematic review and meta-analysis also reported that metformin was associated with a greater risk of preterm birth although less pregnancy-induced hypertension, and lower maternal weight gain compared to insulin, as well as lower maternal weight gain and less macrosomia compared to glyburide in subjects with GDM.\textsuperscript{13} Treatment failure requiring supplemental insulin occurred in 27% of metformin-treated subjects in the two included studies comparing glyburide and metformin. Another systematic review reported that metformin was associated with less maternal weight gain and lower risk of pregnancy-induced hypertension (but not pre-eclampsia), large for dates offspring (but not macrosomia), and neonatal hypoglycemia compared to insulin use for GDM.\textsuperscript{20} Metformin use was not associated with an increased risk of

| TABLE 2 | Comparison of pharmacologic agents to treat GDM |
| --- | --- | --- |
| **Cross placenta?** | Minimal | F/m = 0.5 to 0.7* |
| **Weight gain?** | + | + |
| **Hypoglycemia?** | + | No |
| **Gastrointestinal side effects** | No | +/- |
| **Route of administration** | Sub-q | Oral |

*Fetal to maternal concentration ratio
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preterm birth in this report. As noted previously, a Cochrane review found no difference in specific outcomes between metformin and glyburide. In 2017, Romero et al reviewed the history of metformin use dating back to ancient Egypt and proposed a biologically plausible mechanism of action for its apparent prevention of preeclampsia.

In March of 2018 the SMFM Publications Committee reviewed the available data and concluded:

“...in women with GDM in which hyperglycemia cannot adequately be controlled with medical nutrition therapy, metformin is a reasonable and safe first-line pharmacologic alternative to insulin, recognizing that one-half of women will still require insulin to achieve glycemic control...Clearly, further data are needed to establish long-term safety of these agents.”

The SMFM recommendation has provided support for use of this medication in GDM. However, this pronouncement may have been premature, since possible long-term effects of this drug which crosses the placenta have not been fully explored.

In 2018 a group of authors with expertise in the field published a cautionary response to the SMFM statement, raising a number of concerns. While data on short-term maternal and fetal outcomes are generally favorable, there are open questions regarding potentially beneficial or harmful long-term effects, particularly in view of current interest in fetal programming and epigenetics.

Metformin has anticancer properties and can inhibit cell growth as well as suppress mitochondrial respiration. While first-trimester use is apparently not teratogenic, the early embryo has low levels of the transporters that allow metformin to enter cells and mitochondria. Later in pregnancy these transporters are abundant. Studies of animal models have reported adverse long-term outcomes on body weight and metabolism. Further details concerning these cellular effects and animal models are provided in the above-mentioned publication.

There are few long-term studies of human offspring exposed to metformin in utero. A 2-year follow-up of the MiG trial reported that metformin-exposed offspring had greater subcutaneous fat but no difference in central fat, with no other differences. At age 7 to 9 years, the subgroup of metformin-exposed children at the Adelaide site (average age 7 years) had no difference in weight or body composition, while the Auckland subgroup (average age 9 years) of metformin-exposed offspring were heavier and had greater waist:hip ratios, arm and waist circumference than insulin-exposed controls. Metformin-exposed offspring whose mothers participated in a RCT of treatment of polycystic ovary syndrome (PCOS) during pregnancy had higher fasting glucose levels and systolic blood pressure at age 8 years compared to non-exposed controls. In a larger follow-up study of offspring exposed to metformin in utero in two RCTs of PCOS treatment, 32% of 4-year-olds in the metformin group were overweight or obese compared to 27% in the control group.

SUMMARY OF CONCLUSIONS

1. Both glyburide and metformin cross the placenta; insulin does not.
2. Long-term effects of glyburide and metformin are not well delineated.
3. Insulin is the first-line medication for GDM when glycemic goals are not met by lifestyle modifications.
4. Reserve oral agents for patients who decline insulin after thorough counseling or when insulin is not available.
5. No clear preference between metformin and glyburide:
   a. Metformin may be associated with better outcomes than glyburide, but apparent differences are not consistent and might be explained by suboptimal dosing with glyburide.
   b. Metformin reaches higher fetal:maternal concentrations than glyburide.
   c. Metformin is associated with less weight gain than glyburide, but more GI side effects.
   d. Glyburide may cause hypoglycemia (rare in pregnancy).
6. Either oral agent may not be sufficient to reach glycemic goals; additional insulin may be required.
7. When an oral agent is prescribed thorough counseling and documentation are important.
New tools for counseling on prenatal genetic testing

As new screening options become available, ob/gyns must be able to counsel their pregnant patients appropriately.

by MARY E. NORTON, MD, AND RENÉE L. CHARD, MSC, CGC

Obstetricians and their patients are faced with an increasingly complex array of prenatal screening and diagnostic testing options. With the benefit of more options comes the challenge of providing patients with the information they need to make an informed choice about testing that is consistent with their clinical situation and personal values. In a busy clinical setting, it’s often unrealistic to review the recommended content of pretest counseling as described by professional societies. In some cases, it’s prudent to refer a patient to a genetic counselor for discussion of testing options (Table 1); the National Society of Genetic Counselors and the American College of Medical Genetics and Genomics both provide information that can be helpful in locating genetic counseling services. However, it’s neither practical nor realistic to send every prenatal patient for formal genetic counseling. Therefore, obstetricians need to have a strategy to provide basic pretest education and counseling to their pregnant patients. This article discusses the important elements of pretest counseling that should be provided to every prenatal patient, and some suggestions on how to do such counseling in a manner that is adequate and yet realistic.

Current recommendations for testing

The American College of Obstetricians and Gynecologists (ACOG) makes several recommendations regarding patient counseling about testing for aneuploidy, as well as for carrier screening. According to ACOG, “[a]neuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy...” ACOG also recommends that all women be offered carrier screening that includes, at a minimum, cystic fibrosis (CF) and spinal muscular atrophy (SMA); additional tests may also be recommended depending on the patient’s race and ethnicity. Genetic testing should be an informed patient choice, with an underlying foundation of shared decision making that fits the patient’s clinical circumstances, values, interests, and goals. Clearly, complying with these recommendations is challenging in the context of an initial prenatal visit.

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DR. CHARD is a Certified Genetic Counselor at Maine Medical Partners Women’s Health, Portland.
that must also address other important aspects of prenatal care.

**Elements of routine pretest counseling**

**Review of family history**

While most genetic disorders occur in patients with no relevant family history or risk factors, patients who have a family history of concern often benefit from genetic counseling. ACOG recommends that all women have a family history evaluation for inherited risk.\(^4\) Genetic counselors typically assess family history by creating a three-generation pedigree, but there are also tools available to collect family history information (Tables 2,3).\(^6\) In a busy obstetrical practice, use of this type of family history questionnaire or checklist is usually the most practical. Asking patients to complete the questionnaire prior to the clinic visit can ensure that patients have time to contact family members as needed to collect more accurate information. Any positive responses should be followed up to obtain more detail, including the relationship of the affected family member(s) to the patient, exact diagnosis, age at onset, and severity of disease. Concern is generally greatest when there is an affected first-degree relative (parent or sibling) and less commonly when a more distant relative (aunt, uncle, grandparent, or cousin) has a genetic disorder. An exception is with X-linked disorders, in which case a genetic variant can be passed through unaffected female relatives. Concerns in first-degree relatives, or for X-linked disorders related through female relatives, should prompt consideration of referral for formal genetic counseling.\(^1\)

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Indications for referral to genetic counseling</th>
</tr>
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<tbody>
<tr>
<td>Family history of a known or suspected genetic disorder</td>
<td></td>
</tr>
<tr>
<td>Known carrier of a genetic condition</td>
<td></td>
</tr>
<tr>
<td>Consanguinity (blood relationship of parents, first cousins or closer)</td>
<td></td>
</tr>
<tr>
<td>Fetal structural anomaly on prenatal ultrasound</td>
<td></td>
</tr>
<tr>
<td>Abnormal screening test result, either traditional serum screening or cell-free DNA screening</td>
<td></td>
</tr>
<tr>
<td>Known teratogenic exposure</td>
<td></td>
</tr>
<tr>
<td>Recurrent pregnancy loss (3 or more first-trimester losses, stillbirth, or neonatal or fetal loss with structural anomalies)</td>
<td></td>
</tr>
<tr>
<td>Patient request for additional information regarding genetic test options</td>
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</table>

Importantly, simply ordering expanded carrier screening is not adequate to assess risk for a familial genetic disorder. While expanded carrier screening may include testing for a gene or genes that cause a particular disorder, such panels may not include all variants in a given gene. Therefore, the detection rate of expanded carrier panels is usually lower than targeted testing. Ideally, the specific variant in the family should be identified in order to provide accurate genetic counseling and prenatal testing.

**What is the purpose of prenatal genetic testing? Does every patient want such information?**

The purpose of prenatal genetic testing is to determine if a fetus has a genetic disorder. Obtaining such information can serve several purposes; for most women, results are normal and they receive reassurance. For some fetal disorders, prenatal diagnosis allows the family to prepare for the birth of a child with special needs. Early detection of conditions such as cystic fibrosis may ensure early institution of appropriate care after birth. For a few conditions, prenatal detection may lead to a change in pregnancy management or delivery location. In many cases, however, the family is faced with a decision regarding pregnancy termination when no perinatal interventions are available to improve outcomes.

As patients consider prenatal testing, it is important that they understand the reasons that women choose to undergo, or in some cases to decline, prenatal genetic testing. This part of the conversation can be done with a simple explanation and a question: “There are a number of genetic tests that are available to test for different types of birth defects or genetic disorders. There is a range of conditions that we can find, and some are treatable, while for others, no treatment is available. It is your choice whether to have such testing, or if you would like more information about different tests and options. Are you interested in learning more about testing for birth defects?” Some women may decline testing altogether, and that is an acceptable decision that should be supported and documented in the medical record. For women who are uncertain, or want to hear more about options, the next step is a discussion of the difference between screening and diagnostic testing.
What is the difference between screening and diagnostic testing?

One of the most important basic concepts of genetic testing is the difference between screening tests, which help a patient refine her risks, and diagnostic tests, which tell a patient for certain if her fetus is affected with a genetic disorder. As a general rule, screening tests are noninvasive and include ultrasound, such as nuchal translucency; maternal serum tests (such as first- or second-trimester screening); and cell-free DNA (cfDNA) screening. Diagnostic testing, in contrast, generally requires an invasive procedure such as amniocentesis or chorionic villus sampling for fetal karyotyping or chromosomal microarray. Diagnostic tests are far more comprehensive and accurate, while screening tests carry no miscarriage risk.

Many patients who undergo cfDNA screening are confused by the nomenclature “noninvasive prenatal testing,” which implies that it is a noninvasive alternative to diagnostic testing. In fact, it is more appropriately presented as an alternative to other screening options (“cell-free DNA screening”). In addition to presenting a simple explanation of the difference between these types of tests, there are patient education tools available through ACOG. A short video available through the Washington State Department of Public Health also explains the difference between prenatal screening and diagnostic testing. The Perinatal Quality Foundation’s Genetic Education Modules (GEM) also discuss the different prenatal screening and diagnostic tests that are available, with a “test at a glance” page that clearly illustrates the differences (Table 4).

Regardless of whether a provider refers patients to one of these tools, or explains the tests in person, ensuring that pregnant women understand the difference between screening and diagnostic testing is one of the most important concepts in pre-test counseling (Table 5). Patients who undergo screening may incorrectly assume that they are diagnostic and that such tests indicate with certainty either that a fetus is “normal” with a guarantee that no anomalies are present or is affected.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Resources for collecting family history information (modified from UpToDate®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resource</strong></td>
<td><strong>URL</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Elements of routine pretest counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of family history</td>
<td></td>
</tr>
<tr>
<td>Review of medical history</td>
<td></td>
</tr>
<tr>
<td>Review of medications and medication exposures</td>
<td></td>
</tr>
<tr>
<td>Discussion of the difference between screening and diagnostic testing</td>
<td></td>
</tr>
<tr>
<td>Review of prenatal screening tests for aneuploidy</td>
<td></td>
</tr>
<tr>
<td>Review of prenatal carrier testing</td>
<td></td>
</tr>
<tr>
<td>Discussion of patient’s values and preferences</td>
<td></td>
</tr>
</tbody>
</table>
NEXPLANON is indicated for use by women to prevent pregnancy.

SELECTED SAFETY INFORMATION

Who is not appropriate for NEXPLANON

- NEXPLANON should not be used in women who have known or suspected pregnancy; current or past history of thrombosis or thromboembolic disorders; liver tumors, benign or malignant, or active liver disease; undiagnosed abnormal genital bleeding; known or suspected breast cancer, personal history of breast cancer, or other progestin-sensitive cancer, now or in the past; and/or allergic reaction to any of the components of NEXPLANON.

WARNINGS and PRECAUTIONS

Complications of insertion and removal

- NEXPLANON should be inserted subdermally and be palpable after insertion. Palpate immediately after insertion to ensure proper placement. Undetected failure to insert the implant may lead to unintended pregnancy. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

- Insertion and removal-related complications may include pain, paresthesias, bleeding, hematoma, scarring, or infection. If NEXPLANON is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur. Implant removal may be difficult or impossible if the implant is not inserted correctly, inserted too deeply, not palpable, encased in fibrous tissue, or has migrated. If at any time the implant cannot be palpated, it should be localized and removal is recommended.

- There have been postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. Endovascular or surgical procedures may be needed for removal.

NEXPLANON and pregnancy

- Be alert to the possibility of an ectopic pregnancy in women using NEXPLANON who become pregnant or complain of lower abdominal pain.

- Rule out pregnancy before inserting NEXPLANON.

Educate her about the risk of serious vascular events

- The use of combination hormonal contraceptives increases the risk of vascular events, including arterial events [stroke and myocardial infarction (MI)] or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis (DVT), retinal vein thrombosis, and pulmonary embolism). Women with risk factors known to increase the risk of these events should be carefully assessed. Postmarketing reports in women using the nonradioactive etonogestrel implant have included pulmonary emboli (some fatal), DVT, MI, and stroke. NEXPLANON should be removed if thrombosis occurs.
SELECTED SAFETY INFORMATION (continued)

- Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum.
- Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. Consider removing the NEXPLANON implant if case of long-term immobilization due to surgery or illness.

Counsel her about changes in bleeding patterns
- Women are likely to have changes in their menstrual bleeding pattern with NEXPLANON, including changes in frequency, intensity, or duration. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. In clinical studies of the non-radiopaque etonogestrel implant, changes in bleeding pattern were the most common reason reported for stopping treatment (11.1%). Counsel women regarding potential changes they may experience.

Be aware of other serious complications, adverse reactions, and drug interactions
- Remove NEXPLANON if jaundice occurs.
- Remove NEXPLANON if blood pressure rises significantly and becomes uncontrolled.
- Prediabetic and diabetic women using NEXPLANON should be carefully monitored.
- Carefully observe women with a history of depressed mood. Consider removing NEXPLANON in patients who become significantly depressed.
- The most common adverse reactions (≥10%) reported in clinical trials were headache (24.9%), vaginitis (14.5%), weight increase (13.7%), acne (13.5%), breast pain (12.8%), abdominal pain (10.9%), and pharyngitis (10.5%).
- Drugs or herbal products that induce enzymes, including CYP3A4, may decrease the effectiveness of NEXPLANON or increase breakthrough bleeding.
- The efficacy of NEXPLANON in women weighing more than 130% of their ideal body weight has not been studied. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. Therefore, NEXPLANON may be less effective in overweight women.
- Counsel women to contact their health care provider immediately if, at any time, they are unable to palpate the implant.
- NEXPLANON does not protect against HIV or other STDs.

Please read the adjacent Brief Summary of the Prescribing Information

NEXPLANON is indicated for use by women to prevent pregnancy.

DOSAGE AND ADMINISTRATION

The effectiveness of NEXPLANON does not depend on daily, weekly, or monthly administration. All healthcare providers should receive instruction and training prior to performing insertion and/or removal of NEXPLANON.

A single NEXPLANON implant is inserted subdermally in the upper arm. To reduce the risk of neural or vascular injury, the implant should be inserted at the side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. The implant should be inserted subdermally just under the skin, avoiding the subcutaneous tissues. An implant inserted more deeply than subdermally (deeper implant) may not be palpable and may be difficult or impossible to locate (see Dosage and Administration and Warnings and Precautions). NEXPLANON must not be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant should be removed at this time to allow for replacement by a new implant at the time of removal, if continued contraceptive protection is desired.

CONTRAINDICATIONS

NEXPLANON should not be used in women who have
- Known or suspected pregnancy
- Current or past history of thrombosis or thromboembolic disorders
- Liver or other severe metabolic disease
- Uncontrolled benign or malignant breast disease
- Uncontrolled benign or malignant gynecologic disease
- Known or suspected breast cancer, personal history of breast cancer, or other estrogen-sensitive neoplasia
- Allergic reaction to any of the components of NEXPLANON [see Adverse Reactions]

WARNINGS AND PRECAUTIONS

The following information is based on experience with the etonogestrel implants (IMPLANON® [etonogestrel implant] and NEXPLANON), other progestin-only contraceptives, or experience with combination (estrogen plus progestin) oral contraceptives.

1. Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it is palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed until the implant is removed immediately after insertion. Unnoticed failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesia, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or intrascapular), neural or vascular injury may occur. To reduce the risk of neural or vascular injury, NEXPLANON should be inserted at the side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus. NEXPLANON should be inserted subdermally just under the skin, avoiding the subcutaneous tissues. An implant inserted more deeply than subdermally (deeper implant) may not be palpable and may be difficult or impossible to locate (see Dosage and Administration and Warnings and Precautions). NEXPLANON must be inserted by the expiration date stated on the packaging. NEXPLANON is a long-acting (up to 3 years), reversible, hormonal contraceptive method. The implant should be removed at this time to allow for replacement by a new implant at the time of removal, if continued contraceptive protection is desired.

Table 1: Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>Total Days of Spotting or Bleeding</th>
<th>Treatment Days 91-180 (N = 749)</th>
<th>Treatment Days 271-360 (N = 657)</th>
<th>Treatment Days 631-720 (N = 547)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Days</td>
<td>24%</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>1-7 Days</td>
<td>30%</td>
<td>20%</td>
<td>14%</td>
</tr>
<tr>
<td>8-21 Days</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>&gt;21 Days</td>
<td>35%</td>
<td>35%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Blending patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 1.
14. Fluid Retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

15. Contact Lenses
Contact lens wearers who develop visual changes or less tolerance should be assessed by an ophthalmologist.

16. In Situ Broken or Bent Implant
There have been reports of broken or bent implants while in the patient’s arm. Based on in vitro data, when an implant is broken or bent, the release rate of etonogestrel may be slightly increased. When an implant is removed, it is important to remove it in its entirety (see Dosage and Administration).

17. Monitoring
A woman who is using NEXPLANON should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

18. Drug-Laboratory Test Interactions
See hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

ADVERSE REACTIONS
In clinical trials involving 942 women who were evaluated for safety, change in menstrual bleeding patterns (irregular menses) was the most common adverse reaction causing discontinuation of use of the non-radiopaque etonogestrel implant (IMPLANON® [etonogestrel implant]) (11.1% of women).

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 3.

Table 3: Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies</th>
<th>N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding irregularities*</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Emotional Lability†</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Weight Increase</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>1.6%</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>1.3%</td>
<td></td>
</tr>
<tr>
<td>Depression*</td>
<td>1.0%</td>
<td></td>
</tr>
</tbody>
</table>
†Among US subjects (N = 330), 6.1% experienced emotional lability that led to discontinuation.
‡Among US subjects (N = 330), 2.4% experienced depression that led to discontinuation.

Other adverse reactions that were reported by at least 5% of subjects in the non-radiopaque etonogestrel implant clinical trials are listed in Table 4.

Table 4: Common Adverse Reactions Reported by ≥5% of Subjects in Clinical Trials With the Non-Radiopaque Etonogestrel Implant (IMPLANON)

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Studies</th>
<th>N = 942</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>24.9%</td>
<td></td>
</tr>
<tr>
<td>Vaginitis</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>Weight increase</td>
<td>13.7%</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td>13.5%</td>
<td></td>
</tr>
<tr>
<td>Breast pain</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10.9%</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Leukorrhea</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>influenza-like symptoms</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>7.2%</td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Emotional lability</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4%</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>5.4%</td>
<td></td>
</tr>
<tr>
<td>Insertion site pain</td>
<td>5.2%</td>
<td></td>
</tr>
</tbody>
</table>

In a clinical trial of NEXPLANON, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3.2% of subjects. Additionally, hematomas (0.3%), bruising (0.2%), pain (1.1%), and swelling (0.7%) were reported.

Effects of Other Drugs on Hormonal Contraceptives
Substances decreasing the plasma concentrations of hormonal contraceptives (HCs) and potentially diminishing the efficacy of HCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of progestins, including etonogestrel. Substances increasing the plasma concentrations of HCs: Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, and ketoconazole may increase the plasma concentrations of progesterins, including etonogestrel.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ 

Substances decreasing the plasma concentrations of progestins, including etonogestrel:

Other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use other contraceptive methods during and/or shortly after discontinuation of use of hormonal contraceptives, including etonogestrel.

Counsel women to use other contraceptive methods during and/or shortly after discontinuation of use of hormonal contraceptives, including etonogestrel.

Effects of Hormonal Contraceptives on Other Drugs
Hormonal contraceptives may affect the metabolism of other drugs. Consequently, plasma concentrations may either increase (for example, cyclosporin) or decrease (for example, lamotrigine).

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

USE IN SPECIFIC POPULATIONS

1. Pregnancy
Risk Summary
NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant (see Contraindications). Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose CHCs prior to conception or during early pregnancy. No adverse development outcomes were observed in pregnant rats and rabbits with the administration of etonogestrel during organogenesis at doses of 315 or 781 times the anticipated human dose (60 μg/day) NEXPLANON should be removed if maintaining a pregnancy.

2. Nursing Mothers
Lactation
Risk Summary
Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychosocial development of breastfed infants. Hormonal contraceptives, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less likely to occur in women who have not established lactation; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

3. Pediatric Use
Safety and efficacy of NEXPLANON have been established in women of reproductive age. Safety and efficacy of NEXPLANON are expected to be similar for postpubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

4. Geriatric Use
This product has not been studied in women over 65 years of age and is not indicated in this population.

5. Hepatic Impairment
No studies were conducted to evaluate the effect of hepatic disease on the disposition of NEXPLANON. Use of NEXPLANON in women with active liver disease is contraindicated (see Contraindications).

6. Overweight Women
The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight. It is possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

OVERDOSAGE
Overdose may result if more than one implant is inserted. In case of suspected overdose, the implant should be removed.

NONCLINICAL TOXICOLOGY
In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed. Etonogestrel was not genotoxic in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vitro micronucleus test. Fertility in rats returned after withdrawal from treatment.

PATIENT COUNSELING INFORMATION See FDA-Approved Patient Labeling.

• Counsel women about the insertion of NEXPLANON implant. Provide the woman with a copy of the Patient Labeling and ensure that she understands the information in the Patient Labeling before insertion and removal. If the CSDR and consent form are included in the packaging, have the woman complete a consent form and retain it in your records. The CSDR should be filled out and given to the woman after insertion of the NEXPLANON implant so that she will have a record of the location of the implant in the upper arm and when it should be removed.

• Counsel women to contact their healthcare provider immediately if, at any time, they are unable to palpate the implant.

• Counsel women that NEXPLANON does not protect against HIV or other STDs.

• Counsel women that the use of NEXPLANON may be associated with changes in their normal menstrual bleeding patterns so that they know what to expect.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA.

For more detailed information, please read the Prescribing Information. USP-NF-BPITX-7105019 Revised: 05/17

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WOMN-126530-0000 03/18
with a congenital disorder because a screening test suggests an increased risk. Women should be counseled that all positive screening tests require diagnostic confirmation before irreversible actions (such as pregnancy termination) are undertaken.

**Review of prenatal screening and diagnostic tests for aneuploidy**

Once assured that a patient understands the difference between screening and diagnostic testing, a provider can then discuss options with a more targeted approach. Different patients, providers, and practices may have access to different test options. ACOG recommends that “all women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age,” but does not require that specific tests need to be offered. In the past, women under 35 years old were commonly offered aneuploidy screening, while women 35 and older were often referred to genetic counseling for a comprehensive review of genetic testing options or were offered the options of aneuploidy screening versus diagnostic testing. In contrast, recent recommendations note that while “maternal age may be helpful in adjusting an individual woman’s risk of having a fetus with aneuploidy, it should not be used as the sole determinant of whether aneuploidy screening or diagnostic testing is offered.” Most important is that all women are offered testing, and that the offer of testing be consistent in the practice. Many tools are available that compare and contrast testing options for patients, including the PQF GEM module, the ACOG FAQs or the Washington state video (Table 4). Practices may also create their own brochures, videos, or other tools to describe available options.

**Review of prenatal carrier testing**

Advances in sequencing techniques have made carrier screening for single-gene disorders more comprehensive and less costly, as well as much more complex. As noted above, ACOG recommends that all women be offered some type of carrier screening that includes, at a minimum, cystic fibrosis (CF) and spinal muscular atrophy (SMA); additional tests may also be recommended depending on the patient’s race and ethnicity. Each provider should determine an approach to screening that best fits their population: ethnicity-based, pan ethnic, or expanded carrier screening. In traditional ethnicity-based screening, the conditions included are targeted to those associated with a specific ethnic group, such as Ashkenazi Jewish disease screening or hemoglobinopathy screening for patients of African, Mediterranean, or Middle Eastern ancestry. Due to growing admixture of ethnicities, some are moving towards pan ethnic screening, in which a panel of recommended conditions is offered to all patients regardless of their ancestry. Expanded carrier screening includes additional diseases that are prevalent in other populations, such as sickle cell disease and Tay-Sachs disease. This approach allows for a more comprehensive assessment of genetic risk and reduces the potential for missed diagnoses.

**ACOG resources (many are also available in Spanish)**

<table>
<thead>
<tr>
<th>Fact sheets (FAQs) for patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal Genetic Diagnostic Tests: <a href="https://www.acog.org/-/media/For-Patients/faq164.pdf?dmc=1&amp;ts=20190105T1536373616">https://www.acog.org/-/media/For-Patients/faq164.pdf?dmc=1&amp;ts=20190105T1536373616</a></td>
</tr>
<tr>
<td>Carrier Screening: <a href="https://www.acog.org/-/media/For-Patients/faq179.pdf?dmc=1&amp;ts=20190105T153356549">https://www.acog.org/-/media/For-Patients/faq179.pdf?dmc=1&amp;ts=20190105T153356549</a></td>
</tr>
<tr>
<td>Carrier Screening for Spinal Muscular Atrophy: <a href="https://www.acog.org/-/media/For-Patients/faq197.pdf?dmc=1&amp;ts=20190105T153199405">https://www.acog.org/-/media/For-Patients/faq197.pdf?dmc=1&amp;ts=20190105T153199405</a></td>
</tr>
<tr>
<td>Cystic Fibrosis: Prenatal Screening and Diagnosis: <a href="https://www.acog.org/-/media/For-Patients/faq171.pdf?dmc=1&amp;ts=20190105T1534398157">https://www.acog.org/-/media/For-Patients/faq171.pdf?dmc=1&amp;ts=20190105T1534398157</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington State YouTube video: <a href="https://www.youtube.com/watch?v=-vJGFWJgqu">https://www.youtube.com/watch?v=-vJGFWJgqu</a></td>
</tr>
<tr>
<td>Perinatal Quality Foundation Genetic Education Modules: <a href="https://gem.perinatal-quality.org/default.aspx">https://gem.perinatal-quality.org/default.aspx</a></td>
</tr>
</tbody>
</table>

Most important is that **all women** are offered testing and that the offer of testing be consistent in the practice.
screening is the most comprehensive carrier screening option, with screening panels that can include well over 100 recessively inherited conditions.

Regardless of the approach an obstetrician chooses for his or her practice, it is critical that patients be informed of the benefits and limitations of testing, including a reminder that results cannot completely rule out carrier status, though a negative result significantly reduces the chance that an individual is a carrier. One must also bear in mind that, unlike aneuploidy screening in which only the pregnant woman needs to undergo testing, carrier screening may require testing of the reproductive partner. It is important that a woman knows before undergoing screening that if she is found to be a carrier of an autosomal-recessive condition, testing of the biological father also will be recommended. It should also be noted that the larger the screening panel, the higher the screen-positive rate (up to 60% with very large panels) and the higher the likelihood of needing to test the partner. If the biological father is unknown, not available or unwilling to be tested, that might affect a woman’s decision to pursue carrier screening. As with aneuploidy screening, a woman must also know that if carrier status is confirmed in both members of the couple, diagnostic testing of the fetus would require invasive testing (CVS or amniocentesis). Once again, decisions should take into account a woman’s values, needs and desires.

Discussion of patient’s values and preferences

Final decisions about prenatal genetic testing must consider individual patients’ values and preferences. Patients should not have blood drawn for genetic tests as part of their routine prenatal labs without a conversation and consent. For many women, initial discussions about the purpose of prenatal testing may lead to a mutual decision that the best option is to forgo genetic testing altogether. Others value the certainty and comprehensive nature of diagnostic testing, while many women want to refine their risk with screening tests as a first step.

For some women, it may be helpful to complete a decision aid, such as that available through the PQF GEM website (Tables 4 and 5). Answering questions about the relative value of the information obtained can help women better consider the best option for them.

Table 5

<table>
<thead>
<tr>
<th>Statements to guide shared decision-making with patients considering prenatal testing (from PQF GEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I would want to know if my pregnancy is affected with a genetic condition or congenital anomaly</td>
</tr>
<tr>
<td>I want the most information available about my baby and my pregnancy, even if there is a small risk associated with obtaining that information.</td>
</tr>
<tr>
<td>I would not have a test that could cause miscarriage of pregnancy, even if the chance is very small.</td>
</tr>
<tr>
<td>I would end a pregnancy if affected by a genetic condition or congenital anomaly.</td>
</tr>
<tr>
<td>I want information about my pregnancy before sharing the news with my friends or family.</td>
</tr>
<tr>
<td>I have more anxiety worrying about the possibility that my baby may have special health needs, than if I knew for sure and could prepare.</td>
</tr>
<tr>
<td>I do not want a test that would tell me if I have a genetic condition.</td>
</tr>
<tr>
<td>I would rather know before birth if the baby has a genetic condition or congenital anomaly.</td>
</tr>
<tr>
<td>I want to get as much information about my pregnancy as I can before having diagnostic testing.</td>
</tr>
<tr>
<td>I value information that is more precise for a smaller number of conditions (such as Down syndrome) rather than less precise information about more conditions.</td>
</tr>
<tr>
<td>The cost of the testing options could influence my decision.</td>
</tr>
</tbody>
</table>

Conclusion

The prenatal genetic testing landscape has expanded significantly. While that is often daunting to patients and providers, tools are available to help navigate this process. Reviewing the available tools, and deciding which are most appropriate for each practice, can be helpful in streamlining this component of prenatal care, while ensuring that all patients have access to appropriate information.

DISCLOSURES The authors report no potential conflicts of interest with regard to this article.

FOR REFERENCES VISIT contemporaryobgyn.net/GeneticTestingTools
Does being black influence hysterectomy route and outcomes?

by BEN SCHWARTZ

A minimally invasive approach to hysterectomy is known to cost less, result in fewer complications and speed recovery, but previous research suggests that there may be disparities in choice of route of hysterectomy. A recent study in *Obstetrics & Gynecology* aimed to determine whether, in women undergoing the surgery for benign indications, race has an influence on route of hysterectomy and postoperative complications.

Using ICD-9 codes, the researchers identified patients in the American College of Surgeons National Surgical Quality Improvement Program database who had undergone hysterectomy in 2015. The primary outcome of the study was route of hysterectomy, either minimally invasive or open abdominal and the key exposure was patient race – either black or white. Surgical complications during the 30-day postoperative period were the secondary outcomes.

Of the 15,316 patients included in the analysis, 11,330 were white (74.9%) and 3,806 black (25.1%). Black patients were younger, had higher body mass index, were more likely to have diabetes and hypertension, and had higher uterine weights and a higher incidence of prior abdominal surgery than the included white patients. White patients were more likely to have a diagnosis of endometriosis and a history of prior pelvic surgery.

More patients in the study underwent minimally invasive hysterectomy (n=10,634 [70.3%]) than open hysterectomy (n=4,502 [29.7%]). However, black women underwent open hysterectomy at a much higher rate (50.1%) than white women (22.0%). Even after using logistic regression to account for factors associated with selection of open hysterectomy, black women still had twice the odds of having an open procedure compared to white women. Similar results were also found when the authors limited uterine weight to less than 250 g: Black women had significantly higher odds of undergoing open hysterectomy (adjust OR 1.84, 95% CI 1.61-2.11).

In addition to having higher rates of open hysterectomy, black patients were also more likely to experience complications when undergoing the surgery. However, the proportion with complications varied by hysterectomy type. Compared to white women, black women experienced more total complications (14.1% vs 8.6%, *P* < .001); more major complications, including venous thromboembolism, myocardial infarction, stroke, and pneumonia among others, (4.1% vs 2.4%, *P* < .001); and more minor complications, including urinary tract infection, superficial...
“The patients have provided excellent feedback on the entire experience, from the convenience of providing the service in-house to the friendliness and professionalism of the mammography staff. Our patient capture rate has increased and we are now collecting the revenue that was leaving our practice daily before partnering with ONsite Mammography.

“ONsite Mammography plays a significant role in the overall package of services we provide for our patients.”

- Executive Administrator
ONsite client for 1 1/2 years

“If something sounds too good to be true, it usually is….however, this is the exception. I have become completely satisfied with the concept and the professionalism of the staff at ONsite.”

- Physician
ONsite client for 4 1/2 years

“ONsite has been performing mammograms at our office for 25+ years. Their staff, from the mammography technologists to the radiologist, are of the highest caliber, and constantly provide excellent and compassionate care to our patients. Having ONsite Mammography allows our practice to provide comprehensive and convenient women’s services to our patients.”

- Business Manager
ONsite client for 26 years

ONsite Mammography is the nationwide authority on in-office mammography services. Like those above, our client practices determined, from the outset, that they could trust us - with their patients, staff, providers, and presence in the community. Nothing is more important to us than trust because it is the foundation upon which all else is built.

If you are thinking about adding in-office mammography services to your patient offering or just wish to learn more about its potential for your practice, call ONsite Mammography (we will even arrange for you to speak with some of our client practices). We’re confident we will earn your trust and respect regardless of the outcome.
Syphilis in pregnancy on the rise

by BEN SCHWARTZ

Rates of primary and secondary syphilis in women more than doubled between 2012 and 2016 and the rate of the disease in infants increased 86.9%. A new national case analysis by researchers from the Centers for Disease Control and Prevention (CDC) sheds light on reported risk behaviors that may be contributing to these alarming trends.

The major strength of their study, the authors said, was the reliability and accuracy of the database used to acquire the included data. Identified limitations were the potential for unmeasured bias, lack of information on the exact hospital where each hysterectomy was performed, and no information on surgeon volume or years of experience.

The researchers noted that their findings are similar to results of previous studies and support the hypothesis that there may be clinical differences, particularly with uterine size, between white and black women that influence the surgeon’s decision on how to perform a hysterectomy. However, even after adjusting for these differences, black women still had higher odds of undergoing open hysterectomy. While the higher likelihood of open hysterectomy may be the primary cause for black women having higher odds of complications, the authors believe that further investigation is necessary. They suggest that patient lack of access to higher quality care may be a contributing factor as well.

SOURCE

Rates of primary and secondary syphilis in women more than doubled between 2012 and 2016 and the rate of the disease in infants increased 86.9%
NEWLY EXPANDED AGE INDICATION

GARDASIL 9 has helped protect appropriate 9- to 26-year olds from certain HPV-related cancers and diseases and can now be used in appropriate adults up to age 45.

INDICATION

- GARDASIL 9 is a vaccine indicated in females 9 through 45 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by human papillomavirus (HPV) Types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- GARDASIL 9 is indicated in males 9 through 45 years of age for the prevention of anal cancer caused by HPV Types 16, 18, 31, 33, 45, 52, and 58; precancerous or dysplastic lesions caused by HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58; and genital warts caused by HPV Types 6 and 11.
- GARDASIL 9 does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.
- Recipients of GARDASIL 9 should not discontinue anal cancer screening if it has been recommended by a health care professional.
- GARDASIL 9 has not been demonstrated to provide protection against diseases from vaccine HPV types to which a person has previously been exposed through sexual activity.
- GARDASIL 9 is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; or cervical intraepithelial neoplasia (CIN), vulvar intraepithelial neoplasia (VIN), vaginal intraepithelial neoplasia (VaIN), or anal intraepithelial neoplasia (AIN).

INDICATION (continued)

- Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL 9 protects only against those vulvar, vaginal, and anal cancers caused by HPV Types 16, 18, 31, 33, 45, 52, and 58.
- Vaccination with GARDASIL 9 may not result in protection in all vaccine recipients.

SELECT SAFETY INFORMATION

- GARDASIL 9 is contraindicated in individuals with hypersensitivity, including severe allergic reactions to yeast, or after a previous dose of GARDASIL 9 or GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant].
- Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion.
- Safety and effectiveness of GARDASIL 9 have not been established in pregnant women.
- The most common (≥10%) local and systemic adverse reactions in females were injection-site pain, swelling, erythema, and headache.
- The duration of immunity of GARDASIL 9 has not been established.

DOSAGE AND ADMINISTRATION

- GARDASIL 9 should be administered intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.
  - For individuals 9 through 14 years of age, GARDASIL 9 can be administered using a 2-dose or 3-dose schedule. For the 2-dose schedule, the second dose should be administered 6–12 months after the first dose. If the second dose is administered less than 5 months after the first dose, a third dose should be given at least 4 months after the second dose. For the 3-dose schedule, GARDASIL 9 should be administered at 0, 2 months, and 6 months.
  - For individuals 15 through 45 years of age, GARDASIL 9 is administered using a 3-dose schedule at 0, 2 months, and 6 months.

Please read the adjacent Brief Summary of the Prescribing Information.

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VACC-1265905-0000 10/18
BRIEF SUMMARY OF PRESCRIBING INFORMATION

Indications and Usage

Girls and Women

GARDASIL® is a vaccine indicated in girls and women 9 through 45 years of age for the prevention of the following diseases:

- Cervical, vulvar, vaginal, and anal cancer caused by Human Papillomavirus (HPV) types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- The following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
  - Cervical intraepithelial neoplasia (CIN) grade 2/3 and cervical adenocarcinoma in situ (AIS).
  - Cervical intraepithelial neoplasia (CIN) grade 1.
  - Vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3.
  - Vaginal intraepithelial neoplasia (VIN) grade 2 and grade 3.
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Boys and Men

GARDASIL® is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases:

- Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58.
- Genital warts (condyloma acuminata) caused by HPV types 6 and 11.
- The following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58:
  - Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.

Limitations of Use and Effectiveness

The health care provider should inform the patient, parent, or guardian that vaccination does not eliminate the necessity for women to continue to undergo recommended cervical cancer screening.

Women who receive GARDASIL® should continue to undergo cervical cancer screening per standard of care.

Recipients of GARDASIL® should not discontinue anal cancer screening if it has been recommended by a health care provider.

GARDASIL® has not been demonstrated to provide protection against disease from vaccine HPV types to which a person has previously been exposed through sexual activity.

GARDASIL® has not been demonstrated to protect against diseases due to HPV types other than 6, 11, 16, 18, 31, 33, 45, 52, and 58.

GARDASIL® is not a treatment for external genital lesions; cervical, vulvar, vaginal, and anal cancers; CIN; VIN; VaIN; or AIN.

Not all vulvar, vaginal, and anal cancers are caused by HPV, and GARDASIL® protects only against those vulvar, vaginal, and anal cancers caused by HPV 16, 18, 31, 33, 45, 52, and 58.

GARDASIL® does not protect against genital diseases not caused by HPV.

Vaccination with GARDASIL® may not result in protection in all vaccine recipients.

Dosage

Each dose of GARDASIL® is 0.5 mL. Administer GARDASIL® 9 as follows:

<table>
<thead>
<tr>
<th>Age</th>
<th>Regimen</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 through 14 years</td>
<td>2-dose</td>
<td>0, 6 to 1 months*</td>
</tr>
<tr>
<td>15 through 45 years</td>
<td>3-dose</td>
<td>0, 2, 6 months</td>
</tr>
</tbody>
</table>

*If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.

Method of Administration

For intramuscular use only:

- Shake well before use. Thorough agitation immediately before administration is necessary to maintain suspension of the vaccine. GARDASIL® should not be diluted or mixed with other vaccines. After thorough agitation, GARDASIL® is a white, cloudy liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if particulates are present or if it appears discolored.

Administer GARDASIL® intramuscularly in the deltoid region of the upper arm or in the higher anterolateral area of the thigh.

Observe patients for 15 minutes after administration.

CONTRAINDICATIONS

Hypersensitivities, including severe allergic reactions to yeast (a vaccine component), or after a previous dose of GARDASIL® 9 or GARDASIL®.

WARNINGs AND PRECAUTIONS

Syncope: Because vaccinees may develop syncope, sometimes resulting in falling with injury, observation for 15 minutes after administration is recommended. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following HPV vaccination. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.

Managing Allergic Reactions: Appropriate medical treatment and supervision must be readily available in case of anaphylactic reactions following the administration of GARDASIL®.

ADVERSE REACTIONS

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

The safety of GARDASIL® 9 was evaluated in seven clinical studies that included 15,703 individuals who received at least one dose of GARDASIL® 9 and had safety follow-up; Study 1 and Study 3 also included 7,378 individuals who received at least one dose of GARDASIL® as a control and had safety follow-up. The vaccines were administered on the day of enrollment and the subsequent doses administered approximately two and six months thereafter. Safety was evaluated using vaccination report card (VRC)-aided surveillance for 14 days after each injection of GARDASIL® 9 or GARDASIL®.

The individuals who were monitored using VRC-aided surveillance included 9,097 girls and women 16 through 26 years of age, 1,394 boys and men 16 through 26 years of age, and 5,212 girls and boys 15 through 19 years of age (4,348 girls and 1,778 boys) at enrollment who received GARDASIL® 9; and 7,078 girls and women 16 through 26 years of age and 502 girls 15 through 19 years of age at enrollment who received GARDASIL®. The race distribution of the integrated safety population for GARDASIL® 9 was similar between girls and women 16 through 26 years of age (56.8% White; 25.2% Other Races or Multiracial; 14.1% Asian; 3.9% Black, girls and boys 9 through 15 years of age (62.0% White; 19.2% Other Races or Multiracial; 13.5% Asian; 3.4% Black), and boys and men 16 through 26 years of age (82.1% White; 22.8% Other Races or Multiracial; 9.8% Asian; 3.5% Black). The safety of GARDASIL® 9 was compared directly to the safety of GARDASIL® in two studies (Study 1 and Study 3) for which the overall race distribution of the GARDASIL® cohorts (57.0% White; 26.3% Other Races or Multiracial; 13.5% Asian; 3.2% Black) was similar to that of the GARDASIL® cohorts.

Safety of GARDASIL® 9 in individuals 27 through 45 years of age is inferred from the safety data of GARDASIL® in individuals 9 through 45 years of age and GARDASIL® 9 in individuals 9 through 26 years of age.

Injection-Site and Systemic Adverse Reactions: Injection-site reactions (pain, swelling, and erythema) were solicited using VRC-aided surveillance for five days after each injection of GARDASIL® 9 during the clinical studies. The rates and severity of these solicited adverse reactions occurred within five days following each dose of GARDASIL® 9 compared with GARDASIL® in Study 1 (girls and women 16 through 26 years of age) and Study 3 (girls 9 through 15 years of age) are presented in Table 1. Among subjects who received GARDASIL® 9, the rates of injection-site pain were approximately equal across the three reporting time periods. Rates of injection-site swelling and injection-site erythema increased following each successive dose of GARDASIL® 9. Recipients of GARDASIL® 9 had numerically higher rates of injection-site reactions compared with recipients of GARDASIL®.

Table 1: Rates (%) and Severity of Solicited Injection-Site and Systemic Adverse Reactions Occurring within Five Days of Each Vaccination with GARDASIL® 9 Compared with GARDASIL® (Studies 1 and 3)

| Injection-Site Adverse Reactions | GARDASIL® | GARDASIL® 9 | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any dose | Post any do...
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Systemic Adverse Reactions</th>
<th>No.</th>
<th>N=300</th>
<th>N=299</th>
<th>N=299</th>
<th>N=299</th>
<th>N=300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ≥100°F</td>
<td>2.3</td>
<td>1.7</td>
<td>3.0</td>
<td>6.7</td>
<td>1.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Temperature ≥102°F</td>
<td>0</td>
<td>0.3</td>
<td>0.1</td>
<td>1.2</td>
<td>0.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

The data for women and girls 18 through 26 years of age are from Study 1 (NCT010543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498). N=number of subjects vaccinated with safety follow-up; n=number of subjects with temperature data.

Pain, Any-mild, moderate, severe or unknown intensity.

Swelling, Any-any size or size unknown.

Swelling, Severe-maximum size greater than 2 inches.

Erythema, Any-any size or size unknown.

Erythema, Severe-maximum size greater than 2 inches.

Unsolicited injection-site and systemic adverse reactions (assessed as vaccine-related by the investigator) observed among recipients of either GARDASIL 9 or GARDASIL 3 in Studies 1 and 3 at a frequency of at least 1% are shown in Table 2. Few individuals discontinued study participation due to adverse experiences after receiving either vaccine (GARDASIL 9, 0.1%; GARDASIL 3, 0.1%).

### Table 2: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions Occurring among ≥1.0% of Individuals after Any Vaccination with GARDASIL 9 Compared with GARDASIL (Studies 1 and 3)

<table>
<thead>
<tr>
<th>Injection-Site Adverse Reactions (1 to 5 Days Post-Vaccination, Any Dose)</th>
<th>Girls and Women 16 through 26 Years of Age</th>
<th>GARDASIL 9 N=7071</th>
<th>GARDASIL N=7078</th>
<th>GARDASIL 9 N=299</th>
<th>GARDASIL N=300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>5.5</td>
<td>6.0</td>
<td>4.0</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Bruising</td>
<td>1.9</td>
<td>1.3</td>
<td>0.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Mass</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Induration</td>
<td>0.1</td>
<td>0.0</td>
<td>0.7</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Acute rash or urticaria</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

The data for girls and women 16 through 26 years of age are from Study 1 (NCT010543543), and the data for girls 9 through 15 years of age are from Study 3 (NCT01304498). N=number of subjects vaccinated with safety follow-up.

In an uncontrolled clinical trial with 639 boys and 1,878 girls 9 through 15 years of age (Study 2), the rates and severity of solicited adverse reactions following each dose of GARDASIL 9 were similar between boys and girls. Rates of solicited and unsolicited injection-site and systemic adverse reactions in boys 9 through 15 years of age were similar to those among girls 9 through 15 years of age. Solicited and unsolicited adverse reactions reported by boys in this study are shown in Table 3.

In another uncontrolled clinical trial with 1,295 boys and men and 1,075 girls and women 16 through 26 years of age (Study 2), the rates of solicited and unsolicited adverse reactions following each dose of GARDASIL 9 among girls and women 16 through 26 years of age were similar to those reported in Study 1. Rates of solicited and unsolicited adverse reactions reported by boys and men through 26 years of age in this study are shown in Table 3.

<table>
<thead>
<tr>
<th>Systemic Adverse Reactions</th>
<th>No.</th>
<th>N=299</th>
<th>N=300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature ≥100°F</td>
<td>2.3</td>
<td>1.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Temperature ≥102°F</td>
<td>0</td>
<td>0.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Table 3: Rates (%) of Unsolicited Injection-Site and Systemic Adverse Reactions among Boys 9 through 15 Years of Age and among Boys and Men 16 through 26 Years of Age Who Received GARDASIL 9 (Studies 2 and 3)

<table>
<thead>
<tr>
<th>Boys and Men 16 through 26 Years of Age</th>
<th>N=1394</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</td>
<td></td>
</tr>
<tr>
<td>Injection-Site Pain, Any</td>
<td>63.4</td>
</tr>
<tr>
<td>Injection-Site Pain, Severe</td>
<td>0.6</td>
</tr>
<tr>
<td>Injection-Site Erythema, Any</td>
<td>20.7</td>
</tr>
<tr>
<td>Injection-Site Erythema, Severe</td>
<td>0.4</td>
</tr>
<tr>
<td>Injection-Site Swelling, Any</td>
<td>20.2</td>
</tr>
<tr>
<td>Injection-Site Swelling, Severe</td>
<td>1.1</td>
</tr>
<tr>
<td>Oral Temperature ≥100.0°F</td>
<td>4.4</td>
</tr>
<tr>
<td>Oral Temperature ≥102°F</td>
<td>0.6</td>
</tr>
</tbody>
</table>

The data for GARDASIL 9 boys 9 through 15 years of age are from Study 2 (NCT010543522). The data for boys and men through 26 years of age for GARDASIL 9 are from Study 3 (NCT01304498).

*Unsolicited adverse reactions reported by ≥1.0% of individuals

N=number of subjects vaccinated with safety follow-up.

For oral temperature: number of subjects with temperature data for boys 9 through 15 years of age N=631, for boys and men 16 through 26 years of age N=9,386

Pain, Any-mild, moderate, severe or unknown intensity.

Swelling, Any-any size or size unknown.

Swelling, Severe-maximum size greater than 2 inches.

Erythema, Any-any size or size unknown.

Erythema, Severe-maximum size greater than 2 inches.

Serious Adverse Events in Clinical Studies: Serious adverse events were collected throughout the entire study period (range one month to 48 months post-dose) for the seven clinical studies for GARDASIL 9. Out of the 15,705 individuals who were administered GARDASIL 9 and had safety follow-up, 356 reported a serious adverse event, representing 2.3% of the population. As a comparison, of the 7,337 individuals who were administered GARDASIL 3 and had safety follow-up, 156 reported a serious adverse event, representing 2.1% of the population. For GARDASIL 3, the rate of serious adverse events for each of the reported adverse events was determined to be vaccine-related. The vaccine-related serious adverse reactions were pyrexia, allergic reaction, chest pain, and anaphylaxis.

Deaths in the Entire Study Population: Across the clinical studies, ten deaths occurred (five each in the GARDASIL 9 and GARDASIL 3 groups); none were assessed as vaccine-related. Causes of death in the GARDASIL 9 group included one automobile accident, one suicide, one case of acute lymphocytic leukemia, one case of hypoxic, one case of sudden death, and one case of anaphylaxis.

Systemic Autoimmune Disorders: In all of the clinical trials with GARDASIL 9 subjects were evaluated for new medical conditions potentially indicative of a systemic autoimmune disorder. In total, 2.2% (351/15,703) of GARDASIL 9 recipients and 3.3% (240/7,378) of GARDASIL 3 recipients reported new medical conditions potentially indicative of systemic autoimmune disorders, which were similar to rates reported following GARDASIL 3. Additional control, or saline placebo in historical clinical trials, and Clinical Trials Experience for GARDASIL 9 in individuals who have been previously vaccinated with GARDASIL 3. A clinical study (Study 4) evaluated the safety of GARDASIL 9 in 12- through 26-year-old girls and women who had previously been vaccinated with three doses of GARDASIL 3. The first injection of GARDASIL 3 ranged from approximately 12 to 36 months. Individuals were administered GARDASIL 9 or saline placebo and safety was evaluated using VRC-assisted surveillance for 14 days after each injection of GARDASIL 9 or saline placebo in these individuals. The individuals who were monitored included 608 individuals who received GARDASIL 9 and 350 individuals who received saline placebo. Few (0.5%) individuals who received GARDASIL 9 discontinued due to adverse reactions. The vaccine-related adverse experiences that were observed among recipients of GARDASIL 9 at a frequency of at least 1.0% that occurred at a greater frequency than that observed among saline placebo recipients are shown in Table 4. Overall, the safety profile was similar between individuals vaccinated with GARDASIL 3 and those vaccinated with GARDASIL 9.

AAHS=Amorphous Aluminum Hydroxypatite Sulfate.
with GARDASIL® 9 who were previously vaccinated with GARDASIL® and those who were naïve to any vaccine vaccination with the exception of numerically higher rates of injection-site swelling and erythema among individuals who were previously vaccinated with GARDASIL® (Tables 1 and 4).

### Table 4: Rates (%) of Solicited and Unsolicited Injection- Site and Systemic Adverse Reactions among Individuals Previously Vaccinated with GARDASIL® 9 or Saline Placebo (Girls and Women 12 through 26 Years of Age) (Study 6)

<table>
<thead>
<tr>
<th>Solicited Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</th>
<th>GARDASIL® 9 N=608</th>
<th>Saline Placebo N=305</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Pain</td>
<td>50.3 (38.0)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Lymphadenitis</td>
<td>42.3 (8.5)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Swelling</td>
<td>49.0 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Oral Temperature ≥38°C</td>
<td>6.5 (3.0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unsolicited Injection Site Adverse Reactions (1-5 Days Post-Vaccination, Any Dose)</th>
<th>GARDASIL® 9 N=608</th>
<th>Saline Placebo N=305</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection Site Pruritus</td>
<td>7.7 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Hematoma</td>
<td>4.8 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>1.2 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Mass</td>
<td>1.2 (0.7)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Unsolicited Systemic Adverse Reactions (1-30 Days Post-Vaccination, Any Dose)</th>
<th>GARDASIL® 9 N=608</th>
<th>Saline Placebo N=305</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>19.6 (8.0)</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5.1 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3.9 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain, upper</td>
<td>3.0 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>1.2 (1.0)</td>
<td></td>
</tr>
</tbody>
</table>

For more detailed information, please read the Prescribing Information.

For more detailed information, please read the Prescribing Information.

**Data**

### Human Data

In pre-licensure clinical studies of GARDASIL® 9, women underwent pregnancy testing immediately prior to administration of each dose of GARDASIL® 9 or control vaccine (GARDASIL®). [Data from GARDASIL® are relevant to GARDASIL® 9 because both vaccines are manufactured using the same process and have overlapping compositions.1 Subjects who were determined to be pregnant were instructed to defer vaccination until the end of their pregnancy. Despite this pregnancy screening regimen, some subjects were vaccinated very early in pregnancy because human chorionic gonadotropin (HCG) was detectable. An analysis was conducted to evaluate pregnancy outcomes for women who were enrolled within 29 days before or after vaccination with GARDASIL® 9 or GARDASIL®. Among those pregnancies, there were 62 and 55 with known outcomes (excluding ectopic pregnancies and elective terminations) for GARDASIL® 9 and GARDASIL® respectively, including 44 and 48 live births, respectively. The rates of pregnancies that resulted in a miscarriage were 27.4% (17/62) and 12.7% (7/55) in subjects who received GARDASIL® 9 or GARDASIL® respectively. The rates of live births with major birth defects were 0% (0/44) and 2.1% (1/48) in subjects who received GARDASIL® 9 or GARDASIL® respectively.

A five-year pregnancy registry enrolled 2,942 women who were inadvertently exposed to GARDASIL® within one month prior to the last menstrual period (LMP) or at any time during pregnancy, 2,586 of whom were prospectively followed. After excluding elective terminations (n=107), ectopic pregnancies (n=8) and those lost to follow-up (n=814), there were 1,640 pregnancies with known outcomes. Rates of miscarriage and major birth defects were 6.8% of pregnancies (111/1,640) and 2.4% of live born infants (37/1,527), respectively. These rates of assessed outcomes in the prospective population were consistent with estimated background rates.

In two post-marketing studies of GARDASIL® (one conducted in the U.S. and the other in Nordic countries), pregnancy outcomes among subjects who received GARDASIL® during pregnancy were evaluated retrospectively. Among the 1,740 pregnancies included in the U.S. study database, outcomes were available to assess the rates of major birth defects and miscarriage. Among the 498 pregnancies included in the Nordic study database, outcomes were available to assess the rates of major birth defects. In both studies, rates of assessed outcomes did not suggest an increased risk with the administration of GARDASIL® during pregnancy.

**Animal Data**

Developmental toxicity studies were conducted in female rats. In one study, animals were administered 0.5 mL of a vaccine formulation containing between 1 and 1.5-fold of each of the 9 HPV antigen types and 2 weeks prior to mating, and on gestation day 6. In a second study, animals were administered a single human dose (0.5 mL of GARDASIL® 9) 5 and 2 weeks prior to mating, on gestation day 6, and on lactation day 7. No adverse effects on pre- and post-weaning development were observed. There were no vaccine-related fetal malformations or variations.

**Lactation**

**Risk Summary:** Available data are not sufficient to assess the effects of GARDASIL® 9 on the breastfed infant or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for GARDASIL® 9 and any potential adverse effects on the breastfed child from GARDASIL® 9 or from the underlying maternal condition. For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

**Pediatric Use:** Safety and effectiveness have not been established in pediatric patients below 9 years of age.

**Geriatric Use:** The safety and effectiveness of GARDASIL® 9 have not been evaluated in a geriatric population, defined as individuals aged 65 years and over.

**Immunocompromised Individuals:** The immunologic response to GARDASIL® 9 may be diminished in immunocompromised individuals.
Syphilis in pregnancy
CONTINUED FROM PAGE 26

age group, race and ethnicity group and in every geographical region. The greatest increases were seen in women aged 30 to 34 years (90%) and in Native Americans (420%). The West was the geographic region with the greatest increase.

Looking at prevalence of risk factors, 51% (4,997/9,883) of women with syphilis reported any risk factor. The most commonly reported risk behaviors among pregnant women with syphilis were prior STD (43%) and more than one sex partner in the past 12 months (30%). Methamphetamine was the drug most commonly mentioned, used by 4.5% of pregnant women with syphilis overall and 6.3% of pregnant women with early disease.

A few limitations to the study were identified. Among these were a lack of current data on the number of pregnancies in the United States, which prevented the authors from calculating syphilis rates per 100,000 pregnant women. Data on reported behavioral risk were also limited since they were collected via interviews and reliant on participants reporting sensitive information about which they may have feared legal repercussions. Lack of information about pregnancy outcomes precluded the authors from linking prenatal syphilis cases to reported congenital syphilis cases.

The authors said their findings show that syphilis among pregnant women increased from 2012 to 2016. Given the trend, ob/gyns need to increase their awareness of recommendations from the CDC and the American College of Obstetricians and Gynecologists, which include screening all pregnant women for syphilis at the first prenatal visit and screening women at high risk for contracting the disease on an ongoing basis.

SOURCE

Uterine transplantation from deceased donor results in live birth
by BEN SCHWARTZ

In September 2013 in Sweden, the first birth following uterine transplantation from a living donor was recorded. A new report in The Lancet has documented another milestone in treatment for uterine infertility: the first successful live birth after uterine transplantation from a deceased donor.

The patient, a 32-year-old woman with congenital uterine absence, underwent the transplantation in Hospital das Clínicas, University of São Paulo, Brazil. She had been diagnosed with congenital uterine absence in 2012 and was placed on the uterine transplantation waiting list.

In April 2017, the patient received the uterine transplant from a deceased donor at the University of São Paulo Medical School. She underwent a cesarean section in April 2018 and gave birth to a healthy baby girl.

The authors noted that this procedure is a significant advancement in the field of obstetrics and gynecology, as it offers hope for women who are unable to conceive due to congenital uterine absence. The success of this procedure highlights the potential of uterine transplantation as a viable treatment option for women with this condition.

SOURCE
with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome and presented with uterine agenesis, but no cardiac, renal, or bone structure dysfunctions.

The donor was a 45-year-old woman who had three vaginal deliveries and no signs of sexual disease. Her cause of death was Fischer 4 subarachnoid hemorrhage.

Surgical time from iliac and pelvic vessel preparation to uterus implantation was 2 hours. Immunosuppression followed the Swedish protocol including 1 intraoperative methylprednisolone and 1.5 mg/kg of thymoglobulin as induction therapy. It was continued via tacrolimus and mycophenolate mofetil (MMF) until 5 months post-transplantation, when MMF was replaced by azathioprine. Menstruation first occurred at 37 days post-transplantation and was regular thereafter.

Menstruation first occurred at 37 days post-transplantation and was regular thereafter.

Prior to transplantation, the patient underwent in vitro fertilization, which yielded 16 eggs obtained from a single cycle that produced eight good-quality blastocysts for cryopreservation. At that time, Doppler ultrasound, regular menses and no signs of rejection indicated to the authors of the report that the organ remained in good condition.

The woman’s pregnancy proceeded normally until Week 32, when she presented with signs of pyelonephritis and was treated with ceftriaxone as an inpatient for 10 days. At 35 weeks and 3 days, the patient underwent cesarean delivery, which was in line with the protocol used by the Swedish transplant team. During delivery, the transplanted uterus was removed and the patient’s vaginal orifice was closed.

The newborn weighed 2550 g and measured 45 cm in length. Her Apgar scores were 9 at 1 minute, 10 at 5 minutes and 10 at 10 minutes. At 7 months and 20 days, when the authors wrote the article, the baby continued to breastfeed and had normal growth parameters.

The authors believe that the success of this transplant from a deceased donor and the ensuing live birth expands the options for childbirth among women with infertility attributable to uterine factors. While the Swedish study demonstrated success with assisted reproduction and uterine transplantation, the requirement for a live donor is a major limitation and, as such, donors are in short supply.

Uterine transplantation is still considered experimental by many countries, but the authors believe that this recent success shows that the procedure is promising. Future studies, they said, should continue to expand upon the existing research to improve and refine the technique so that women with uterine factor infertility can have the option of a healthy pregnancy.

Ben Schwartz is the associate editor of Contemporary OB/GYN.

SOURCE

STUDY
1 in 7 antibiotic scripts may be unnecessary
by Judith M. Orvos, ELS

Antibiotic resistance associated with overprescribing of the drugs is a known threat to public health and has been the subject of educational campaigns throughout the world. However, an analysis of recent US insurance claims data, using a novel classification scheme, calls into question how well those messages are translating into clinical practice.

Published in BMJ, the findings show that in 2016, 1 in 7 enrollees in employer-provided insurance plans filled at least one prescription for an antibiotic on an outpatient basis that was inappropriate. The data reflect claims experience for more than 19 million individuals, including adults aged 18 to 64 and children aged 0 to 17 years.

For the study, the authors developed a classification scheme to determine whether each of 91,738 ICD-10-CM diagnosis codes “always,” “sometimes,” or “never” justified antibiotics. For each antibiotic prescription filled in 2016, the scheme was used to classify all diagnosis codes in claims during a look-back...
Focus on fracture
Gateway to evaluating osteoporosis

As an aging population turns to ob/gyns for wellness exams, more questions are being asked about bone health.

by KRISTI TOUGH DESAPRI, MD, NCMP, CCD

With an aging population women are now spending more than 1/3 of their lives in postmenopausal years. Aging skeletons and maintenance of bone health are important midlife issues. Many women see ob/gyns for their annual comprehensive exams and have questions about their bones. In addition, women present with various risk factors for fracture (i.e. being underweight, having early menopause (age < 45 years), use of certain medications such as glucocorticoids or aromatase inhibitors), or have sustained a prior fracture. Often, ob/gyns treat various medical and gynecologic conditions that affect bone health, and they may discover untreated fractures.

It is crucial that ob/gyns are aware of screening guidelines for osteoporosis and how to evaluate women at high risk for fracture and provide appropriate treatment, when necessary.

In the United States, 2 million osteoporotic fractures occur every year, yet the number of patients being treated for serious fractures, such as hip fractures, is decreasing.1-3 Adding to the complexity, there is increasing diversity in the types of specialists who diagnose and treat osteoporosis. Ob/gyns are the gatekeepers of health care for many postmenopausal women and in some cases, their only contact with the health care system. The following cases will focus on identifying and treating women at high risk of first or recurrent fractures.

CASE 1 Secondary fracture prevention

Jane, a 70-year-old with a prior wrist fracture, presents for her annual gynecologic exam. Last year, her T score was -2.7 and you started her on weekly alendronate, which she reports taking consistently. The patient also tells you she has new back pain and she has lost 1 inch of height since her last exam. Dual energy X-ray absorptiometry (DXA) with vertebral fracture assessment (VFA) reveals two new vertebral fractures at T12 and L1. How do you counsel and manage this patient?

DR. DESAPRI is clinical assistant professor of ob/gyn, University of Chicago Women’s Care, Chicago, Il.
Jane has sustained multiple osteoporotic and fragility fractures. Her diagnosis is now severe osteoporosis. Independent of bone mineral density (BMD), a prior fracture increases risk of subsequent fracture by 85%. About two-thirds of vertebral fractures go clinically undiagnosed, leading to additional fractures, chronic pain, deformity, and height loss. Therefore, it is important to recognize and intervene on these "silent" fractures to prevent future fractures at all skeletal sites. In a recent large, population-based cohort study, risk of a second major osteoporotic fracture after a first fracture was greatest 1 to 5 years following the initial event. In individuals who were examined over a 10-year period, 20% of 1311 had re-fractures within 1 year and 34% within 2 years. In addition, risk of having a second fracture was 41% higher in women than in men and risk of second fracture increased with advancing age, especially in those > 70 years.

Not only is timely diagnosis important, but prompt treatment of osteoporotic fractures matters. Fracture liaison services (FLS), often housed in orthopedic departments, can help treat patients more urgently. A meta-analysis showed that perceived physician knowledge about osteoporosis (and its clinical consequences) contributes to patients feeling their educational needs are met. Understandable written literature on osteoporosis and medication are common demands from patients.

Before you choose the next best therapy for Jane, she should undergo a secondary bone loss evaluation (if she did not have one previously). This includes a complete blood count (CBC), comprehensive metabolic panel (CMP, including serum calcium and phosphorus), testing for thyroid-stimulating hormone (TSH), 25 hydroxy-vitamin D level, serum protein electrophoresis (SPEP), parathyroid hormone (PTH), celiac disease (with tissue transglutaminase and IgA), and a 24-hour urine calcium and creatinine collection. If these tests were previously collected and normal, additional tests could include a 24-hour urine cortisol and single urine NTX (N-telopeptide) to determine resorption status. Conservative treatment is appropriate for acute management of Jane’s back pain, with oral analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and/or transdermal lidocaine. Opioids and possible referral to orthopedic surgery may be necessary if acute and chronic pain cannot be well managed with a conservative approach.

In patients whose pain fails to respond to oral, intravenous (IV) or subcutaneous antiresorptive therapies (i.e. BMD decreases or they fracture while on medications), anabolic agents can be effective for reducing vertebral and nonvertebral fracture. However, these drugs should not simply be reserved for rescuing patients who have failed prior treatments. Osteoporosis specialists are starting to recommend sequential therapy in high-risk patients (i.e. those with prior fracture or multiple risk factors for fracture, such as advancing age or low BMD), starting with anabolic therapy for up to 2 cumulative years, followed by antiresorptive therapy. Treatment with anabolic therapy such as teriparatide and abaloparatide are recommended to build bone mass and lay down new bone via the bone modeling cycle.

Both teriparatide and abaloparatide are self-administered daily with small 31-gauge needles and carry a black-box warning that restricts use to 2 years due to the potential for osteosarcoma detected in rodents. However, in more than 16,000 patients who received teriparatide in controlled clinical trials and observational studies over a span of 15 years, there have been no human reports to date of osteosarcoma linked to teriparatide or abaloparatide.

Teriparatide is a recombinant PTH, requires refrigeration, and has been approved by the US Food and Drug Administration since 2002. Generic options are available in Europe and will come to US markets soon. Abaloparatide is a synthetic analog of PTH-related protein (PThRP). It preferentially binds the RG conformational state of the PTH1R on osteoblasts, to stimulate more bone modeling (formation) than resorption. It does not require refrigeration. ACTIVE (Abaloparatide Comparator Trial In VerTebral Endpoints) was a phase 3, double-blind, randomized controlled trial to evaluate fracture reduction in 2,463 osteoporotic postmenopausal women with three treatment arms: placebo, abaloparatide, and teriparatide (open label). Although not powered...
to show differences in fracture efficacy between the two active therapies, there was a longer time to first major osteoporotic fracture for abaloparatide versus teriparatide (\(P < 0.03\)) and greater increases in BMD for abaloparatide versus teriparatide at femoral neck, hip, and spine sites at 6 and 12 months.\(^{11}\)

In the ACTIVExtend trial, 18 months of abaloparatide followed by 2 years of weekly alendronate (total 43 months of treatment) showed significant vertebral 84% relative risk reduction (RRR) for vertebral fractures (\(P < 0.001\); 39% RRR for non-vertebral fractures (\(P < 0.038\)) and 50% RRR for major osteoporotic fractures (clinical spine, humerus, shoulder and hip) (\(P < 0.01\)).\(^{12}\)

As described above, sequential therapy yields the largest BMD gain when an anabolic agent is followed by an antiresorptive. By contrast, when an antiresorptive such as alendronate is followed by teriparatide, hip BMD is slower to increase and BMD drops to below baseline for 12 months. When a more potent antiresorptive such as denusomab is used, there is a more attenuated rise in hip BMD while BMD drops below baseline for 24 months. Spine BMD seems to be minimally affected by the sequence. Histomorphometric and bone turnover studies have pointed to a transient increase in cortical porosity and increases in bone remodeling to explain this effect.\(^{13}\) As background, cortical bone comprises 80% of our skeletal mass, found in the long bones and vertebra.

Other ongoing trials have explored combination therapy with teriparatide and denusomab. To date, combination treatment is reserved for the highest-risk patients failing multiple single therapies and under the care of osteoporosis experts.\(^{14}\) In summary, the paradigm for evaluating and treating osteoporosis and its fractures is undergoing a shift. As effective therapies are being developed, more is understood about sequencing and duration of therapy.

**CASE 2 Use of FRAX to stratify fracture risk**

Mary is a 60-year-old postmenopausal woman with baseline T score -2.2 at the femoral neck. Her femoral neck BMD is 0.590 g/cm\(^2\) on DXA. Mary reports a final menstrual period at age 51 and eats two calcium-rich foods/day, exercises 3 days per week, and has no personal or family history of fall/fracture. She weighs 140 lb and is 5 feet 2 inches tall. How do you interpret and share the DXA results with this patient?

Mary has low bone mass (formerly called osteopenia) on her DXA. Women with low bone mass represent the largest cohort of women who fracture.\(^{15}\) Therefore, it is important not to solely rely upon a T score > -2.5 as a reassurance that patients are not risk for fracture. Discussing how low BMD may contribute to fracture, in addition to advancing age, female sex, and prior fracture is more appropriate management. Annual measurement on a wall-mounted stadiometer is important. Capturing height loss > 1.5 inch since adult peak height or > 0.8 inch since last height measured may detect clinically silent vertebral fractures.

Women with low bone mass may also need a laboratory evaluation for bone loss, and certainly counseling on lifestyle factors (smoking, exercise) and appropriate calcium and vitamin D intake.

In addition, the FRAX tool (https://www.sheffield.ac.uk/FRAX/) is a free, online resource that helps risk-stratify patients and calculates their 10-year risk of hip and major osteoporotic fracture (defined as hip, forearm, spine, humerus.) Thresholds for treatment recommendations are a 10-year risk of hip fracture > 3% and of major osteoporotic fracture > 20%.\(^{16}\) Mary has a calculated 10-year risk of hip fracture of 1.6% and of major osteoporotic fracture of 10%. Although she does not meet criteria for treatment based on this statistical model, there are certain variables not captured in FRAX, such as falls and low spine BMD. Another risk calculator called the Garvan model (https://www.garvan.org.au/bone-fracture-risk) does capture T scores at any skeletal sites and history of falls.\(^{17}\)

Current recommendations by most professional organizations (National Osteoporosis Foundation, International Society of Clinical Densitome-
try, American College of Obstetricians and Gynecologists, and United States Preventive Services Taskforce (USPSTF) suggest beginning DXA at age 65 or earlier in women who have risk factors for bone loss. Specifically, in its June 2018 update, the USPSTF recommended BMD testing for women aged 50 to 64 whose 10-year predicted risk of major osteoporotic fracture (calculated using the FRAX model without BMD) is ≥ 9.3 % (equivalent to that of a 65-year-old white woman with no other FRAX clinical risk factors). The goal of this calculation is to identify who may benefit from screening and possibly treatment to prevent a first fracture.

A recent study addressed an alternate treatment regimen with IV zoledronate for older postmenopausal women, which may apply to the patient in this case. In the trial, 2000 older postmenopausal women (average age 71) with low bone mass (average T-score spine -1.2, femoral neck -1.6) were treated with IV zoledronate every 18 months for 6 years (4 injections). Compared to placebo, there were significant reductions in fragility fractures (composite of nonvertebral fractures and radiologically detected vertebral fractures (HR 0.63 [95% CI, 0.50-0.79; P < .001] and nonvertebral fractures (HR 0.66 95% CI, 0.51-0.85; P < .01). Evidence validates treatment of low bone mass for the appropriate patient. Although treatment for every woman with low bone mass is not routinely recommended, those who meet FRAX thresholds or who lose BMD dramatically require evaluation and possible treatment.

**CASE 3 Individualized therapy**

Martha is a 55-year-old postmenopausal woman who was treated with hormone therapy (HT) for 3 years (age 50-53) for bothersome vasomotor symptoms (VMS). When she chose to transition off HT at age 53 her baseline spine T score was -2.3. Martha’s current spine T score is -2.7. She has never sustained a fracture, has maintained height, and takes supplemental calcium, vitamin D, and escitalopram for anxiety. Given Martha’s T score, you start her on denosumab, a subcutaneous antiresorptive that is given every 6 months. She would like to know how long she will remain on this medication. What do you tell this patient?

For many postmenopausal women with symptoms of menopause, HT will alleviate symptoms and reduce risk of osteoporotic fracture. In the Women’s Health Initiative, HT reduced observed clinical vertebral fractures (relative risk [RR], 0.65; 95% CI, 0.46-0.92) and hip fractures (RR, 0.67; 95% CI, 0.47-0.96) compared with placebo. There does not appear to be a rebound increase in fractures after stopping HT. In fact, in the estrogen-alone arm, prior estrogen users (31.1 per 1000 person-years) had fewer fractures than placebo users (36.9 per 1000 person-years, HR, 0.85; 95% CI 0.73-0.98; P = 0.03).

After a patient loses BMD, treatment with denusomab, a human monoclonal antibody to a receptor activator of nuclear factor kappa-B ligand (RANKL), is acceptable. The mechanisms of action and potency of bisphosphonates and denusomab differ. For that reason, drug holidays are recommended for bisphosphonates but not for denusomab. With 10 years of safety and efficacy use of denusomab, studies have shown BMD of hip and spine continue to increase without plateau and new nonvertebral and vertebral fracture rates remain low in those on treatment. In the pivotal trial, 3 years of denusomab showed reductions in vertebral (RRR 68%), non-vertebral (RRR 20%), and hip fractures (RRR 40%). In addition, denusomab is now approved for glucocorticoid-induced osteoporosis.

There are reports and concerns over multiple vertebral fractures following discontinuation of denusomab. In patients receiving more than two doses of the drug, the fractures have been reported as early as 7 months following the last dose (average 19 months after last dose). Patients at highest risk are those with prior vertebral fracture as the rapid bone turnover rates following discontinuation may target trabecular...
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TREATING OSTEOPOROSIS

bone in the spine. If denusomab therapy is halted or delayed for any reason, the patient should be transitioned to another therapy. BMD returns to baseline following 12 months off denusomab.

A newer paradigm, “treat to target,” recommends treating patients to a specific goal. The goal could be T score (usually > -2.5) and/or to an acceptable low fracture risk (i.e. 5 years from last fracture) to ensure they are out of critical fracture window. Patients who continue to need treatment may continue or be transitioned to another therapy, and those who have met target may discontinue therapy with follow-up DXA and periodic bone health evaluation. To answer Martha’s question about duration of denusomab therapy, thus far, 10 years of continuous use of denusomab has been studied and prescribed. In the case of denusomab and the “treat to target” paradigm, if a patient’s goal BMD is met, transition to another antiresorptive for 1 to 2 years is recommended. Patients on bisphosphonates who have met target can stop treatment and continue DXA surveillance.

In summary, the goal of any osteoporosis intervention should be to reduce fracture with informed osteoporosis education and shared decision-making to select appropriate therapy.

Conclusion

Therapies for osteoporosis and for patients at high risk for fracture have expanded. New treatment paradigms about which ob/gyns should be aware include the following:

1. Recommending anabolic therapy first: This applies, in particular, to patients who are at highest risk for fracture, such as those who have recently fractured or who have very low T scores.

2. Screening based on USPSTF guidelines: DXA screening is recommended for all women > age 65. For women aged 50 to 64 who have risk factors for fracture, BMD evaluation with DXA is warranted if FRAX calculation (without BMD) is ≥ 9.3% (equivalent to that of a 65-year-old white woman with no other FRAX clinical risk factors). However, clinical tools should not replace clinical judgment for patients who may be at high risk for fracture and may need earlier screening and/or benefit from treatment.

3. Implementing goal-directed treatment or “treat to target”: The idea is to individualize osteoporosis treatment so that patients continue medication until goal BMD is met (i.e. T score > -2.5) and they are below acceptable fracture thresholds. For certain medications, such as denusomab, drug holidays are not recommended.

Ob/gyns are often the gatekeepers of health care for postmenopausal women. Thus, it is essential that we play integral roles in diagnosing, evaluating, and initiating treatment for women with osteoporosis and those at high risk for fracture.

DISCLOSURE The author reports no potential conflicts of interest with regard to this article.

FOR REFERENCES VISIT contemporaryobgyn.net/osteoporosis

Hyperglycemia in GDM CONTINUED FROM PAGE 14

Whether these results are generalizable to pregnancies in patients with GDM rather than PCOS is not known.

While metformin has also been recommended for treatment throughout the first trimester in patients with PCOS based on retrospective non-randomized reports of lower miscarriage rates, the largest RCT found no improvement. Neither does metformin prevent GDM in women with PCOS.

Conclusion

There are major advantages to oral rather than injected antihyperglycemic medications, particularly relating to simplicity and greater patient satisfaction. However, the yet-to-be-determined long-term effects of these medications, both of which cross the placenta, compel caution in their use during pregnancy. They are not contraindicated but should be considered second-line options when insulin is declined or unavailable. Documentation of thorough patient counseling as to what is known and what is unknown about their fetal effects, as well as the likelihood of needing supplemental insulin, is appropriate.

DISCLOSURE The author reports no potential conflicts of interest with regard to this article.

FOR REFERENCES VISIT contemporaryobgyn.net/hyperglycemia
Can grit prevent burnout \textit{continued from page 9}

\textbf{Take-home message}

We live in an era of accelerating change, and of astonishingly rapid expansion of medical knowledge. To keep pace we must all be lifelong learners. But while this relentless pace of change is generating extraordinary advances in health care it also breeds burnout. Fortunately, all of us have the impetus for lifelong learning and the antidote to burnout hardwired into our personalities: grit. Without grit we would never have gotten into medical school, never matched into a residency program and never mastered the many skills required to be great ob/gyns. But to continue to thrive, we need to stay gritty by maintaining a keen interest in our field, and constantly strive to be better clinicians through deliberate practice (i.e., lifelong learning). This may involve reading \textit{Contemporary OB/GYN} and other journals, participating in the American Board of Obstetrics and Gynecology’s Maintenance of Certification program, perfecting surgical and sonographic skills and engaging in continuous quality improvement in our practices. Finally, we need to always keep in mind our higher purpose: caring for the gynecological and obstetrical health of women in a safe, efficient and effective manner.

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\textbf{WE WANT TO HEAR FROM YOU}

tell Dr Lockwood what you thought of this editorial on grit and burnout.

\hspace{1cm}

\textbf{FOR REFERENCES VISIT}

\textit{contemporaryobgyn.net/BurnoutAndGrit}

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\textbf{GEM} is an interactive site including videos, narratives, and tools designed to educate your patients and staff about genetic testing options. The goals of GEM are to reduce clinic time spent on routine education, to educate office staff to answer basic questions, and to provide useful tools to describe risk, and compare and contrast testing options.

\textbf{After reviewing the Genetic Education Modules …}

1. Providers will be able to answer patient questions and provide non-directive information about prenatal testing options.
2. Providers will be able to use the time available for patient counseling more efficiently.
3. Patients will appreciate their personal responsibility in making decisions about prenatal testing.

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\textbf{Perinatal Quality Foundation} | \textbf{www.perinatalquality.org}
Counseling on complex contraceptive dilemmas

This first in our new series discusses how to effectively balance contraception needs and seizure control in patients with epilepsy.

by CHARISSE LODER, MD, MSC

As ob/gyns, we find ourselves taking care of women with complex medical conditions that impact their reproductive health decision-making. Office visits for family planning present an opportunity to talk to patients about their fertility desires and to review safe and effective birth control options, while also discussing risks of pregnancy with a given medical condition or while taking certain medications. According to the American College of Obstetricians and Gynecologists (ACOG), counseling around pregnancy should include optimizing control of chronic medical conditions prior to conception.1

One important resource available to us is the Centers for Disease Control and Prevention (CDC) U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC), which provides guidance on use of contraceptive methods for a wide range of medical conditions, such as hypertension, renal disease and seizure disorder, and addresses potential medication interactions.2 Categories 1 and 2 indicate that a contraceptive method is safe and without restrictions for the specific medical condition and the advantages of the method generally outweigh any theoretical risks, respectively. Category 3 suggests that the theoretical or proven risks of the contraceptive method outweigh the benefits. Category 4 means that there is an unacceptable risk to the patient with use of the contraceptive method. The full US MEC chart is available for download or purchase and an easy-to-use mobile application is available in the Apple or Google Play Store.

Women with epilepsy

Epilepsy is a neurologic disorder that affects about 1.5 million women in the United States and is characterized by seizures that temporarily disrupt brain function. Antiepileptic drugs (AEDs) are the treatment mainstay.3

AEDs and pregnancy

Exposure to AEDs in the first trimester is associated with an increased risk of fetal malformation. Valproate is associated with neural tube and cardiac fetal malformations. Phenobarbital exposure in pregnancy increases risk of cardiac malformations. Both lamotrigine and levetiracetam appear to be safe in pregnancy.4 The American Academy of Neurology recommends 0.4 mg of folic acid supplementation for women with epilepsy (WWE) who want to become pregnant.5

Download the full US Medical Eligibility Criteria chart at https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/summary.html

Dr. Loder is a clinical instructor, Michigan Medicine, University of Michigan, Ann Arbor.
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Limited data are available with regards to use of contraception in women with epilepsy. One recent international survey of reproductive-aged women with epilepsy found that the most common AEDs were lamotrigine and levetiracetam. Almost half of women with epilepsy used a hormonal contraceptive method (46.6%) and 17% used an intrauterine device (IUD).6

**CASE** Elaina, a 25-year-old G0, presents to discuss birth control. Her medical history is complicated by a history of a seizure disorder that is well-controlled on an antiepileptic medication. Otherwise, Elaina’s medical history is significant for a bicornuate uterus. As a teenager, she used a birth control implant, but she had it removed following a skin infection with methicillin-resistant Staphylococcus aureus at the insertion site. Elaina is planning to become married in 6 months and would like to become pregnant shortly after her wedding.

**WHAT POTENTIAL CONCERNS ARE THERE IN CHOOSING A CONTRACEPTIVE METHOD FOR ELAINA, CONSIDERING HER AED USE?**

A. Change in kidney function
B. Decrease in contraceptive effectiveness
C. Liver toxicity
D. Increased thromboembolism risk

**ANSWER: B**

In helping a patient like Elaina choose a contraceptive method, an ob/gyn needs to balance medical history, medication use, and fertility desire. While the contraceptive implant and intrauterine devices are generally recommended in women with epilepsy, Elaina’s history of complication with an implant and bicornuate uterus, in combination with wanting to conceive in the next year make these unsuitable choices. Likewise, because the injectable progestin, depot medroxyprogesterone acetate (DMPA) can delay fertility for up to 1 year, you would not recommend this option.7 Given those restrictions, the choices for this patient are combined hormonal contraception and progestin-only pills (POPs).

It is important to clarify Elaina’s antiepileptic medication use in order to appropriately counsel her because significant drug interactions exist between contraceptive steroids and AEDs. These drug interactions can occur in either direction, where some AEDs may decrease serum contraceptive hormone level, thus decreasing contraceptive effectiveness and increasing the risk for unintended pregnancy and some hormonal contraceptive methods may lower serum levels of AEDs, thereby increasing the frequency of seizures.

**AED/contraception interactions**

**Enzyme inducers**

Several AEDs are characterized as enzyme-inducers (Table 1), meaning that they enhance metabolism of contraceptive steroids, and may impact counseling and medical decision-making around contraception for WWE.8 The epilepsy foundation (www.epilepsy.com) provides helpful information about enzyme-inducers for patients and providers.9 As a result, the US MEC

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**TABLE 1** Antiepileptic drugs characterized by enzyme-inducing properties

<table>
<thead>
<tr>
<th>Enzyme-inducing AEDs</th>
<th>Non-enzyme-inducing AEDs</th>
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<tbody>
<tr>
<td>Carbamezapine (Tegretol®)</td>
<td>Acetazolamide (Diamox®)</td>
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<tr>
<td>Clobazam (Onfi®)</td>
<td>Clonazepam (Klonipin®)</td>
</tr>
<tr>
<td>Eslicarbazepine (Aptiom®)</td>
<td>Clorazepate (Tranxene®)</td>
</tr>
<tr>
<td>Felbamate (Felbatol®)</td>
<td>Diazepam (Valium®)</td>
</tr>
<tr>
<td>Lamotrigine* (Lamictal®)</td>
<td>Ethosuximide (Zarontin®)</td>
</tr>
<tr>
<td>Oxcarbazepine (Trileptal®)</td>
<td>Gabapentin (Neurontin®)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Lacosamide (Vimpat®)</td>
</tr>
<tr>
<td>Phenytoin (Dilantin®)</td>
<td>Levetiracetam (Keppra®)</td>
</tr>
<tr>
<td>Primidone (Mysoline®)</td>
<td>Pregabalin (Lyrica®)</td>
</tr>
<tr>
<td>Rufinamide (Inovelon®)</td>
<td>Tiagabine (Gabitril®)</td>
</tr>
<tr>
<td>Topiramate (Topomax®)</td>
<td>Valproic Acid (Depakot®)</td>
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</table>

Adapted from the Epilepsy Foundation
https://www.epilepsy.com/living-epilepsy/women/all-women/contraception
indicates that in women who use enzyme-inducer AEDs, both combined hormonal contraception and POPs are category 3, reflecting that the risks outweigh the benefits of use. Finally, data suggest that topiramate decreases serum levels of ethinyl estradiol among combined hormonal contraceptive users and the US MEC recommends against use of estrogen-containing methods for topiramate users. The etonogestrel implant is considered safe for women with epilepsy and more information needs to be collected on the effects of enzyme-inducers on efficacy.

**Choosing the best method**

Ultimately, you must consider the pros and cons of each contraceptive method for Elaina (Table 2). Both combined hormonal contraception and POPs remain ideal options, given her future plans for pregnancy and medical history. If Elaina is taking an enzyme-inducing drug, you can recommend a higher-dose combined hormonal contraceptive pill (50 ug ethinyl estradiol) or one that contains a higher-dose, long-acting progestin (levonorgestrel, desogestrel). However, you would not recommend using combined hormonal contraception with concurrent lamotrigine use without consultation with her neurologist. If Elaina is not taking an enzyme-inducing drug, both combined hormonal contraceptive methods and POPs are safe. It is important to counsel her that POPs need to be taken each day within a 3-hour window and are associated with irregular menstrual bleeding. Her visit today is a good opportunity to discuss safety of AEDs in pregnancy and to provide preconception counseling.

**TABLE 2**

<table>
<thead>
<tr>
<th>Contraceptive method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrier methods</td>
<td>No medication interactions.</td>
<td>Increased failure rate. Requires preparation and dedicated use.</td>
</tr>
<tr>
<td>Progestin-only pills</td>
<td>Good for short-term reproductive life goals. No interactions with lamotrigine.</td>
<td>Decreased efficacy in enzyme-inducing drugs.</td>
</tr>
<tr>
<td>Combined hormonal contraception</td>
<td>Good for short-term reproductive life goals.</td>
<td>Interacts with both lamotrigine AND enzyme-inducing drugs.</td>
</tr>
<tr>
<td>Progestin injection</td>
<td>No medication interactions.</td>
<td>May cause undesired infertility for up to 12 months.</td>
</tr>
<tr>
<td>Progestin implant</td>
<td>No known medication interactions.</td>
<td>Not aligned with fertility goals. Not contraindicated but would not recommend with history of MRSA infection.</td>
</tr>
<tr>
<td>Intrauterine device</td>
<td>Most effective.</td>
<td>Contraindicated due to uterine anomaly.</td>
</tr>
</tbody>
</table>

MRSA = methicillin-resistant Staphylococcus aureus

**Lamotrigine**

Use of estrogen-containing contraceptives by women who take lamotrigine is concerning because the drugs are metabolized in the same pathway. As a result, estrogen-containing methods decrease the concentration of lamotrigine and may reduce seizure control in WWE. This drug interaction can be overcome by increasing lamotrigine concentrations. Additionally, we recommend a monophasic estrogen-containing pill and using the method continuously (skipping placebo pills or hormone-free weeks) to minimize changes in serum concentrations of lamotrigine. We recommend a team-based approach between the obstetrician-gynecologist, neurologist, and patient to provide patient education and so that dose adjustments can be appropriately made to meet fertility goals while maintaining good seizure control.

**Contraceptive methods without drug-drug interactions**

Both copper and levonorgestrel intrauterine devices are considered safe in WWE regardless of which antiepileptic drug they use. The progestin Injectable is considered safe in women with epilepsy and is listed as Category 1 by the US MEC. Due to the high progestin levels, the injectable is not thought to be susceptible to enzyme-inducer activity. The etonogestrel implant is safe for women with epilepsy and more information needs to be collected on the effects of enzyme-inducers on efficacy.

**Comparing**

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MRSA = methicillin-resistant Staphylococcus aureus

**FOR REFERENCES VISIT contemporaryobgyn.net/ContraceptionCounseling**
PARIS—Lack of any hard and fast guidelines for best clinical practices means that the management of moles and melanoma during pregnancy is a challenge, said Dr. Marie Aleth Richard reporting at the European Academy of Dermatology and Venereology (EADV) Congress last September in Paris.

Dr. Richard, of Hôpital de la Timone, Marseille, France, said that melanoma is a hormonally responsive tumor. Increased levels of hormones such as estrogen, progesterone and beta en-endorphin can increase melanocyte stimulation and cause an increase in pigmentation. Some melanomas have progesterone and estrogen receptors. As well as altered hormone levels, pregnancy also induces a state of immunosuppression, which decreases tumor surveillance and allows tumor progression.

Changes in lesions should not be attributed to pregnancy, she said, but any changing lesion should be immediately biopsied and excised.

Nevi during pregnancy
Many clinicians believe that pregnancy comes with common changes in moles. While there are slight transient dermoscopic changes in nevi during pregnancy, normal nevi should only experience slight and non-significant clinical changes. Several studies have shown that changes in nevi size are only seen on the front of the body. "Pregnancy does not induce significant physiologic changes in nevi besides those on the breasts and abdomen, which grow with skin expansion," Dr. Richard said. There is also no evidence to show that there is a darkening of nevi during pregnancy, another common misconception. "Changes that occur in the nevi of pregnant patients should not be disregarded as a physiologic consequence of pregnancy. Any histopathological features consistent with melanoma should be viewed as melanoma," she said.

The risks of biopsies and mole excisions under local anesthetic during pregnancy remain theoretical, Dr. Richard said. "The low doses of lidocaine and epinephrine that are used in dermatologic surgery are considered safe." This means that biopsies and excisions, which should be obtained promptly from any suspicious or changing mole in pregnant women, can be performed safely during all stages of pregnancy.

Melanoma in pregnancy
Traditionally, clinicians have held the belief that women who are pregnant at the time of melanoma diagnosis have a poorer prognosis and a higher risk of progression than non-pregnant women. However, pregnancy-associated melanoma (PAM) prognosis does not appear to be worse than melanoma in non-pregnant controls. Nonetheless, measures should be taken to protect the fetus in the treatment and imaging of PAM.

"All surgical procedures can be done safely during pregnancy. Biopsy, excision and flap closure can all be done in the first trimester of pregnancy. Local anesthesia can be used in all these situations," Dr. Richard said.

Sentinel lymph node (SLN) status is the most important prognostic factor in patients with greater than 1 mm of melanoma.
Recession preparation for physicians

Although practices may be on the upswing now, prudent ob/gyns can take steps to ensure their practices can withstand a downturn.

by IKE DEVJI, JD

Given the current turbulent political and economic state of both the United States and many other key world powers, a variety of financial experts are predicting something ranging from a significant economic slowdown to another full-blown recession. Although times have been good, physicians should examine the lessons many doctors learned the hard way and act now, while they still have the time and resources to prepare. Worst case scenario, those predicting rough seas are wrong, and you’ve merely made your continued success more predictable and better defended.

Know your numbers

“Work as hard as you can” is not a business plan. You must understand key issues at your practice like your fixed expenses, cash flow, projected earnings, and the options available to manage them. Many practices and their owners lack the liquidity to sustain their current high levels of fixed business and lifestyle overhead with existing cash. Think about what an earning or cashflow change would do to your business. Is the core personal and business planning you have in place complete? Would it adequately protect your business and family in a crisis? What are your essential overhead items and what would you cut or change first, both personally and in your practice, to reduce overhead so it could be reallocated? Be sure you know your “survival number” and plan to be able to sustain it.

Protect assets, manage risks

Implement strategies that will guard the assets you have and protect the gaps in your planning that expose them, while you have both the resources and legal right to do so. Don’t self-insure against predictable risks that can be transferred away for a fixed cost. Work with an experienced broker to implement personal and professional liability insurance and make sure you have all the right kinds of insurance at the right amounts. Many doctors were put in harm’s way when faced with unexpected exposures they may have survived in regular conditions but were unable to in tougher times.

As a minimum, have in place the following:

- Disability insurance (all three kinds)
- Personal liability insurance, including a seven-figure umbrella
- All the required specialty business liability insurance in additional to malpractice coverage
- Required personal and business life insurance

Spend less, save more

Consider temporarily holding on any significant purchases or capital outlay that don’t produce income or significant long-term savings. If such purchases are necessary, think about how and if any such investment is protected. Having cash reserves available was key to the survival of many physicians during the recession. Know how long you would be able to meet your current business and personal overhead if your cash flow was suddenly stopped or significantly decreased.

Keep more of each dollar earned

When earnings are restricted by market conditions, it’s more important
than ever to keep more of every dollar you earn. Identify areas of loss or leakage in your practice, such as those due to billing and coding, collections, and reducible expenses, and act on them. Reconsider the scope of your accounting and business and personal tax planning and ask your advisors to identify any opportunities you are not taking advantage of. These could include health savings accounts and retirement plans, or even more active measures like energy efficiency and cost segregation studies. By the same token, avoid overly aggressive, questionable planning that can actually create additional expenses and liability, such as an IRS audit.

**Market your business**

Your business is in a competitive space, and your market position and growth need to be protected like that of any other business. Make it easy for patients and other providers to find you and work with you. Your medical practice is a service business that needs to compete on the best service, value, and care. Review the balance of high and low profit services your practice provides and look at new revenue opportunities and potential practice areas. Finally, get good help on these issues by delegating internally and consulting outside experts. Most doctors don’t ask for referrals to practice management consultants, CPAs, and lawyers until they are at the helm of a sinking ship—they should actually use them to ensure smooth sailing.

**Attorney Ike Devji** has practiced in the areas of asset protection, risk management, and wealth preservation law exclusively for the last 15 years. He helps protect a national client base with over $5 billion in personal assets that includes several thousand physicians and is a contributing author to multiple books for physicians and a frequent medical conference speaker and CME presenter.

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T Treating moles and melanoma

T Treating moles and melanoma, and SLN biopsy is generally considered safe in pregnant women. Patients should be made aware that SLN biopsy does not increase overall survival and that complications are more common in the second or third trimester.

‘‘Biopsies and excisions...can be performed safely during all stages of pregnancy.’’

When risk of metastasis is low (e.g. at stages 1-2ab), there is no need for imaging. Imaging can be performed in later disease stages, and more extensively in stage three. Imaging modalities that use ionizing radiation and radionuclides should be limited in pregnant women.

“These treatments are associated with a risk of teratogenesis and miscarriage in the first trimester, as well as fetal injury and childhood cancer,” Dr. Richard said. Chest radiographs with appropriate shielding, ultrasonography and MRI are generally the techniques of choice in pregnant women, although CT scans without contrast and nuclear medicine studies can be performed if necessary. “Decisions about imaging should be made on a case-by-case basis, and the risk of lymph node involvement, for example, should be considered,” she said.

After a PAM, oral contraceptives and hormone replacement therapy do not seem to increase risk for melanoma. There is no increased risk of melanoma after ovarian stimulation for in vitro fertilization, no effect of a subsequent pregnancy after a diagnosis of melanoma or PAM, and no need to defer pregnancies in women with localized or low-risk melanoma.

"Women with an increased risk of melanoma recurrence should be advised to wait for 2 to 3 years before becoming pregnant again,” she said. This is when recurrence is most common.

PD-1 and PD-L1 play a key role in maintaining fetal tolerance, and PD-1 and PD-L1 inhibitors for the treatment of melanoma may therefore affect pregnancy. In animal studies, anti-PD-1/PD-L1 significantly increased the risks of spontaneous abortions. “The use of an anti-PD-1/PD-L1 like pembrolizumab before a future pregnancy, such as an adjuvant setting in a young woman with a melanoma with high risk of recurrence, might also
Unnecessary antibiotic scripts

period that began 3 days before antibiotic prescription fills and ended on the day fills occurred. The main outcome was the proportion of fills in each of four mutually exclusive categories: “appropriate” (associated with at least one “always” code during the look-back period), “potentially appropriate” (associated with at least one “sometimes” but no “always” codes), “inappropriate” (associated only with “never” codes), and “not associated with a recent diagnosis code” (no codes during the look-back period.

The claims data analyzed were from the 2016 Truven MarketScan Commercial Claims and Encounters database, which contains claims for people aged 0 to 64 years who receive employer-sponsored health insurance. The authors said they “erred on the side of assuming appropriate antibiotic use” by, for example, classifying several diagnosis codes as “sometimes” even when oral antibiotics are rarely necessary.

Overall, the researchers found that 23.2% of the outpatient antibiotics prescriptions written were inappropriate, and 28.5% were not associated with a recent diagnosis code. During the study period, 14.1% of the individuals in the claims database filled at least one inappropriate antibiotic prescription, including 10.6% of the children and 15.2% of the adults. Of the inappropriate prescriptions, 70.7% were written in an office-based setting, and 6.2% in urgent care centers, and 4.7% in emergency departments.

In subgroup analyses, 31.4% of antibiotics prescriptions to adults were appropriate, compared with 48.7% of those written for children. The most commonly prescribed antibiotics were azithromycin (19.0%), amoxicillin (18.2%), and amoxicillin-clavulanate (11.6%). The most common diagnoses associated with the appropriate fills were urinary tract infection, streptococcal pharyngitis/tonsillitis, and bacterial pneumonia. Acute bronchitis, acute upper respiratory tract infection, and respiratory symptoms such as cough were the diagnoses most frequently associated with inappropriate prescribing.

Limitations of the study noted by the authors included reliance on diagnosis codes assigned by clinicians, use of a classification scheme developed on the basis of consensus, inability to capture fills or visits paid for out of pocket or prescriber specialty, and assessment of antibiotic appropriateness solely based on indication and not choice of agent or duration of therapy. Nevertheless, the researchers said, their data “highlight the importance of conducting future studies to assess the 64.0% of outpatient antibiotic prescription fills that are either only potentially appropriate or not associated with a recent diagnosis code.” They also believe that their classification scheme “could be a valuable tool for policymakers and researchers interested in measuring and improving the appropriateness of outpatient antibiotic prescribing.”

Judith M. Orvos is an editorial consultant for Contemporary OB/GYN.
A PGY-2 GYN admission note documented that the patient had 2 weeks of "subjective" fevers, chills, and abdominal pain, as well as diarrhea. The progress note referred to the CT findings, which documented an "ill-defined collection of extra luminal gas pockets," and an official report stated that the CT findings are "most concerning for abscess formation" without any suspicion of viscus perforation. Resident B countersigned the PGY-2 note and on the same page entered her own note stating, among other things, that the patient was now presenting with a "cuff abscess," and that treatment would be intravenous antibiotics, which according to a February 22 PGY-3 OB/GYN note consisted specifically of vancomycin, cefepime, and metronidazole. The note also indicated that the patient's pain was well controlled, she did not complain of bloating, and although she had fevers, there were no chills, nausea or vomiting. She was noted to be tachycardic at that time. Her wound culture had grown gram-negative bacteria.

A nursing note thereafter documented that the patient’s temperature was 100.3°F and she was complaining of pelvic discomfort. The PGY-3's note 13 hours later stated that the patient's pain was well controlled, her abdomen was soft and mildly distended with bowel sounds present, and WBC 16.0, and said that this is an "improving vaginal cuff abscess, with the patient still on antibiotic coverage." A February 24 note by resident Dr. A stated that the woman’s pain was controlled, she was tolerating an oral diet, and she did not have fever, chills, night sweats, or peritoneal signs. Dr. A also noted decreased vaginal discharge and indicated that antibiotic coverage with vancomycin, cefepime, and metronidazole was to be continued. In the Assessment & Plan, Dr. A indicated “possible CT with contrast.” An “addendum” made by the PGY-4 approximately 1½ hours later indicated that the patient was still complaining of abdominal pain and that vaginal discharge was present, although she did not have a fever.

The Defendant attending was consulted by phone and the plan discussed was a CT of the woman’s pelvis and abdomen, with a possible trip to the operating room to “open cuff and drain abscess.” The next significant note was made retrospectively at 6:00 p.m. by the Defendant. In it, previous events were described, including the findings of the aforementioned CT scan, and it stated that the patient did well after the February 7 surgery until prior to the emergent February 21 presentation. Defendant attending’s note referred to CT-documented free air and an increase in the size of the cuff abscess. The official report largely correlated with Defendant attending’s progress note reference, indicating that the large amount of loculated ascites of the abdomen and pelvis had markedly increased in size and that the extraluminal gas had been present and persistent since the February 21 scan, and was now suspicious for a perforated viscus.

Defendant attending went on to note that she was calling for a general surgery consult to rule out occult bowel perforation and that she was awaiting the consult and entertaining the possibility of an exploratory laparotomy. The consult in question was performed by Dr. D, whose consult said the purpose was to rule out a perforated viscus. The note also indicated that the patient had developed progressive diffuse abdominal pain, nausea, vomiting, and subjective fevers over the past 2 weeks at home. Dr. D also documented that the patient was presenting with intra-abdominal ascites, and free air, all of which was concerning for a perforated viscus and bowel injury, and that a plan was being formulated to perform exploratory laparotomy.

The exploratory laparotomy was performed by Defendant attending and general surgeon Dr. E as primary physicians. According to the handwritten brief operative note, the preoperative diagnosis was perforated viscus and the postoperative diagnosis was sigmoid colon perforation with purulent peritonitis and abscess, with specific notation of a small perforation along the anterior aspect of the distal sigmoid. After initial in-
traoperative examination of the small bowel, further "exploration" revealed that there was a "small necrotic-appearing perforation in the lateral aspect of the rectosigmoid colon." Repair of the perforation involved resection of the rectosigmoid colon and formation of a colostomy.

The patient was intubated in the intensive care unit for 24 hours and extubated on February 25. During the remainder of her hospitalization she received multiple consults, specifically by the medicine service, the infectious disease service, nutrition, general surgery, and gynecology. On March 3 an interventional radiology procedure was done to drain the woman's abscess, and on March 10 there was a note concerning a proposed interventional radiology procedure, although it indicated that there was "nothing to drain. A note made on March 10, stated that "abscesses at this time overall are decreased," but "not resolved."

The patient was discharged that day from the Defendant hospital site with Visiting Nurse Service arrangements having been made and instructions including ostomy management. On September 8, her colostomy was reversed and during that procedure, her left fallopian tube and ovary also were removed, without the intervention of Defendant attending or anyone from the GYN service.

ALLEGATION

Plaintiff alleged that negligent attempts to remove fibroids and perform a vaginal hysterectomy resulted in perforation of the patient’s sigmoid colon, requiring surgical repair and a temporary colostomy and causing persistent pain and suffering. Plaintiff also alleged a delay in diagnosis and failure to timely consult with proper specialists such as surgery and infectious disease. A claim also was made of pain and suffering as well as scarring, sepsis, post-traumatic stress disorder and diminished sexual and intimate relations.

DISCOVERY

Our urogynecology expert opined that the hysterectomy was indicated based on the patient’s history of fibroid uterus, menorrhagia, and resultant anemia. A vaginal approach was proper given her prior surgical history. The expert also opined that there was no evidence of a bowel perforation prior to discharge from the hospital after the surgery. He suggested that the perforation was delayed and likely a result of deserosilization.

At her deposition, the patient claimed that she had a "tumor" from the colostomy incision and could not work secondary to pain. She testified that she was in pain from the time of the February 7 surgery through her return to the hospital on February 21.

She stated her colon was perforated in three places and she was distressed at needing a colostomy. She required home care for a month after discharge and “went into a depression” because of the colostomy. It was discovered that the patient had been suffering from thyroid cancer since 2016. She further could not substantiate a lost earnings claim with any documentation.

RESOLUTION/TRIAL

The patient's attorneys interposed a $2 million demand for settlement. They asserted through their trial experts that, in addition to the prior allegations of surgical negligence and delay, defendants failed to use less invasive treatments such as hormone therapy, hysteroscopy or endometrial ablation. Our expert countered that the woman’s fibroid was too large for alternative measures and neither hormones nor ablation would provide the definitive treatment the patient desired. He opined that consent was properly obtained and that the surgery itself was properly performed without clinical or radiographic evidence of a perforation at the time of the operation. The issues that went to the jury involved the propriety of the informed consent and the performance of the hysterectomy itself. After brief deliberation, a verdict was rendered in favor of the defendants.

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Was this bowel perforation the result of negligence?

Informed consent and surgical route are the main focuses of this case.

**FACTS**

The patient had a significant past medical history, including a gastric banding procedure for morbid obesity (body mass index 44), and admission for laparoscopic removal of the lap band when it “slipped.” Her various clinic records—primarily in gynecology/urology—documented a history of fibroid uterus with menorrhagia and an initial disinclination to undergo surgery to deal with it.

Notes about surgery for the woman’s fibroids indicate that the procedure was scheduled for February 7 and express concern about “risk of operation.” On February 7, the patient was admitted to defendant hospital for the surgery, which was documented as having occurred from 10:50 a.m. to 12:16 p.m. The residents who assisted Defendant attending were Drs. A and B. A vaginal hysterectomy was performed, and the woman’s right fallopian tube and right ovary were removed. Defendant attending indicated she could not completely visualize the left fallopian tube due to its adherence to the bowel.

A vaginal hysterectomy was performed and the woman’s, right fallopian tube and right ovary were removed.

After surgery, the patient was admitted to the Post-Anesthesia Care Unit (PACU), where she stayed until approximately 4:30 p.m. At that time, her blood pressure (BP) was 95/62, pulse 72. The hemoglobin was 7.2 and the hematocrit was 25.2, both of which were consistent with the admission values. In addition, it was noted that “GYN aware and stated patient can be discharged to home,” and a correlating PACU nursing note entry timed at 4:30 p.m. stated that the patient was sleeping on and off, in very little pain, with no bleeding noted, that the complete blood count results were “seen by GYN” and that Drs. A and B stated that the patient could be discharged. The surgical specimens sent to pathology were fibroid uterus and cervix together with a right fallopian tube, although there was no mention of the ovary. The patient was instructed to present to the clinic within 2 weeks or to the Emergency Department if she had increased bleeding, fever, severe and/or persistent pain, and other related symptomatology.

On February 21 at 8:18 a.m., the woman presented to the Defendant hospital with a complaint of abdominal pain, swelling, and diarrhea for 1 day, and a history of “two weeks of fever and chills.” Vital signs revealed a BP of 106/94, pulse 102, and a temperature 98.5°F. Two hours later, the patient’s BP was 88/54, pulse 89, and temperature 98.3°F. An abdominal x-ray documented no free air under the diaphragm and a follow-up computed tomography (CT) scan was scheduled. Laboratory studies at that point were remarkable for a white blood cell (WBC) count of 16.4. The patient was admitted to the service of the OB/GYN attending, Dr. C.

**FOR MORE LEGALLY SPEAKING**

**TURN TO PAGE 48**

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*Andrew I Kaplan, Esq* is a partner at Aaronson, Rappaport, Feinstein & Deutsch, LLP in New York City, specializing in medical malpractice defense and healthcare litigation. This case was handled by one of his partners.
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