IN VITRO MATURATION

Improving the odds in infertility

Seang Lin Tan, MD

17P: Choosing a compounder
Joe Cabaleiro, RPH

FM MYTHBUSTERS
Mild, moderate, severe decelerations
David A. Miller, MD

PROTOCOLS FOR HIGH-RISK PREGNANCY
Preeclampsia management
Baha M. Sibai, MD
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OUR MISSION
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GRAND ROUNDS
26
Improving the odds in infertile patients
AYSE SEYHAN, MD
BARIS ATA, MD
SEANG LIN TAN, MD
Subfertile women have another option for achieving pregnancy: in vitro maturation of oocytes.

FETAL MONITORING MYTHBUSTERS
21
Fetal heart monitoring: mild, moderate, and severe decelerations
DAVID A. MILLER, MD
This third column in the series reviews the scientific data behind the efforts to classify decelerations.

17P: Choosing a quality compounding pharmacy
JOE CABALEIRO, RPH
Compounding pharmacies can be an effective option for meeting certain patients’ needs. This article offers advice on finding a compounder to which you can confidently refer patients.

13
CLINICAL INSIGHTS
SSRIs raise risk of newborn pulmonary hypertension

42
Is there a doctor on board? What to do in an in-flight medical emergency
STEVEN M. SELBST, MD
Physicians are morally and ethically obligated to volunteer to help with in-flight medical emergencies. Here’s what you need to know before you’re asked to get involved.

49
CLASSIFIED

54
CALENDAR/AD INDEX

55
PROTOCOLS FOR HIGH-RISK PREGNANCIES
BAHA M. SIBAI, MD
Identifying and managing pre eclampsia
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The top ob/gyn clinical and practice management resources from ModernMedicine.com

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   US health regulators cleared for marketing a device to determine oxygen saturation of the abdomen of certain newborns.
   contemporaryobgyn.net/oximeter

2. Early signs vitamin D might ease menstrual cramps
   A small study suggests women plagued by menstrual cramps may find relief with vitamin D3.
   contemporaryobgyn.net/cramps

3. Study supports soy cholesterol benefits for some
   A new study hints that soy might benefit a wider range of people.
   contemporaryobgyn.net/equol

4. Free texting program helps prevention, management of heart disease
   The American College of Cardiology has launched a texting program to help prevent and manage CV disease.
   contemporaryobgyn.net/ACCText

5. FDA rejects premature birth gel
   FDA has rejected a vaginal gel aimed at reducing the risk of premature birth.
   contemporaryobgyn.net/contragel

6. Preventing maternal influenza in pregnancy may improve neonatal outcomes
   Offspring of women who receive influenza immunization during pregnancy have better intrauterine growth and fewer respiratory illnesses.
   contemporaryobgyn.net/imunize

7. ACOG addresses impacts of breast cancer treatments
   ACOG has released new guidelines on caring for breast cancer patients, covering the effects of breast cancer therapies.
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Recommend

Changing expectations
Newly proposed GDM screening protocol: unanswered questions remain

You would think that after 40 years of study and practice, all issues surrounding the management of gestational diabetes mellitus (GDM) would be settled. Based on criteria derived from studies in the early 1970s by O’Sullivan and Mahan, the American College of Obstetricians and Gynecologists (ACOG) estimates that about 2% to 5% of our pregnant population is affected.\(^1\)

Now a vigorous debate has developed concerning whether to adjust traditional GDM screening methods and criteria.\(^2\)

At stake is a possible tripling in the number of patients defined as affected by GDM and a substantial increase in the cost of prenatal care.

**Evolution of current practice**

The basis for our current screening strategy derives from the pioneering work of O’Sullivan and Mahan who established thresholds for fasting, 1-hour, 2-hour, and 3-hour glucose values that predicted a 50% risk of future diabetes.\(^3\)

Although the original intent of 3-hour glucose tolerance testing (GTT) was to predict future diabetes, the current focus is identification of pregnant women at risk for adverse pregnancy outcomes such as macrosomia, neonatal hyperbilirubinemia, shoulder dystocia, and birth injury.\(^4\)

Shockingly, the clinical value of GDM screening and management only recently has been established by randomized trials.\(^5\)\(^6\) And while we expend ever-greater efforts toward managing glucose values during pregnancy, less effort and success has been realized in achieving universal postpartum screening and long-term prevention, the rationale behind O’Sullivan and Mahan’s original work.\(^7\)

There has always been debate surrounding the proper methods for screening for GDM. Indeed, it has taken multiple international conferences to derive the screening system we use today: a system of essentially universal screening with a 1-hour, 50-g glucose challenge test followed by a diagnostic 3-hour, 100-g GTT when patients fail the 1-hour screen. Once a woman has been diagnosed with GDM, as a field we have embraced very aggressive glucose monitoring and control while largely ignoring women whose testing is normal or borderline. However, the reality is that glucose tolerance in pregnancy is a continuum and GDM is not a discrete disease. Indeed, one abnormal value on a 3-hour GTT is associated with adverse pregnancy outcomes.\(^8\)

**Toward a more rational screening paradigm**

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) group sought to identify screening values that optimally identified pregnancies at risk for perinatal complications.\(^9\) The HAPO study was a large, prospective, multinational cohort study of more than 23,000 women who received a 75-g, 2-hour GTT at 24 to 32 weeks. Participants had fasting, 1-hour, and 2-hour glucose venous plasma levels measured. No interventions were tested in this observational study. Among the outcomes were birth weight >90th percentile, neonatal hypoglycemia, hyperinsulinemia, hyperbilirubinemia, newborn percentage of body fat >90th percentile, shoulder dystocia/birth injury, preeclampsia, and NICU admission. Not surprisingly, the HAPO study demonstrated a positive linear relationship between screening glucose values and adverse perinatal outcomes. Moreover, the study authors found that perinatal risks began to increase in women with glucose values previously considered “normal.”

Following up on this study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) offered recommendations on diabetes screening during pregnancy that included\(^3\):

1. Screening all high-risk women at the first prenatal visit for preexisting diabetes with either hemoglobin A\(_{1c}\) (>6.5%), fasting glucose (>92 mg/dL), or random glucose (>200 mg/dL). Women with fasting glucose between 92 mg/dL and 126 mg/dL would be considered to have GDM.

2. Universal screening with 1-step testing at 24 to 28 weeks with a 75-g, 2-hour GTT.

3. Glucose thresholds were based on their prediction of three perinatal outcomes: birth weight >90th percentile,
CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Left congenital diaphragmatic hernia with liver and intestines in the left chest and small, poorly developed lungs.

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Left congenital diaphragmatic hernia with liver and intestines in the left chest and small, poorly developed lungs.
EDITORIAL

umbilical cord C-peptide levels >90th percentile (as a surrogate for fetal hyperinsulinemia), and neonate percent body fat >90th percentile. These thresholds are the average glucose values at which the odds for the three perinatal outcomes reached 1.75 times the odds of pregnancies with mean glucose values in the HAPO cohort. The IADPSG has proposed thresholds of 92 mg/dL, 180 mg/dL, and 153 mg/dL for fasting, 1-hour, and 2-hour glucose values, respectively. Unlike previous paradigms, only one abnormal value would be required to make a diagnosis of GDM, and it is anticipated that more than 16% of the population will be diagnosed with GDM.

The controversy

Currently, there are no randomized trials to support the recommended modifications to GDM screening. Remember that the rationale for treatment for GDM as we currently define it has only recently been made apparent. I believe that this proposed change would only minimally reduce the incidence of macrosomia and neonatal fat stores. Only a randomized trial can help us to better appreciate the advantages, potential detriments, and unintended consequences of this new approach to GDM testing. Moreover, adoption of the IADPSG guidelines could easily overwhelm our maternity care system. Currently, there is no evidence-based guidance informing us how to manage the additional women who now will be diagnosed with GDM. Do they need the same aggressive management we employ today for GDM? Would nutrition counseling be sufficient? A number of questions must be answered before we can embrace the new criteria.

Adoption of the IADPSG guidelines also will be very expensive. One cost-utility analysis determined that changing criteria would not be cost effective if only obstetrical care were considered. Indeed, the new screening criteria attain cost-effectiveness only if coupled to aggressive postpartum follow-up with intense management of diet and exercise to reduce future diabetes risks. Unfortunately our healthcare system has always placed a greater emphasis on managing women in the antepartum and intrapartum periods, with poor attention being paid to post-delivery management. Although an accepted part of care, the use of postpartum screening for diabetes after GDM has been abysmally poor. As such, under the current systems new GDM criteria would likely be far too expensive for the minimal benefits they would accrue for our patients.

Take-home message

In my opinion, there are just too many questions left unanswered concerning the proposed GDM screening paradigm. Implementation could lead to the aggressive treatment of 16% of our pregnant population for GDM, generating excess costs without proven benefits. Unfortunately, new studies are not forthcoming to answer many of the outstanding questions. Perhaps the NIH Consensus Conference scheduled this fall will add clarity. In the interim, I support ACOG’s recommendation: “At this time, the Committee on Obstetric Practice continues to recommend a two-step approach to screening and diagnosis. All pregnant women should be screened for GDM, whether by patient history, clinical risk factors, or a 50-g, 1-hour glucose challenge test at 24 to 28 weeks of gestation. The diagnosis of GDM can be made based on the result of the 100-g, 3-hour oral glucose tolerance test, for which there is evidence that treatment improves outcome.”

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REFERENCES


SSRIs raise risk of newborn pulmonary hypertension

Although the risk for persistent pulmonary hypertension (PPH) in newborns is low (i.e., 2 per 1,000 live-born infants), selective serotonin reuptake inhibitors (SSRIs) taken by mothers after the 20th week of pregnancy more than double the risk for this life-threatening condition, according to the findings of a Nordic population-based cohort study.

Researchers from Sweden, Finland, Norway, Denmark, and Iceland used health registry data on more than 1.6 million infants born after the 33rd week of pregnancy during the years 1996 to 2007. Among approximately 30,000 women who were dispensed SSRIs during pregnancy, about 11,000 used them after the 20th week of gestation; 33 of their newborns, or about 3 per 1,000 live-born infants, had PPH. Of the approximately 17,000 babies exposed to SSRIs in early pregnancy, 32 had PPH. The corresponding figure for the 158,840 never exposed was 1,935 (1.2 per 1,000 live-born infants).

All of the SSRIs studied (i.e., sertraline, citalopram, paroxetine, fluoxetine, fluvoxamine, and escitalopram) had similar risks, suggesting a class effect. In addition, taking SSRIs before the 6th week of pregnancy also slightly increased the risk for PPH: adjusted odds ratio 1.4 (95% CI, 1.0–2.0). Although the mechanism by which SSRIs influence the development of PPH is unknown, experts suspect the accumulation of SSRIs in the lungs, combined with the potential of serotonin to induce vasoconstriction and to mediate pulmonary arterial smooth muscle cell proliferation through the serotonin transporter, has something to do with it.


Cancer survivors have poorer health behaviors

Cancer survivors are more likely than their healthy counterparts to be current smokers, to rate their overall health as “poor,” and to report less participation in moderate to strenuous exercise, according to the results of a study from the Mayo Clinic.

The authors reviewed the health behaviors and previous cancer histories of 18,510 women age 35 years and older presenting for screening mammography. Almost 15% of the women reported a cancer history. Only 13.6% of the cancer survivors compared with 21.5% of the women without a cancer history reported their health as “excellent.” Similarly, they were more likely to rate their overall health as poor (15.8% vs 9.1%, respectively).

Compared with 63.3% of women who never had cancer, 56.5% of the cancer survivors reported engaging in regular moderate or strenuous exercise. Cancer survivors, particularly those between the ages of 30 and 49, were more likely to smoke than those who never had cancer (6.3% vs 5.5%, respectively) and they were less likely than noncancer participants to use alcohol monthly or more frequently (66.9% vs 71.4%). Younger survivors (age 30 to 49 years) were the most frequent (79.2%) regular drinkers, defined as at least one drink per month.

Significant differences emerged between survivors of different types of cancers. Cervical cancer survivors were among the least likely to engage in regular screening mammography. They reported the highest rate of current smoking, the highest percentage of consuming at least four caffeine drinks daily, the highest regular use of alcohol, and the highest rates of being overweight or obese and of gaining the most weight at 5 and 10 years. Ironically, they were the most likely to rate their health as “excellent” and the least likely to rate their health as “poor.”


Weight loss may prevent diabetic incontinence

Overweight women with diabetes can cut their risk for developing urinary incontinence (UI) by shedding 5% to 10% of their body weight or as little as 15 pounds (7.7 kg), according to findings from the Look AHEAD trial, a multicenter, randomized, controlled trial of overweight and obese individuals with type 2 diabetes.

The trial involved 2,739 women, 45 to 76 years of age, with body mass indices (BMI) of 25 kg/m² or greater.
The women were stratified into two groups. The first received intensive lifestyle intervention and modification counseling designed to promote weight loss of at least 7% per year. Professionals encouraged the women to consume low-calorie, low-fat diets, to control portions with liquid meal replacements, and to exercise at least 175 minutes per week. These women checked in weekly for 6 months and then three times monthly for another 6 months. The second group received far more limited diabetes support and education: In 1 year, they attended only three group sessions that focused on diet, physical activity, and social support.

At 1 year, those who lost the weight were 25% less likely to develop UI in general and 40% less likely to have stress UI. Each kilogram of weight lost reduced the odds of developing UI by 3% ($P=0.01$). Weight losses of 5% to 10% reduced the odds by almost half (47%; $P=0.002$).

The study did not show that weight loss improved resolution rates of UI at 1 year. “It is possible that weight loss is more effective for the prevention than for the treatment of UI in women who already have type 2 diabetes,” concluded the authors. However, only about one-quarter of the women had UI at study entry. Future research should recruit women with UI and type 2 diabetes and use detailed assessments to document specific changes in their condition, the authors suggest.


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**Privacy and Security Mobile Device Project launched**

Physicians using smartphones and other mobile devices to access patients’ electronic health records are increasingly at risk for data breach, but a new initiative from the Office of the National Coordinator for Health Information Technology (ONC) of the US Department of Health and Human Services (HHS) may allay some fears about possible violations of Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules.

In January, ONC’s Office of the Chief Privacy Officer announced initiation of the Privacy and Security Mobile Device Project in conjunction with the HHS Office for Civil Rights to develop security best practices for personal mobile devices that are used outside healthcare facilities considered “Covered Entities” under HIPAA to access, store, or work in protected health information files. Devices include laptops, tablets, smartphones, personal data assistants, and data storage devices (such as USB drives). The goal is to help healthcare professionals to secure information from cyber attack or data loss without compromising the convenience of remote access.

Developed by a team of cybersecurity and healthcare subject matter experts, ONC’s Cybersecurity Checklist, “10 Best Practices For The Small Healthcare Environment,” comprises administrative, technical, and physical safeguards with specific, practical steps for implementation. Best practices discussed include password choice and protection (as well as forgotten passwords), virus detection and antivirus software, firewalls, accessing HIPAA-protected information, controlling physical access, limiting network access, disaster planning, maintaining good habits of computer use, mobile device protection, and creating a security culture.


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**Incidence of high-risk oral HPV increasing**

About 7% of Americans are infected with oral human papillomavirus (HPV), according to a recent cross-sectional study. Prevalence is almost 3 times higher in men than in women, about 8 times higher in those who are sexually active than in those who are not, and variably higher among cigarette smokers, former and current marijuana users, and heavy alcohol drinkers.

Data was assessed from 5,579 men and women aged 14 to 69 years who were participating in the National Health and Nutrition Examination Survey (NHANES) 2009-2010, which is a statistically representative sample of the civilian noninstitutionalized US population. Participants were given a 30-second oral rinse, gargled with mouthwash, after which researchers assessed DNA purified from oral exfoliated cells.

Overall prevalence of oral HPV in the study group was 6.9% (95% confidence interval [CI], 5.7%-8.3%). The most prevalent type of HPV detected was HPV-16 with a 1.0% overall prevalence rate. Men were more than 5 times as likely as women to be infected with HPV-16 and had a higher incidence of HPV-positive oral squamous cell carcinomas (OSCCs).

Previous studies have reported that about 90% of HPV-positive OSCCs are caused by HPV-16, and that
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those who are infected with oral HPV-16 are about 50 times more likely to develop HPV-positive OSCCs.

Sixty- to 64-year-old participants had the highest incidence (11.4%; 95% CI, 8.5%-15.1%), followed by 30- to 34-year-olds (7.3%; 95% CI, 4.6%-11.4%). The prevalence rate among men was 10.1% (95% CI, 8.3%-12.3%) versus 3.6% in women (95% CI, 2.6%-5.0%). Incidence among those with no history of sexual activity was 0.9% (95% CI, 0.4%-1.8%) versus 7.5% (95% CI, 6.1%-9.1%) among those who are sexually active.

Prevalence increased with number of sexual partners: 20% of those with more than 20 lifetime sexual partners were infected, and it also was higher among those who first performed oral sex at 18 years of age or younger.


Caffeine and estradiol: a complicated relationship

As little as two cups of caffeinated coffee per day is enough to lower free estradiol concentrations in white women and raise them in Asian women. As little as one cup of caffeinated soda or green tea is enough to increase free estradiol concentrations among women of all races.

The findings come from a small study conducted from 2005 to 2007 by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Researchers followed 259 participants for up to two menstrual cycles. Participants provided fasting blood samples for hormonal assessment.

On average, the women consumed 90 mg of caffeine per day, equivalent to one cup of caffeinated coffee. Overall, 66% of caffeine intake came from coffee, 17% from tea, 14% from soda, 3% from chocolate, and 0.003% from caffeinated medications.

Study authors found that ≥200 mg per day caffeine was inversely associated with free estradiol concentrations among white women (β=-0.15; 95% CI, -0.26 to -0.05) and positively associated among Asian women (β=0.61; 95% CI, 0.31-0.92), but that ≥240 mL (one cup) of caffeine from soda and/or green tea was positively associated with free estradiol concentrations among all races (β=0.14; 95% CI, 0.06-0.22 and β=0.26; 95% CI, 0.07-0.45, respectively).

Black women who consumed 200 mg or more per day from coffee had slightly elevated estradiol levels, but the increase was not statistically significant. All the changes in estradiol levels were insufficient to affect ovulation.

The authors noted that almost 90% of American women between the ages of 18 and 34 years consume the caffeine equivalent of 1.5 to 2 cups of coffee per day. They concluded that interactions between race and caffeine intake on total and free estradiol concentrations are significant and require more research.


Noninvasive DNA test: highly specific for fetal aneuploidy

Results from an international multicenter study suggest that a new plasma-based DNA test detects nearly all cases of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome), in addition to Down syndrome, with low false-positive rates.

The MaterniT21 test, developed by the Sequenom Center for Molecular Medicine, uses circulating cell-free DNA fragments isolated from maternal plasma and determines the fetal fraction using a published method relying on differentially methylated markers.

Maternal plasma samples were gathered at 27 prenatal diagnostic centers from women at high risk for fetal aneuploidy who were undergoing diagnostic testing in the late first and early second trimester. Results from the blinded testing of 212 pregnancies with trisomy 21 and their 1,484 matched controls already appeared in Genetics in Medicine.

Simultaneous with that study, the authors tested 62 trisomy 18 and 12 trisomy 13 blinded samples, along with samples from controls. They calculated a detection rate of 100% for trisomy 18 and 91.7% for trisomy 13. Corresponding false-positive rates were 0.28 and 0.97, respectively.
“The study provides strong evidence that secondary screening using maternal plasma samples from high-risk pregnancies will simultaneously identify nearly all cases of trisomy 18 and 13,” the authors write.

Interpretation of the massively parallel shotgun-sequencing (MPSS) test was possible in 99.1% of samples for the 3 aneuploidies, yielding an overall detection rate of 98.9%. The 3 false-negatives involved 2 Down syndrome pregnancies and 1 trisomy 13 pregnancy. Full clinical interpretation was not possible for 17 pregnancies, even after testing twice.

The manufacturer is in discussion with the US Food and Drug Administration to determine necessary preclinical and clinical studies required to support a premarket approval application for an in vitro diagnostic device for trisomy 21.


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**Cefpodoxime fails test in uncomplicated cystitis**

When compared with ciprofloxacin, cefpodoxime failed to meet criteria for noninferiority in women with uncomplicated bladder infections, according to the findings of a randomized, double-blind trial.

The study involved 300 women aged 18 to 55 years with acute uncomplicated cystitis. The researchers gave the women either 250 mg ciprofloxacin orally twice daily for 3 days or 100 mg of cefpodoxime proxetil orally twice daily for 3 days.

The researchers predicted that cefpodoxime would be noninferior to ciprofloxacin by a 10% margin. Using an intent-to-treat approach in which they considered women lost to follow-up as having been cured, they calculated an overall cure rate at 30 days of 93% (139/150) in the women who received ciprofloxacin versus 82% (123/150) in the women receiving cefpodoxime (difference of 11%; 95% CI, 3%-18%).

Among women lost to follow-up considered as having been treatment nonresponders, the clinical cure rates were 83% (124/150) in the ciprofloxacin group versus 71% (106/150) in the cefpodoxime group (difference of 12%; 95% CI, 3%-21%). Microbiologic cure rates were 96% (123/128) and 81% (104/129), respectively.

At the first follow-up visit, scheduled for 5 to 9 days after completion of treatment, more than twice as many women in the cefpodoxime group as in the ciprofloxacin group had vaginal colonization with *Escherichia coli* (40% vs 16%, respectively).

Experts had hoped that cefpodoxime would prove to be an effective alternative to ciprofloxacin so that clinicians could reserve use of ciprofloxacin for more severe, recalcitrant infections, thus helping to minimize antimicrobial resistance to fluoroquinolones.

But the authors concluded, “Our findings . . . do not support the use of cefpodoxime as a first-line fluoroquinolone-sparing antimicrobial for acute uncomplicated cystitis.”


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**Maternal vitamin D linked to child’s language impairment**

Pregnant women with low serum 25(OH)-vitamin D concentrations (≤46 nmol/L) are more than twice as likely as women with levels that are ≥72 nmol/L to have a child whose language development is impaired by age 5 or 10 years.

“The findings suggest that the trend over the past decade of a reduction in vitamin D levels among women of reproductive age has significant implications for offspring neurodevelopment and public health more generally,” stated the authors of the prospective longitudinal study.

Researchers included 743 white women from Perth, Western Australia. They measured the women’s serum vitamin D levels at 18 weeks of pregnancy and grouped the women into quartiles. They measured offspring behavior using the Child Behavior Checklist at 2, 5, 8, 10, 14, and 17 years of age. They also used the Peabody Picture Vocabulary Test to assess receptive language at 5 and 10 years of age.

A significant association between vitamin D quartiles and the proportion of offspring with language difficulties at age 5 and 10 years was noted. As maternal 25(OH)-vitamin D levels during pregnancy decreased, the proportion of mothers who had offspring with mild to moderately severe language difficulties increased. No significant associations were noted between maternal vitamin D insufficiency and behavioral or emotional problems in offspring at any age.

Woman claims retained laparotomy pad caused ulcerative colitis

A 25-YEAR-OLD Illinois woman delivered a baby by cesarean. During the procedure a laparotomy pad was left inside her abdomen. She subsequently experienced abdominal pain, bleeding, and diarrhea, and was readmitted to the hospital 4 months after the cesarean delivery. A computed tomography scan revealed the laparotomy pad. Surgery was performed to remove the pad and an abscess that had formed around it. The patient was hospitalized for a week and also was diagnosed with ulcerative colitis. The woman sued those involved with the delivery, claiming that the retained pad caused or contributed to her ulcerative colitis and that she would require colon removal surgery in the future.

LEGAL PERSPECTIVE
In retained foreign object cases, the hospital usually admits that the care was below standard and the issue often becomes the damages related to the hospitalization and reoperation if necessary. In this case, the hospital admitted liability several months prior to trial but denied that the retained sponge caused the ulcerative colitis. It claimed that the damages should be limited to the consequences stemming from surgical removal of the pad, and the defense claimed that there is no known cause of ulcerative colitis and that the patient was likely to have a good result even if she required colon removal in the future.

The surgeon and the circulating nurse’s employer/agency settled prior to trial for $525,000. The jury returned a $1.367 million verdict for the plaintiff, which was subject to a setoff from the previous settlement, so a judgment for $842,500 was entered.

Birth trauma in large infant blamed for cerebral palsy

HAVING GAINED 70 POUNDS with her pregnancy, a Michigan woman developed gestational diabetes. She went into labor at term, had a 16-hour labor including 2 hours of pushing, and delivered vaginally. The female infant weighed 10 pounds, 12 ounces; she required resuscitation to establish breathing, had poor tone, and developed seizures. She was diagnosed with a fractured clavicle, had 3 intracranial hemorrhages, and spent 3 weeks in neonatal intensive care. Subsequently, she was diagnosed with cerebral palsy secondary to birth trauma. The child, now a teenager, requires 24-hour care and is unable to walk or talk.

In the lawsuit that followed, the patient claimed that the obstetrician and nurses should have anticipated a large fetus and should have performed an ultrasound to determine estimated weight before labor. She argued that this would have resulted in a recommendation for cesarean delivery.

The obstetrician argued that radiographic imaging performed shortly after birth revealed abnormal brain development and that and other genetic testing indicated that the child’s problems were due to pontocerebellar hypoplasia. The parents argued the child did not have this condition or she would have died in infancy, and if she did have it, the injuries alleged were unrelated to it.

The jury returned a verdict for the child in the amount of $144 million.

Failure to diagnose genetic disorder prenatally claimed

A NEW JERSEY WOMAN in her second trimester of pregnancy went to a maternal/fetal specialist for an ultrasound, which showed a jaw abnormality in the fetus.
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¹ F. Ueland, et al, Effectiveness of a Multivariate Index Assay in the Preoperative Assessment of Ovarian Tumors Obstet Gynecol 2011;117:1289–97

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The patient delivered a child who suffers from Treacher Collins syndrome, causing her to have a misaligned jaw and trachea. She has required resuscitation several times, is deaf and disfigured, and has undergone a dozen operations.

The patient sued the perinatologist and claimed the abnormality on ultrasound should have led to diagnosis of the syndrome, a genetic defect that can lead to misalignment of parts of the body. She alleged that she would have chosen to terminate the pregnancy if she had been advised of the diagnosis, thus avoiding the lifetime care needed for the child.

A $2.25 million settlement was reached.

Preterm delivery of triplets after cervical conization

A TEXAS WOMAN went to her gynecologist with the desire to become pregnant. The 32-year-old underwent an examination, and the Pap smear performed during the visit revealed squamous intraepithelial moderate dysplasia. A biopsy performed 2 months later confirmed the presence of dysplasia. A retest 2 months later also suggested dysplasia. One month later the gynecologist performed a cone biopsy, and the patient subsequently had almost 2 years of normal Pap smears.

The woman then went to a reproductive specialist and was started on medication to stimulate ovulation. Four months later she was diagnosed with a triplet pregnancy. At 24 weeks’ gestation the patient was admitted to a hospital in preterm labor and subsequently delivered very premature infants. One fetus did not survive the delivery; the two who survived suffered severe consequences of prematurity: developmental delays, autism, poor muscle tone, hyperactivity, and attention deficits. Later, one of the children died from unrelated causes before this case concluded.

In the lawsuit filed on behalf of the surviving twins, the woman claimed that her cervix had been weakened by the cone biopsy, causing her to be unable to carry the pregnancy to term. She also claimed that the reproductive specialist failed to warn her of the potential for having an incompetent cervix after undergoing a conization, and she contended that she should have been referred to a perinatologist when the pregnancy was diagnosed.

A confidential settlement was reached with the reproductive specialist and his group only because the suit against the ob/gyn was dismissed prior to the settlement.

Preterm labor and SROM result in infant death

IN OKLAHOMA a 21-year-old woman presented at a hospital at 22 weeks’ gestation with premature labor. A family practice physician took over her care. An attempt was made to stop the labor but 2 hours later spontaneous rupture of membranes (SROM) occurred and the decision was made to give oxytocin to induce labor. The fetus was breech and during the delivery the head became entrapped. The infant did not survive.

The patient sued, claiming that the family physician had been negligent in administering oxytocin and restarting labor. She contended that he should have tried to keep the fetus in utero and should have transferred her to a tertiary care center.

The physician claimed that the patient was fully dilated at the time she arrived at the hospital and the delivery could not have been stopped even if she had not had SROM. He also claimed the child was previable in any event. A defense verdict was returned.

Bowel perforation after tubal ligation alleged

A 24-YEAR-OLD TEXAS WOMAN underwent a laparoscopic bilateral tubal ligation performed by her gynecologist. Two days later the woman went to an emergency department and was found to be septic. She underwent immediate surgery to repair a pinpoint bowel perforation and subsequently had a bowel resection and an outpatient procedure for ventral hernia repair. In her suit against the gynecologist the patient claimed that she had not been properly informed of the risk of bowel injury and that the physician had failed to properly perform the procedure, failed to recognize the bowel injury, and failed to timely and adequately follow up after the procedure.

The physician claimed that the patient was well informed of the risk of bowel injury and that the injury was not evident during the operation. He also claimed that the patient was contributorily negligent in delaying the diagnosis and treatment for her complication. She had failed to follow up as instructed: She had been told to go to the hospital for evaluation where the gynecologist had privileges, but she went to one where he did not have privileges and then left against medical advice. By the time she called 2 days later, she was told to go to the nearest emergency room.

A defense verdict was returned.
Fetal heart monitoring: mild, moderate, and severe decelerations

This third article in the Fetal Monitoring Mythbusters series reviews the scientific data behind the efforts to classify decelerations

The first column in this series reviewed standard electronic fetal monitoring (EFM) definitions and categories proposed by the National Institute of Child Health and Human Development (NICHD). The second reviewed the evidence underlying atypical variable decelerations. This column will explore the evidence behind the classification of decelerations as mild, moderate, and severe.

Published evidence will be stratified according to the method outlined by the US Preventive Services Task Force (USPSTF), summarized in the Table.

Level I and Level II evidence is derived from randomized, controlled trials or well-designed cohort or case-control analytic studies that include “appropriate attention to potential confounding variables.” Evidence that does not rise to these standards does not meet USPSTF criteria for classification as Level I or Level II and therefore is not capable of establishing statistically significant relationships.

Early in the evolution of EFM, Hon, Kubli and others empirically grouped decelerations into mild, moderate, and severe categories based on depth and duration. Kubli reported fetal scalp blood pH values of 7.29, 7.26, and 7.15 in the setting of mild, moderate, and severe variable decelerations, respectively. However, this study did not distinguish between clinically benign respiratory acidemia caused by elevated Pco₂ and potentially pathologic metabolic acidemia caused by tissue hypoxia, anaerobic metabolism, and accumulation of lactic acid.

Furthermore, it did not attempt to control for important confounding factors such as the presence or absence of normal baseline rate, moderate variability, or accelerations. Consequently, evidence from this study does not qualify as Level I or Level II.

Subsequently, Krebs reported 5-minute Apgar scores <7 in 8.3% of newborns with severe variable decelerations in the last 30 minutes of monitoring compared with only 3.4% of newborns with mild or moderate decelerations. This study did not control for baseline rate, moderate variability, or accelerations, and did not evaluate newborn acid-base status. Therefore, the

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**Table: Hierarchy of research design**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>Level I</td>
<td>Properly conducted randomized controlled trial (RCT)</td>
</tr>
<tr>
<td>Level II-1</td>
<td>Well-designed controlled trial without randomization</td>
</tr>
<tr>
<td>Level II-2</td>
<td>Well-designed cohort or case-control analytic study</td>
</tr>
<tr>
<td>Level II-3</td>
<td>Multiple time series with or without the intervention; dramatic results from uncontrolled experiments</td>
</tr>
<tr>
<td>Level III</td>
<td>Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees</td>
</tr>
</tbody>
</table>

Adapted from US Preventive Services Task Force.

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If you have a question on fetal monitoring, we’d like to hear from you. Those of interest to a wide audience will be answered in future installments of Fetal Monitoring Mythbusters. Send your question to pfurnberg@advanstar.com.
Evidence does not meet the USPSTF definition of Level I or Level II.

Gianpubilo studied 26 newborns with metabolic acidemia (ie, umbilical artery base deficit $\geq 12$ mmol/L) and 30 newborns without metabolic acidemia. In the acidemic group, the second stage of labor was accompanied by significantly more decelerations and a greater area under the baseline during decelerations. This study did not evaluate the classification of decelerations as mild, moderate, or severe.

Newborn outcomes in 1,859 term pregnancies were the focus of a study by Berkus. When accelerations were present, deceleration categories had no differential impact on 5-minute Apgar scores $<7$ or umbilical artery pH values $<7.15$. This study did not control for baseline rate or variability, and did not differentiate between respiratory and metabolic acidemia.

Kazandi studied 96 singleton pregnancies and reported that mild, moderate, and severe decelerations were associated with progressively higher rates of 5-minute Apgar scores $<7$ and umbilical artery pH values $<7.2$. However, this study also failed to control for baseline rate, variability, and accelerations, and did not distinguish respiratory from metabolic acidemia.

**Toward a system of stratification**

Parer sought to demonstrate a relationship between deceleration categories, neonatal acidemia, and low 5-minute Apgar scores. He cited four studies in support of such a relationship. One study stratified EFM tracings according to baseline variability but did not distinguish between respiratory and metabolic acidemia. None of the three remaining studies controlled for baseline rate, variability, or accelerations, and none attempted to distinguish respiratory acidemia from metabolic acidemia.

Consequently, none of these studies demonstrated an independent relationship between deceleration categories and adverse neonatal outcome.

Despite the absence of evidence supporting an independent link with adverse newborn outcome, some authors have suggested that mild, moderate, and severe deceleration categories can separate EFM tracings into five distinct color-coded categories representing the five colors of the US Department of Homeland Security Advisory System, with green as the lowest risk of fetal acidemia, through blue, yellow, and orange, to red, representing the highest risk.

This five-tier system contrasts with the three-tier EFM classification system (Category I, Category II, and Category III) introduced in the 2008 NICHD consensus report. However, the five-tier system has not been shown to stratify neonatal outcomes into five distinct groups.

In one study, 2,472 cases from a single institution were assigned to color-coded categories based in part on mild, moderate, or severe decelerations. Green, blue, yellow, orange, and red categories were associated with neonatal metabolic acidemia (base deficit $>12$ mmol/L) in 6%, 10%, 14%, 23%, and 26% of cases, respectively. However, closer inspection of the data reveals that the blue and yellow groups were associated with statistically similar rates of neonatal acidemia ($P>0.11$) and the orange and red groups were statistically identical ($P>0.99$), yielding only three distinct groups, consistent with the three EFM categories introduced by the NICHD.

In addition, the results of this study are unlikely to be applicable to the general population because the incidence of neonatal metabolic acidemia in the 2,472
single-institution deliveries was 11.6%, more than five times higher than the rate of 0.7% to 2% that would be expected.\(^{15,16}\) In the normal green group, the incidence of metabolic acidemia was 6%, at least three times higher than what would be expected from a mixed group of normal and abnormal EFM tracings.

Another study of 341 deliveries used a modified five-tier classification system to evaluate the risk of neonatal acidemia.\(^{17}\) The five tiers were based, in part, on mild, moderate, and severe deceleration categories. There were no cases in tier five, and the remaining four tiers identified only two statistically distinct risk groups.

**Further investigation needed**

To date, no study has confirmed that mild, moderate, or severe deceleration categories can independently stratify adverse neonatal outcomes. This is underscored by the 2008 NICHD acknowledgement that such systems require further research investigation to establish clinical significance.\(^1\) Intrapartum EFM was incorporated into clinical practice before it was appropriately validated by scientific evidence.

Fortunately, similar errors can be avoided in the future by predicating the adoption of new EFM claims on scientific evidence derived from properly designed analytic research. Classification of decelerations as mild, moderate, and severe has not met this standard. Consistent with the recommendations of the 2008 NICHD consensus report, the safest approach is to avoid assigning undue clinical significance to mild, moderate, or severe deceleration categories.

The next article in this series will explore the myths and realities of existing data regarding intrapartum fetal head compression.

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**The safest approach is to avoid assigning undue clinical significance to mild, moderate, or severe deceleration categories.**

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**REFERENCES**


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**DR. MILLER** is professor of clinical obstetrics, gynecology, and pediatrics in the Division of Maternal-Fetal Medicine, Keck School of Medicine, University of Southern California, and in the Department of Pediatrics, Children’s Hospital Los Angeles. He is a consultant for Clinical Computer Systems and is in partnership with GE Healthcare to promote multidisciplinary fetal monitoring education.
TOVIAZ is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Important Safety Information

TOVIAZ is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients with known hypersensitivity to the drug or its ingredients or to DETROL® (tolterodine tartrate) tablets or DETROL® LA (tolterodine tartrate extended release capsules).

Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine, in some cases after the first dose. Patients should be advised to promptly discontinue fesoterodine therapy and seek immediate medical attention if they experience edema of the tongue, laryngopharynx, or difficult breathing.

TOVIAZ tablets should be used with caution in patients with clinically significant bladder outlet obstruction, decreased gastrointestinal motility, controlled narrow-angle glaucoma, or myasthenia gravis.

The recommended starting dose of TOVIAZ is 4 mg once daily swallowed whole. Based upon individual response and tolerability, the dose may be increased to 8 mg once daily. Doses greater than 4 mg are not recommended in patients with severe renal insufficiency (CLCR <30 mL/min), or in patients taking a potent CYP3A4 inhibitor. TOVIAZ is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).

The most frequently reported adverse events (≥4%) for TOVIAZ were: dry mouth (placebo, 7%; TOVIAZ 4 mg, 19%; TOVIAZ 8 mg, 35%) and constipation (placebo, 2%; TOVIAZ 4 mg, 4%; TOVIAZ 8 mg, 6%).

OAB=overactive bladder.


For more information, visit www.ToviazHCP.com.

Please see brief summary of prescribing information on next page.
The following is a brief summary only; see full Prescribing Information for complete product information.

**INDICATIONS AND USAGE**
Toviaz is a muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

**CONTRAINDICATIONS**
Toviaz is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Toviaz is also contraindicated in patients with known hypersensitivity to the drug or its ingredients, or to tolterodine tartrate tablets or tolterodine tartrate extended-release capsules.

**WARNINGS AND PRECAUTIONS**

**Angioedema:** Angioedema of the face, lips, tongue, and/or larynx has been reported with fesoterodine. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life-threatening.

**Bladder Outlet Obstruction:** Toviaz should be administered with caution to patients with clinically significant bladder outlet obstruction because of the risk of urinary retention.

**Decreased Gastrointestinal Motility:** Toviaz, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility, such as those with severe constipation.

**Hepatic Impairment:** Toviaz has not been studied in patients with severe hepatic impairment and therefore is not recommended for use in this patient population.

**Renal Impairment:** Doses of Toviaz greater than 4 mg are not recommended in patients with severe renal impairment.

**Concomitant Administration with CYP3A4 Inhibitors:** Doses of Toviaz greater than 4 mg are not recommended in patients taking a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, clarithromycin, or fluconazole). No dose adjustments are recommended in the presence of moderate CYP3A4 inhibitors (e.g., erythromycin, diazepam, verapamil, and grapefruit juice). While the effect of weak CYP3A4 inhibitors (e.g., cimetidine) was not examined by clinical study, some pharmacokinetic interaction is expected, albeit less than that observed with moderate hepatic CYP3A4 inhibitors.

**Myasthenia Gravis:** Toviaz should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

**ADVERSE REACTIONS**

**Clinical Trials Experience:** The safety of Toviaz was evaluated in Phase 2 and 3 controlled trials in a total of 2859 patients with overactive bladder, of which 2288 were treated with fesoterodine. Of this total, 782 received Toviaz 4 mg/day, and 785 received Toviaz 8 mg/day in Phase 2 or 3 studies with treatment periods of 6 to 12 weeks. Approximately 80% of these patients had >30 weeks exposure to Toviaz in these trials. A total of 1964 patients participated in two 12-week Phase 3 efficacy and safety studies and subsequent open-label extension studies. In these two studies combined, 554 patients received Toviaz 4 mg/day and 566 patients received Toviaz 8 mg/day. In Phase 2 and 3 placebo-controlled trials combined, the incidences of serious adverse events in patients receiving placebo, Toviaz 4 mg, and Toviaz 8 mg were 1.9%, 3.5%, and 2.9%, respectively. All serious adverse events were judged to be at least possibly related to study medication by the investigator and reported more than once.

**Post-marketing Experience:** The following is a brief summary only; see full Prescribing Information for complete product information.

**Drug-Laboratory Test Interactions:**

**Drug-Laboratory Test Interactions:** Interactions between Toviaz and laboratory tests have not been studied.

**OVERDOSAGE:**
Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. There is no experience with specific overdosage treatments. The symptoms of anticholinergic overdose include dry mouth, constipation, urinary retention, and other anticholinergic pharmacological effects.

**Pediatric Use:** The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients. The safety and effectiveness of Toviaz in pediatric patients have not been established.

**Geriatric Use:** Toviaz should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Nursing Mothers: It is not known whether fesoterodine is excreted in human milk. Toviaz should be administered with caution to nursing mothers.

**ADVERSE REACTIONS:**

**Gastrointestinal disorders:**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Placebo</th>
<th>4 mg/day</th>
<th>8 mg/day</th>
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</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>7.0</td>
<td>18.6</td>
<td>34.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.3</td>
<td>2.0</td>
<td>2.9</td>
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</tbody>
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**Respiratory disorders:**

<table>
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<th>Disorder</th>
<th>Placebo</th>
<th>4 mg/day</th>
<th>8 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry cough</td>
<td>0.5</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.1</td>
<td>3.2</td>
<td>4.2</td>
</tr>
</tbody>
</table>

**Skin disorders:**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Placebo</th>
<th>4 mg/day</th>
<th>8 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>0.5</td>
<td>0.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**System organ class**

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Placebo</th>
<th>4 mg/day</th>
<th>8 mg/day</th>
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<td>N=554</td>
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<tr>
<td>N=566</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N=556</td>
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</table>

ALT - alanine aminotransferase; GGT - gamma-glutamyltransferase

Patients also received Toviaz for up to 3 years in open-label extension phases of one Phase 2 and the Phase 3 controlled trials. In all open-label trials combined, 657, 701, 529, and 105 patients received Toviaz for at least 6 months, 1 year, 2 years, and 3 years, respectively. The adverse events observed during long-term, open-label studies were similar to those observed in the 12-week, placebo-controlled studies, and included dry mouth, constipation, urinary retention, and abnormal pain. Similar to the controlled studies, most adverse events of dry mouth and constipation were mild to moderate in intensity. Serious adverse events, judged to be at least possibly related to study medication by the investigator and reported more than once during the open-label treatment period of up to 3 years, included urinary retention (2 cases), diverticulitis (3 cases), constipation (2 cases), irritable bowel syndrome (2 cases), and electrocardiogram QT corrected interval prolongation (2 cases).

**Post-marketing Experience:** The following events have been reported in association with fesoterodine use in clinical trials and/or postmarketing experience: Blurred vision, uveitis, narrow-angle glaucoma, and only where the potential benefits outweigh the risks.

**Drug Interactions:**

**Antimuscarinic Drugs:** Coadministration of Toviaz with other antimuscarinic agents that produce dry mouth, constipation, urinary retention, anticholinergic effects, or impairs sweating, may increase the frequency and/or severity of such effects. Anticholinergic agents may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility.

**CYP3A4 Inhibitors:** Doses of Toviaz greater than 4 mg are not recommended in patients taking potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and clarithromycin. Coadministration of the potent CYP3A4 inhibitor ketoconazole with Toviaz led to a doubling of the maximum blood concentration (Cmax) and area under the concentration versus time curve (AUC) of 2-hydroxymethylfuroteline (5-HMT), the active metabolite of fesoterodine. Compared with CYP3D6 extensive metabolizers not taking ketoconazole, further increases in the exposure to 5-HMT were observed in subjects who were CYP2D6 poor metabolizers taking ketoconazole.

There is no clinically relevant effect of moderate CYP3A4 inhibitors on the pharmacokinetics of fesoterodine. Following blockade of CYP3A4 by coadministration of the moderate CYP3A4 inhibitor fluconazole 200 mg for 5 days, the average (95% CI) of Cmax and AUC increased by 5% (−14% to 33%) and 2% (−34% to 34%), respectively.

**CYP3A4 Inducers:** No dosing adjustments are recommended in the presence of moderate CYP3A4 inducers, such as rifabutin or rifampin.

**Oral Contraceptives:** In the presence of fesoterodine, there are no clinically significant changes in the plasma concentrations of combined oral contraceptives containing ethinyl estradiol and levonorgestrel.

**Drug Interactions:** Fesoterodine interacts with a CYP2D6 substrate, citalopram, which is metabolized by CYP2D6.

**Use in Specific Populations**

**Pregnancy:** Pregnancy Category C. There are no adequate and well-controlled studies using Toviaz in pregnant women. No drug-related teratogenicity was observed in reproduction studies performed in mice and rabbits. In mice at 6 to 27 times the expected exposure at the maximum recommended human dose (MRHD) of 8 mg based on body surface area (BSA) and oral dose, decreased maternal food consumption in the absence of any fetal effects was observed. In rabbits at 3 times the MRHD (1.5 mg/kg/day), cleft palate was observed at each dose (15, 45, and 75 mg/kg/day), at an incidence within the background historical range. In rabbits treated at 3 to 11 times the MRHD (27 mg/kg/day, oral), incompletely ossified subcutaneous tissue were observed in fetuses (at an incidence within the background historical range). In rabbits at 3 times the MRHD (1.5 mg/kg/day, subcutaneous), decreased maternal food consumption, decreased maternal body weight gain, and decreased maternal body weight at term were observed. Oral administration of 30 mg/kg/day fesoterodine to mice in a pre- and post-natal development study resulted in decreased body weight of the dams and delayed ear opening of the pups. No effects were noted on mating and sexual behavior of the F1 males or females

**Pediatric Use:** The pharmacokinetics of fesoterodine have not been evaluated in pediatric patients.

ALT - aspartate aminotransferase; GGT - gamma-glutamyltransferase
IN VITRO MATURATION OF OOCYTES

Improving the odds in infertile patients

Subfertile women for whom in vitro fertilization with controlled ovarian hyperstimulation has been unsuccessful or impractical have another option for achieving pregnancy: in vitro maturation of oocytes

BY AYSE SEYHAN, MD; BARIS ATA, MD; SEANG LIN TAN, MD

Currently, in vitro fertilization (IVF) is the most successful technique for the treatment of subfertility. A major advance that led to higher pregnancy rates was the introduction of controlled ovarian hyperstimulation (COH) for the induction of multiple follicle development followed by the simultaneous transfer of multiple embryos. Unfortunately, controlled COH comes at a cost because there can be financial and psychological burdens and health risks. Direct cost of medications and indirect costs, such as the time commitment and the inconvenience associated with intensive monitoring, are major limitations of COH. The most important disadvantage of COH is ovarian hyperstimulation syndrome (OHSS), a potentially life-threatening complication. In addition, it has been suggested that COH has detrimental effects on developing oocytes and the embryos derived from these oocytes.¹

In vitro maturation (IVM) of oocytes is an established technique that provides a treatment option for subfertile patients without the risks and costs associated with COH. IVM differs from IVF in two ways: There is no need for COH with exogenous gonadotropins, and oocytes are collected before they attain full maturity. Immature oocytes can resume meiosis in vitro when removed from the meiotically inhibiting environment of the small antral follicles. Collection and IVM of these already existing immature oocytes provide multiple mature oocytes that can be fertilized in vitro.

Take-home messages

- For subfertile women, in vitro maturation is an option with less cost and risk than controlled ovarian hyperstimulation.
- Patient age, number of oocytes collected, and presence of IVM oocytes at collection are key predictors of pregnancy after IVM.
Both clinical and laboratory aspects of IVM have improved continuously since 1991, when the first live birth following transfer of embryos derived from immature oocytes collected from unstimulated ovaries was reported.

The first successful IVM cycles combined with preimplantation genetic screening and percutaneous testicular sperm aspiration have been reported by our team. IVM has enabled successful treatment of patients with empty follicle syndrome in previous stimulated IVF cycles. Patients can undergo several IVM cycles; we previously reported a series of patients who achieved repeated live births with IVM treatment. Further, in vitro-matured oocytes and the embryos derived from them can be successfully cryopreserved. Currently, IVM success rates exceed 35% per cycle in appropriately selected patient groups.

IVM cycle monitoring and management

At the McGill University Health Centre and Montreal Reproductive Centre, IVM cycle monitoring starts with a baseline ultrasound scan performed in the early follicular phase of the menstrual cycle, between days 2 to 5 of a natural menstrual cycle or a withdrawal bleed, induced with the use of a progestogen in amenorrheic women. The aim of the baseline scan is to rule out the presence of an ovarian cyst or uterine pathology and measure the number of antral follicles. The antral follicle count seems to be the single most important predictor of the
number of retrievable oocytes. The next scan is performed between days 6 and 8 of the cycle. When the largest follicle reaches 10 mm to 12 mm in diameter and the endometrial thickness is at least 6 mm, a single dose of 10,000 IU human chorionic gonadotropin (HCG) injection is given. Oocyte collection is scheduled at 38 hours after HCG injection.

We have reported that the implantation and clinical pregnancy rates were the highest in cycles when the leading follicle was 12 mm at the day of HCG administration. In HCG-primed IVM cycles compared with nonprimed IVM cycles, the rate of oocytes with dispersed cumulus cells was found to be higher, which resulted in higher blastocyst development.

When the endometrial thickness is less than 6 mm on the day of the second scan and the leading follicle also is small, we delay HCG administration/oocyte collection. A short course of gonadotropins is added to stimulate the growth of both follicles and the endometrium. We administer 150 IU/day to 300 IU/day of human menopausal gonadotropin to this group of patients. The duration of follicle-stimulating hormone priming depends on the patient’s response varying between 3 and 6 days.

The key point is to reach the follicle size of 10 mm to 12 mm to yield 1 or 2 mature oocytes on the day of collection, which results in better pregnancy rates. However, in IVF cycles the aim is to reach an 18-mm follicle size to enable us to collect the maximum number of mature oocytes.

**Oocyte collection procedure**
The oocyte retrieval is done under transvaginal ultrasound guidance and the principles are mostly the same as those for IVF with a few modifications in both the technique and equipment. A smaller-gauge needle (19 G-20 G) with a shorter bevel is used. The aspiration pressure is lowered to 75 mm Hg to 80 mm Hg to minimize the risk of oocyte denudation because immature oocytes need the presence of surrounding granulosa cells for nuclear maturation. Multiple needle punctures are usually required because lower aspiration pressures and thick aspirate may block the fine-bore needle lumen.

**Embryology laboratory procedures**
The initial oocyte identification procedure is similar to conventional IVF: The follicular aspirate is examined under a stereomicroscope for cumulus-oocyte complexes. We also filter the follicular aspirate through a nylon mesh strainer with 70 μm pores. The filtered aspirate is reexamined under stereomicroscope after washing with N-(2-Hydroxyethyl) piperazine-N’-(2-ethanesulfonic acid) buffered human serum albumin containing medium. This facilitates identification of small, immature oocytes. Maturation status of the oocytes is assessed immediately after collection. Oocytes reaching the MII stage on the day of collection are denuded and fertilized together with any in vivo-matured oocytes, while immature oocytes are cultured in IVM medium and evaluated periodically. Intracytoplasmic sperm injection (ICSI) has been commonly practiced in IVM cycles because of a theoretical concern of zona pellucida hardening during the in vitro culture period. Another reason for preferring ICSI to IVF in IVM cycles is that some immature oocytes are denuded for assessment of polar-body extrusion. Oocytes devoid of cumulus cells may have a lower in vitro fertilization rate as a result of decreased chemotactic potential for sperm in the medium.

Culture conditions for fertilized oocytes and cleavage-stage embryos derived from in vitro-matured oocytes are the same as those in IVF cycles.

**Embryo transfer**
The timing of embryo transfer and the number of embryos to be transferred are based on the quality of available embryos on day 3 and the patient’s age.

**Luteal-phase support**
The luteal-phase support protocol employed in our IVM program includes 600 mg/day vaginal micronized progesterone and 6 mg/day or 12 mg/day oral estradiol valerate. Estrogen is started on the day of oocyte collection and progesterone supplementation is postponed to the day of fertilization for luteal-phase support. Luteal-phase support is continued until 12 weeks’ gestation if pregnancy is achieved.
Pregnancy rates
Female age, number of oocytes collected, and presence of in vivo-matured oocytes at the time of collection are the most important predictors of pregnancy in an IVM cycle.5-7 Young women with polycystic ovaries (PCO) seem to be the best candidates for IVM treatment. With the initiation of our modified IVM protocol, we achieved a greater than 50% clinical pregnancy rate in such cycles in young women with polycystic ovaries.15 However, for women between 35 and 40 years, implantation and clinical pregnancy rates were 10.1% and 29.3%, respectively, in the same period.11

Pregnancy loss
We recently demonstrated similar aneuploidy rates in IVM embryos and IVF embryos.14 Once pregnancy is achieved, pregnancy outcome of IVM treatment is equivalent to IVF treatment outcome.

In a retrospective analysis of 1,581 women who had a positive pregnancy test following assisted reproduction treatment (ART) with IVM, IVF, or ICSI in our unit during a 5-year period, pregnancy loss rates seem similar in IVM and conventional IVF (17.5% for IVM pregnancies, 17% for IVF, and 18% for ICSI pregnancies, respectively; P=0.88).15 The clinical miscarriage rate was significantly higher in IVM pregnancies (25.3%) than in IVF (15.7%) and ICSI (12.6%) pregnancies (P=0.0049), but the difference can be attributed to the higher incidence of polycystic ovarian syndrome (PCOS) among IVM patients. Although only 8% and fewer than 1% of women in the IVF and ICSI groups had PCOS, respectively, the incidence of PCOS in the IVM group was 80%. The clinical miscarriage rates in women with PCOS were statistically similar after IVM and after IVF (24.5% vs 22.2%; P=0.72).

Obstetric outcome and congenital abnormalities
Cesarean delivery rate, birth weight, incidence of low birth weight and very low birth weight infants, and Apgar scores were not found to be different between infants conceived with IVM and IVF. There is no demonstrated increase in incidence of congenital and chromosomal abnormalities in children conceived after IVM. Compared with spontaneous conceptions, the observed odds ratios (ORs) for any congenital abnormality were 1.42 (95% confidence interval [CI], 0.52–3.91) for IVM, 1.21 (95% CI, 0.63–2.32) for IVF, and 1.69 (95% CI, 0.88–3.26) for ICSI, respectively.16 The follow-up data on IVM children’s long-term health outcome revealed physical growth and neuromotor development similar to that of spontaneously conceived children.17

Potential advantages of IVM in different patient groups
High responders to ovarian stimulation
Women younger than 35 years old with high antral follicle counts achieve the highest pregnancy rates with IVM. This group of patients also possesses a high risk of OHSS following COH. Women with PCO or PCOS undergoing IVM may benefit from total elimination of OHSS risk and may achieve pregnancy rates comparable to conventional IVF. In 2009, we achieved an embryo implantation rate of 19.5% and a clinical pregnancy rate per embryo transfer of 55.2% in women with PCO or PCOS with an average age of 32.6±3.6 years.18

Normal responders to ovarian stimulation
To achieve high pregnancy rates in IVF cycles, multiple embryos are transferred in each cycle, resulting in increased incidence of multiple pregnancies. In the year 2006 approximately one-third of all live births following ART in the United States were the result of multiple-infant deliveries.19 Increased awareness of the high mortality and handicap associated with iatrogenic multiple pregnancies has led to an emerging trend internationally to reduce the number of embryos transferred. Single-embryo transfer is promoted through professional guidelines or legal restrictions.

This fact questions the additional benefit of COH in ART cycles. IVM has the potential to provide similar pregnancy rates following fresh embryo transfer with IVF if single-embryo transfer is implemented to the routine practice.13 At least 1 in vivo-matured oocyte is retrieved in a substantial proportion of IVM cycles. The possibility of repeating treatment in consecutive menstrual cycles in case of

**POWER POINTS**

- When follicles are 10 mm to 12 mm in size, 1 to 2 oocytes can be retrieved.
- Oocytes without cumulus cells decrease the likelihood that IVF will be successful.
- Young women with polycystic ovaries are the best candidates for IVM.
treatment failure can be considered another advantage of IVM.

**Poor responders to gonadotropin stimulation**

Some women produce very few follicles after COH IVF treatment. Various interventions have been investigated including the use of high doses of gonadotropins, repeating IVF with a different stimulation protocol, and adjuvant therapies to improve IVF outcome. However, most of these strategies have limited success. With the recognition of side effects of COH and physiology of follicular recruitment, the benefits of other stimulated cycles or using high doses of gonadotropins are questionable. IVM may provide a better option in such cases.

IVM in an unstimulated cycle or combined with natural-cycle IVF may provide a reasonable approach because it is more patient friendly and less drug oriented. In fact, in 8 women with a poor response, defined as 4 or fewer growing follicles or 4 or fewer oocytes collected in a previous stimulated IVF cycle, we achieved a similar transfer in the subsequent IVM cycle. Six women reached embryo transfer (75%), and 1 achieved a live birth, yielding a 16.7% live birth rate per transfer in this small group of genuine poor responders.20

**Oocyte donation**

Oocyte donation is a valuable option, and the clinical indication for it is expanding. Oocyte donors routinely undergo COH in order to maximize the number of mature oocytes available for donation; however, these donors are young and have high antral follicle count, which places them at high risk of OHSS.

The inconvenience of the numerous injections required and the long-term risks associated with fertility medications and repeated stimulated cycles create reluctance in some potential donors. Oocyte donation cycles are a good target for IVM because young women with high antral follicle counts have a high number of oocytes and achieve good pregnancy rates. Avoiding ovarian stimulation decreases the risks and inconvenience for oocyte donors.

We collected an average of 12.8 immature oocytes from 12 oocyte donors with a mean age of 29 years. Sixty-eight percent of the oocytes matured in vitro and 62 embryos were available for transfer to 12 recipients with a mean age of 37.7 years. On average, 4 embryos were transferred (range, 2-6) and a clinical pregnancy rate of 50% was achieved.21

**Fertility preservation**

IVF and embryo cryopreservation is the only method of female fertility preservation approved by the American Society of Clinical Oncology and the American Society of Reproductive Medicine.

COH and embryo cryopreservation appear to be the most suitable approach for patients who have a male partner, sufficient time to complete COH, and do not have estrogen-sensitive malignancies.

IVM expands the fertility preservation options for women who are not suitable for COH for various reasons. These patients may undergo immature oocyte collection and cryopreserve resultant embryos. IVM is a reasonable option for patients with limited financial resources; in addition, it eliminates the inconvenience of injections. Moreover, IVM enables oocyte retrieval at any phase of the menstrual cycle and completion of the fertility preservation procedure in 2 to 10 days subsequently, preventing a delay in treatment of the primary disease.22

We reported 3 women without male partners seeking fertility preservation prior to chemotheraphy, who first presented in the luteal phase of their menstrual cycle and who were scheduled to undergo immediate gonadotoxic treatment.23 Five to 7 immature oocytes were recovered with luteal-phase oocyte retrieval from these patients. Following IVM of the immature oocytes, 3 to 5 oocytes matured and were cryopreserved. Two of these 3 women later underwent 1 and 2 more collections, respectively, in the follicular phase of the next cycle(s) and additional immature oocytes were vitrified following IVM.

Similar maturation and fertilization rates recently have been reported for immature oocytes collected in the follicular or luteal phase of the menstrual cycle.24

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<table>
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<tr>
<th>Ingredients</th>
<th>RepHresh† Vaginal Gel</th>
<th>Replens™ Vaginal Moisturizer</th>
<th>K.Y.™ Long Lasting Vaginal Moisturizer</th>
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† RepHresh and Replens are registered trademarks of Li'l Drug Store Products. ** K.Y. is a registered trademark of McNeil-PPC, Inc. Biotene is trademark owned by GlaxoSmithKline
from ovarian biopsy specimens and can be vitrified following IVM because cryopreserving ovarian tissue saves the primordial and primary follicles and immature oocytes within the antral follicles, allowing retrieval from the tissue for IVM. This combination of ovarian tissue cryobanking and IVM represents a new strategy for fertility preservation, providing previously unavailable options for some patients and improving the services provided by a fertility preservation program.23

**IVM alternative to ovarian stimulation with gonadotropins coupled with intruterine insemination**

Treatment with COH combined with intruterine insemination (IUI) has been applied empirically for different types of infertility. Typically the treatment involves 8 to 10 days of gonadotropin injection, several ultrasound scans, and insemination. The pregnancy rate is 10% to 15%.

The major complication of this treatment is a multiple pregnancy, which may occur in up to 30% of cases. However, as a result of limitations in the number of embryos to be transferred and efforts to promote the transfer of single embryos in IVF cycles, the incidence of multiple births is less than 10% in IVF or IVM cycles. Most multiple pregnancies in fertility treatment are attributable to the use of gonadotropins in IUI cycles.

By comparison, IVM treatment involves 2 scans, oocyte collection, and embryo transfer with a 30% to 40% clinical pregnancy rate per cycle.24 The cumulative pregnancy rate will be higher for patients with spare embryos. Multiple pregnancy rates with single-embryo transfer range from 0% to 4.5%; in other words, IVM with single-embryo transfer reduces the likelihood of multiple pregnancy by 94%.25

For several reasons, IVM may replace ovarian stimulation with IUI. In Canada, the cost of a stimulated IUI currently is $2,000 per cycle whereas IVM costs $4,000. If IVM costs decline over the next few years, it will be a cost-effective alternate to IUI by reducing the multiple pregnancy rates and giving subfertile women a better chance of becoming pregnant.

**Social oocyte freezing**

Because fertility declines sharply with age, women over the age of 35 who have delayed childbearing may face difficulty in conceiving and increased risk of miscarriage and delivering a child with congenital abnormalities.

Although embryo cryopreservation is the standard recommendation for fertility preservation, oocyte cryopreservation overcomes the limitation of the need for a contribution of a male partner, and in women younger than 35, it allows them to avoid the obstacles of age-related subfertility and gives them the opportunity to become pregnant at their discretion.

Data indicate that approximately 20 frozen oocytes are needed to achieve a satisfactory clinical pregnancy rate.26 Multiple COH IVF cycles are needed to achieve this number of oocytes; however, IVM can be offered to these patients with the advantages of lower cost, less medication, simplicity, and total elimination of the risk of OHSS.

**Conclusion**

Although IVM is a relatively new technology, it plays an important role for patients who are at high risk of OHSS, those with recurrent unexplained IVF failures, poor responders, and those who are facing imminent gonadotoxic chemotherapy and who desire fertility preservation.

Currently, IVM has the advantage over conventional IVF because it reduces the use of gonadotropins and cost to patients and eliminates ovarian hyperstimulation. In addition, it is the most patient-friendly treatment in reproductive medicine.

With further improvement in understanding oocyte maturation and an increase in success rates, IVM represents an attractive treatment option for subfertile patients.27

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**POWER POINTS**

Immature oocytes can be collected from ovarian biopsy specimens and vitrified following IVM.

Most multiple pregnancies resulting from ART can be attributed to the use of gonadotropins in IUI cycles.

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**DR. SEYHAN and DR. ATA** are clinical research fellows in the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, McGill University Health Centre, Montreal, Canada. **DR. TAN** is the James Edmund Dodds Professor, Department of Obstetrics and Gynecology, McGill University Health Centre, and Medical Director of the Montreal Reproductive Centre at the McGill University Health Centre. None of the authors reports a conflict of interest with respect to the content of this article.
REFERENCES


17P: Choosing a quality compounding pharmacy

In terms of cost, customization, and convenience, compounding pharmacies can be an effective solution to meeting certain patients’ needs, for example, 17P. This article offers advice on finding a compounding pharmacy to which you can confidently refer patients.

BY JOE CABALEIRO, RPH

The words “compounding” or “compounded” are words heard more frequently in everyday medical practice and hospitals. What is compounding, and how does it benefit patients? The intent of this article is to define what a compounding pharmacy is, how compounding can benefit patients, and to assist the reader in selecting a compounding pharmacy. Because compounded 17-alpha hydroxyprogesterone (17P) recently has been the focus of attention, this article will primarily address compounded 17P. However, other compounded formulations are often used in obstetrics and gynecology.

Compounding is the traditional art of preparing medications to meet a patient’s specific needs. Since the beginning of the pharmacy profession, medications have been custom prepared; only in the last few decades have mass-produced manufactured products become the primary source of medications.

Take-home messages

- Until fairly recently all pharmaceuticals were compounded rather than mass produced.
- Compounding pharmacies are regulated on federal and state levels, use products from FDA-regulated sources, must meet federal quality standards, and have state-licensed pharmacists.

The National Association of Boards of Pharmacy (NABP) defines compounding as follows:

Compounding means the preparation, mixing, assembling, packaging or labeling of a drug or device (i) as a result of a practitioner’s prescription drug order or initiative based on the pharmacist/patient/prescriber relationship in the course of
Compounding may bring to mind an image of a pharmacist leaning over a balance or mixing drugs in a mortar and pestle. But today’s sophisticated, sterile compounding pharmacies look more like modern laboratories, with highly precise electronic balances and clean rooms with air many times purer than a typical operating room.

Although commercially available manufactured products are an effective way to treat the majority of patients, compounding—the creation of custom-made medications in the pharmacy—may be the solution to some medication problems, such as patient sensitivity to inactive ingredients, drug shortages, commercially unavailable medications, discontinued drugs, or doses that are not commercially available.

**Allergy/intolerance**

Some patients may respond to a manufactured medication but may not tolerate a particular excipient (ie, pharmacologically inactive carrier), dye, or base. This is not uncommon in medications applied to sensitive vaginal mucosa. A compounding pharmacy can prepare an alternative form of the medication using a different base or omitting ingredients to which the patient is sensitive. The pharmacy also can incorporate the active ingredient into a base the patient is known to tolerate.

**Drug shortages**

When a medication is not available from the manufacturer, a compounding pharmacy may be able to prepare an alternative preparation to meet the patient’s needs. Recently, desiccated thyroid tablets used to treat hypothyroidism were in short supply due to manufacturing problems. Compounding pharmacies were able to obtain the active pharmaceutical ingredient and use it to prepare dosage forms to meet patients’ needs during the shortage.

**Commercially unavailable medications**

Examples of compounded medications used in obstetrics and gynecology include progesterone suppositories for the treatment of infertility and boric acid capsules and suppositories used vaginally for treatment of *Candida* vaginitis. “All Purpose Nipple
Key criteria for selecting a 17P compounding pharmacy

Licensure and accreditation
- Can the pharmacy demonstrate it is licensed in the state(s) in which it does business?
- Is the pharmacy accredited by the Pharmacy Compounding Accreditation Board?

Sourcing and validating ingredients
- Can the pharmacy demonstrate ingredients are purchased from an FDA-licensed distributor?
- Can the pharmacy provide a certificate of analysis for each ingredient in its compounded 17P?

Preparation
- Is the 17P prepared using the same formulation as Delalutin?
- Are the vials terminally sterilized using dry heat?

Quality assurance
- Can the pharmacy produce a certification document demonstrating its clean room is certified to meet clean air standards?
- Does the pharmacy perform regular media challenge testing of its staff?
- Does the pharmacy perform regular glove-fingertip testing of its staff?

Quality control
- Can the pharmacy demonstrate sterility test results for each batch of 17P?
- Can the pharmacy demonstrate endotoxin test results for each batch of 17P?
- Can the pharmacy demonstrate potency test results for each batch of 17P?

Ointment” or “Dr. Newman’s Nipple Cream” are common names for compounded combinations of mupirocin, betamethasone, and miconazole or clotrimazole used to treat sore and infected nipples during breastfeeding. Pharmacists also prepare specialized medications combining topical amitriptyline, gabapentin, lidocaine, and estradiol for the treatment of vulvodynia.1,3

Discontinued medications
Manufacturers may discontinue making a medication for various reasons, such as economic considerations. In 1956, 17P was approved under the trade name Delalutin. Bristol-Myers Squibb stopped manufacturing the drug in 1999. In 2003, the Meis, et al trial was published; subsequently, at the request of prescribers, compounding pharmacies began to prepare compounded 17P.4

Regulation of compounding pharmacies
Compounding pharmacies are regulated on both national and state levels. Compounded medicines are prepared using ingredients that must come from US Food and Drug Administration (FDA) licensed and inspected repackers. These repackers must in turn obtain ingredients from FDA-registered manufacturers. In some cases, these manufacturers are the same ones that supply manufacturers of brand-name pharmaceuticals. The FDA also has authority to inspect any pharmacy’s facilities, equipment, and ingredients. In addition, the FDA and the Federal Trade Commission have authority over false and misleading marketing practices by both retail and compounding pharmacies.

Compounding pharmacists should follow national standards and guidelines set by the US Pharmacopeia (USP). Since 1820, USP has set standards for the quality, purity, identity, and strength of medicines, food ingredients, and dietary supplements.5 The USP has rigorous standards for compounding both sterile and nonsterile medications, and the USP Standards are considered a “Standard of Care” that can be legally enforced by boards of pharmacy and the FDA (See “Key criteria for selecting a 17P compounding pharmacy”).

State boards of pharmacy license pharmacists and pharmacies. State pharmacy laws, enforced by these boards, govern the processes and equipment pharmacists use to prepare compounded medicines. Since 1995, many state boards of pharmacy have developed comprehensive regulations for compounding. In several cases, this includes requiring compliance with the USP’s compounding standards. States also have requirements that mandate recordkeeping, labeling, and proper procedures for sterile compounding and other aspects of pharmacy practice.

The USP, along with six other national pharmacy organizations, is a founding member of the Pharmacy Compounding Accreditation Board (PCAB; http://www. pcab.info). PCAB sets quality standards and serves as a voluntary accrediting organization for compounding pharmacies. It also verifies that accredited pharmacies comply with quality assurance, control, and improvement standards through the use of on-site surveys performed by experienced.
Bio-Oil® is a skincare oil that helps improve the appearance of scars, stretch marks and uneven skin tone. It contains natural oils, vitamins and the breakthrough ingredient PurCellin Oil™. For comprehensive product information and results of clinical trials, please visit bio-oil.com. Bio-Oil is the No.1 selling scar and stretch mark product in 11 countries. $11.99 (2fl.oz.).
Compounding of 17-alpha hydroxyprogesterone

Compounding of 17P involves several important steps.

Sourcing and validating ingredients

A quality final preparation begins with acquisition of quality ingredients. The vast majority of compounding pharmacies purchase their ingredients from FDA-licensed distributors whose facilities are licensed and inspected by the FDA, although a pharmacy may also legally purchase directly from an FDA-registered manufacturer and perform the quality verifications described in this article independently. FDA-licensed repackers purchase ingredients directly from manufacturers that are required to be registered with the FDA.

When the distributor receives an ingredient, it must verify the purity of each batch by submitting a sample for laboratory analysis. The laboratory generates a certificate of analysis (COA) that confirms that a regulated pharmaceutical ingredient meets its product specification. Distributors make the COA available to the compounding pharmacy, and the pharmacy can use the COA to document and verify the quality of the ingredients used. When evaluating the quality of a compounding pharmacy, ask whether the pharmacy can provide a COA for all ingredients in the compounded 17P.

Preparation

The initial studies to establish the use of 17P in preventing preterm birth were conducted with Delalutin. Delalutin contained a straightforward formulation consisting of 250mg/mL of 17P in castor oil, with 46% benzyl benzoate as a solvent and 2% benzyl alcohol as a preservative. Subsequent studies have used the same formulation. Compounded 17P should be prepared using this same formulation because it has a history of safety and efficacy.

17P injection is an oil-based liquid. It can be sterilized in one of two ways: cold sterilized by passing it through a 0.2 micron filter or dry-heat sterilized in a convection oven. Dry-heat sterilization is preferred for two reasons:

1) Dry-heat sterilization allows the 17P to be “terminally sterilized”: ie, placed into the final dispensing container and then sterilized. Terminally sterilized medications represent the lowest-risk sterile pharmaceutical products. The preparation is sterilized in its final container so there is no risk of contamination from manipulation after sterilization.

2) Dry-heat sterilization is considered more effective than sterilization by filtration. Sterility assurance level (SAL) is a term used in microbiology to describe the probability of a single unit being nonsterile after it has been subjected to the sterilization process. Dry-heat sterilization is considered to have an SAL of 10^-6; that is, if one million units are sterilized, there will be only one sterilization failure. In contrast, sterilization by filtration has a SAL of 10^-6: one sterilization failure per 1,000 units sterilized. This provides two more parameters for evaluating the quality of a compounding pharmacy: Does the pharmacy compound 17P using the same formula as Delalutin, and does the pharmacy use dry heat to terminally sterilize its 17P?

The USP publishes written standards for medicines and their ingredients. These standards are legally enforceable and are used by regulatory agencies and manufacturers to ensure that pharmaceuticals are of the appropriate identity, strength, quality, purity, and consistency. Included in these standards is a chapter known as “USP <797>” that outlines conditions and practices sterile compounding pharmacies should follow to ensure and verify the quality of their...
preparations. The USP <797> standards are a lengthy, comprehensive document that incorporates critical requirements with which the top-tier compounding pharmacies are able to demonstrate compliance.

For compounded 17P, it is critical to select a pharmacy that is fully USP <797>-compliant. USP <797> is legally enforceable by the FDA, many state boards of pharmacy also require compliance, and pharmacies accredited by the PCAB have been surveyed and deemed compliant.

**Facility**

When preparing any sterile product, there is a risk of airborne microbiological contamination. The International Organization for Standardization (ISO) has published standards for airborne particulates. ISO classification refers to the number of particles 0.5 μm or larger per cubic meter. ISO-5 air contains no more than 3,520 particles per cubic meter. USP <797> requires that a pharmacy prepare 17P in an ISO-5 environment located within an ISO-7 environment clean room. For comparison, typical room air is ISO class 9 and contains 35.2 million particles 0.5 μm or larger per cubic meter. Alternatively, USP <797> permits the preparation of 17P in a compounding aseptic isolator (a “glove box”). These devices also contain an ISO-5 environment, and must be located in an ISO-8 clean room.

**Media challenge testing**

This procedure involves preparing simulated sterile compounds with a bacterial growth media that is very sensitive to any contamination. Regular testing is used to demonstrate that sterile compounders have been able to maintain asepsis throughout a compounding procedure.

**Glove fingertip testing**

The hands of medical personnel represent a potential risk to the patient in every healthcare setting. For example, improperly disinfected gloves can present an infection risk to the patient through direct contact with tissues during surgery. Similarly, manipulation of any sterile injection during preparation can present an indirect risk to the patient from a contaminated preparation. The glove-fingertip test involves culturing the fingertips of the gloves worn by compounding personnel to validate that they are able to don and work with them in an aseptic environment without contaminating the preparations.

**Sterility and endotoxin testing**

Whether a medication is manufactured or compounded, there is the risk for bacterial and endotoxin contamination if proper preparation techniques are not followed. Both bacterial contamination and endotoxins can cause adverse reactions in humans ranging from fever and chills to irreversible and fatal septic shock. The severity of an endotoxin reaction depends on the level of endotoxins in the injected product and the route of administration.

The intrathecal route of administration is associated with the highest risk for the most severe reactions; the most common reactions for the intravenous and intramuscular routes include fever and chills. Microbiological and endotoxin contamination can be introduced during the manufacture of pharmaceutical ingredients, during preparation and packaging, or as a result of using single-dose containers that lack appropriate bacteriostatic agents in a medical office setting. Sterility and endotoxin testing of compounded preparations can be performed in-house or by an outside laboratory.

**Potency testing of the finished preparation**

Finished preparation testing involves submitting a sample to an outside laboratory to determine the actual strength of the finished preparation. In the case of 17P, the USP/NF allows a variance of ±10% of the labeled amount.

Four key questions about quality can assist your objective evaluation of a compounding pharmacy:

- Can the pharmacy produce potency, sterility, and endotoxin test results for each batch of 17P it dispenses?
• Does the pharmacy terminally sterilize its 17P vials?
• Does the pharmacy prepare its 17P in a clean room or isolator conforming to USP <797> requirements?
• Does the pharmacy perform media challenge testing and fingertip testing of its sterile compounding personnel?

Legal concerns
A frequent question regarding 17P is whether it can be legally compounded. If so, can other brand-name, FDA-approved drugs be legally compounded?

Brand-name, FDA-approved products are typically granted a 17-year patent. The manufacturer owns the exclusive right to manufacture and market the product in the United States. In the case of the FDA-approved 17P injection Makena (KV Pharmaceuticals, St. Louis, Missouri), the circumstances are somewhat different. Makena was brought to the market as an orphan drug. The active ingredient in it, 17-alpha hydroxyprogesterone, was once patented and marketed as Delalutin. That patent has now expired. Therefore, 17P is not a patentable ingredient; however, the manufacturer was granted 7-year exclusivity to market the commercial version of the drug.

Pharmacies are not manufacturers, and therefore cannot manufacture or market a commercial version of 17P. However, they still can fill prescriptions for compounded 17P because 17P is not patented. On March 30, 2011, the FDA issued a press release stating that it would not take enforcement action against pharmacies that compound 17P on the basis of a valid prescription for an individual patient.10

Conclusion
There has been a great deal of controversy surrounding the introduction of a manufactured version of the 17P injection. This is a rare instance where prescribers have a choice of a newly introduced commercial product or a compounded preparation they already may have been using for years.

One positive aspect of this development is that it has highlighted the need for providers to ensure that if they are prescribing compounded 17P, they use objective measures to verify that they are working with a high-quality compounding pharmacy. Prescribers are encouraged to visit the compounding pharmacy that provides their 17P, and, using the tools and knowledge presented in this article, validate the quality of their compounded 17P.11

MR. CABELLEIRO is Executive Director of the Pharmacy Compounding Accreditation Board, Washington, DC. He has no conflicts of interest to disclose with regard to the content of this article.

REFERENCES
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Is there a doctor on board? What to do in the case of an in-flight medical emergency

Managing a patient with a medical emergency while on a commercial airline flight can be a challenge. Physicians have a moral and ethical duty to help if possible, but you’re not in this alone. Help is available from the flight crew, other passengers, and ground-based medical teams.

BY STEVEN M. SELBST, MD

A ny physician who agrees to assist with a medical request on an airplane has a difficult task. He or she must try to provide care with an incomplete history because this patient will not be known to the clinician and may not even be able to relate a history. The responder will also have to make medical decisions with an incomplete examination, because the patient will not be undressed and often is in a sitting position.

Furthermore, the equipment available on the airplane is likely to be minimal compared with what the clinician is accustomed to having available in a medical office or emergency department. The emergency must often be managed in the cramped quarters of a narrow aisle in an overcrowded airplane. Add the inevitable engine noise, and the situation is even more difficult. Finally, the responder sometimes lacks the knowledge and confidence to handle many emergencies (eg, when an ob/gyn must assist with an elderly passenger).

How often do medical emergencies occur on an airplane?
In-flight emergencies are common. One recent study estimates that a medical event occurs in 1 of 14,000 passengers worldwide; another study estimated 1 medical event for every 11,000 passengers. A 2000 Federal Aviation
Agency (FAA) study involving ground-based medical support found a rate of 13 medical events per day on US domestic flights. Most of the medical events that occur in the air are minor in nature. Less than half of the medical events in the air are serious enough to require ground-based medical assistance. Only 13% are serious enough for the pilot to change course.

There is no standardized reporting system, so minor emergencies often are not reported. Some believe that we need a standardized reporting system for all in-flight emergencies with debriefing of all those involved. This might improve the ability of the airline industry and physicians to better manage these events in the future.

Which emergencies are likely to occur?
Most medical events onboard a commercial flight are not serious. About 65% are related to preexisting problems, 28% to new medical conditions, and 7% to traumatic injury, such as a burn from a hot drink or an injury from falling luggage. Fainting, dizziness, and hyperventilation are the most common events. Cardiac, neurologic, and respiratory problems are the most common serious events and account for most flight diversions. Chest pain, asthma, and gastrointestinal (GI) complaints also are common.

Deep vein thrombosis with resulting pulmonary embolism is a concern for passengers on long flights, although the incidence of this is unknown. Thromboembolism is more likely on flights 8 hours or longer, and it occurs more in passengers who have nonaisle seats where they are less likely to move around the cabin. However, thromboembolism does not seem to be more likely in the economy seats that may have less leg room than business class.
Cabin pressure may contribute to some medical emergencies on airplanes.1 Cabin pressure on commercial aircraft is adjusted to that found at 5,000 to 8,000 feet above sea level. For most people, this is not a problem, but for those with cardiopulmonary disease, this can increase the risk of hypoxia. As a result of the atmospheric pressure in the cabin, arterial oxygen partial pressure (PaO₂) decreases from 95 mmHg to 60 mmHg in a normal person.1,15 A 3% to 4% reduction in oxyhemoglobin saturation may be found, which would be trivial in a healthy person but could lead to significant hypoxia in someone with underlying cardiopulmonary disease or compromise. Newer A380 airuses have a standard cabin altitude of 6,000 feet, improving oxygen levels compared with other aircraft.11

TABLE 1 Medications in the emergency medical kit

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<td>Dextrose 50%, injectable 50 mL (or equivalent)</td>
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<td>Nitroglycerin tablets</td>
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<td>Major analgesic, injectable or oral</td>
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<td>Sedative anticonvulsant, injectable</td>
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<td>Antiemetic, injectable</td>
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<td>Bronchodilator (inhaler)</td>
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<td>Atropine, injectable</td>
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<td>Corticosteroid, injectable</td>
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<td>Diuretic, injectable</td>
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<td>Oxytocin</td>
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<td>0.9% saline (min. 250 mL)</td>
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<tr>
<td>Acetylsalicylic acid, oral</td>
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<td>Oral beta blocker</td>
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<tr>
<td>List of meds (trade and generic)</td>
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<tr>
<td>Basic instructions</td>
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</table>

Information from Ballough JG,19 and Thibeault C, et al.19

Available for 85% of reported in-flight emergencies.16 The 2000 FAA study found that 69% of all in-flight emergencies occurring aboard US aircraft between 1996 and 1997 were attended by a health professional: a physician (40%), a nurse (25%), or a paramedic (4%).3

In another study, a doctor responded in 75% of occurrences, and nurses and paramedics responded in 11%.7 Some airlines now work in conjunction with remote emergency response centers (ie, MedAire, MedLink) with 24-hour services staffed by board-certified emergency physicians.6,10,11,17 Detailed information such as vital signs or electrocardiogram readings can be electronically sent to emergency personnel on the ground for advice and direction on how to manage the patient in the air.7 About 9% of in-flight incidents generated a call for ground-based medical advice.18

Airline flight attendants and pilots can be helpful because they must be trained in cardiopulmonary resuscitation, including the use of automated external defibrillators (AEDs), and they must recertify every 2 years.6 However, they should not be expected to function at the level of emergency medical personnel, nor should they be expected to administer medications or start an intravenous (IV) bolus.19

Equipment

The FAA requires that all air carriers with a payload capacity of more than 7,500 pounds (typically a flight with ≥30 passengers) and with at least 1 flight attendant have an AED.18 There must also be an enhanced medical kit (EMK) with a variety of medications and equipment for children and adult patients (Tables 1 and 2).19,20 Thibeault et al notes that, although seldom used, oxytocin was included in the enhanced medical kit because “it is impossible to eliminate the possibility of an onboard delivery despite passenger clearance efforts.”20

Most EMKs have tubing to attach a portable oxygen source to a bag and mask device. Flow is limited to 2L to 4L per minute.21 An air carrier may elect to

POWER POINTS

The FAA estimates that 13 medical events occur on domestic flights each day.

Less than half of in-flight medical events require ground assistance.

65% of in-flight medical events are related to preexisting problems.

What help is available on a commercial airplane?

Personnel

Fortunately, a doctor is frequently on board during a medical emergency. A study in 1991 found that physician travelers were
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carry additional equipment, such as more life-support drugs and a simple first-aid kit (bandages, antiseptic swabs, tape and scissors, ammonia inhalants). Some have over-the-counter medications as well as basic and advanced life-support cards. Medications and batteries on board have an expiration date, and the FAA recommends that airlines replace all medications annually.\textsuperscript{19} It is often necessary and wise to ask other passengers to volunteer their medications when they are not available in the EMK.\textsuperscript{21} Unfortunately, there is no international regulation requiring the complete kit to be available on flights outside the US.

**Is it your responsibility to respond?**

When the flight attendant announces, “Is there a doctor/nurse/medical provider on board?” some will choose to keep reading their magazines, others will pretend to be asleep, but some will jump into action and volunteer to help. In the United States, Canada, and the United Kingdom, physicians are not legally obligated to respond to an emergency unless there is a preexisting physician-patient relationship.\textsuperscript{11} Some European countries (eg, France, Germany) impose a legal obligation for a physician to respond when help is requested by the crew.\textsuperscript{22} The country in which the aircraft is registered has jurisdiction, but it is possible that the laws of the country where the incident occurs or where the patient resides may play a role.\textsuperscript{1,22} Regardless, all physicians have a moral and ethical duty to help if possible. From a medical-legal standpoint, doing so is very low risk: There has never been a documented case of a physician being sued for providing assistance during an in-flight medical emergency.\textsuperscript{1}

The person who responds to a medical emergency is protected by the Air Carrier Act of 1998, which states: “An individual shall not be liable for damages for any action brought in a Federal or State court arising out of the acts or omissions of the individual in providing or attempting to provide assistance in the case of an in-flight medical emergency, unless the individual is guilty of gross negligence or willful misconduct.” The volunteer must act in good faith and may receive no monetary compensation in order to be protected by this Act.\textsuperscript{1,17} Demanding a monetary reward may expose the physician to further litigation.\textsuperscript{31} Accepting a travel voucher, a free drink, or a seat upgrade is not considered monetary compensation.\textsuperscript{1}

**How to proceed in an emergency**

In the event of a medical emergency on an airplane, identify yourself to the flight crew as a medically qualified person. Sometimes the crew will ask for proof, but this is unusual, and the physician may not be able to show evidence of his or her degree or license. In any attempt to help, do not put yourself in danger. Obtain a history from the passenger if possible or family and friends accompanying the person. Make an effort to

---

**TABLE 2** Medical equipment in the emergency medical kit

- Stethoscope
- Sphygmomanometer
- Oropharyngeal airways (range)
- Syringes (range)
- Needles (range)
- IV catheters (range)
- IV tubing
- Swabs, gloves
- Sharps box
- Urinary catheter
- Tourniquet
- Gauze, tape
- Surgical masks
- Flashlight, batteries
- Thermometer (nonmercury)
- Emergency tracheostomy catheter (or large-gauge IV)
- Umbilical cord clamp
- Bag-valve-mask
- Basic life-support, advanced life-support cards
- List of equipment

Abbreviation: IV, intravenous.
Information from Ballough JJ,\textsuperscript{19} and Thibeault C, et al.\textsuperscript{19}
find an interpreter if necessary. Obtain verbal consent to examine and treat the passenger. Assume implied consent if the passenger is unconscious or incapacitated.

Try to clear the immediate area around the passenger in need so there will be room to provide care. Obtain equipment and examine the patient using the stethoscope and sphygmomanometer when available. Many airline crews will initially bring only the basic first-aid kit when asked for equipment. Ask for the enhanced EMK, but do not open it unless necessary. It’s wise to welcome the help of other passengers who may be medical professionals. After evaluation of the patient, inform the flight crew of your suspected diagnosis. Do not give medical treatment if you do not feel comfortable or confident administering such therapy. Don’t hesitate to ask for help and establish communication with a ground-based medical team if available. Document your findings, actions, and communications with airline personnel and the ground-based medical team.

Consider diversion of the airplane if the passenger has chest pain, shortness of breath or dyspnea, severe abdominal pain, persistent unresponsiveness, signs of a stroke, refractory seizure, or severe agitation. The ultimate decision to divert is up to the captain, although on-board or ground-based physicians may offer advice. A diversion can cost $3,000 to $100,000, depending on whether fuel needs to be dumped before landing and whether other passengers will then need overnight accommodations.

Some basic guidelines
If the passenger is acutely agitated, give a benzodiazepine. If he or she needs to be restrained, avoid injury by asking for the assistance of 4 or 5 people (1 for the passenger’s head and 1 for each extremity). Place the restrained passenger in the left lateral recumbent position. Never restrain the person in the prone position because this may interfere with respiration. Monitor vital signs after the passenger is restrained.

In the case of an allergic reaction, give diphenhydramine. For a suspected or documented case of anaphylaxis, give intramuscular epinephrine and steroids.

If the passenger has angina, consider giving morphine (3 mg IV), oxygen, nitroglycerin (0.4 mg sublingual every 5 minutes as needed), and aspirin (325 mg) from the EMK. Use caution when giving nitroglycerin if the patient is hypotensive. Request that the captain fly the plane at a lower altitude to increase cabin pressure and improve oxygenation.

If the passenger is dehydrated, consider giving IV normal saline, 1 L for an adult or 20 mL/kg for a child.

If the passenger has a seizure, keep him or her safe by moving objects away. Do not place anything in the mouth. Check for fever and hypoglycemia and treat these if present. Give diazepam (0.1-0.3 mg/kg IV or intramuscularly (IM) for children or 5 mg IV or IM for an adult.)

If the patient is short of breath (has asthma or chronic obstructive pulmonary disease), give an inhaled bronchodilator and consider giving steroids. Request that the captain fly the plane at a lower altitude.

If the passenger has syncope, consider serious causes. If vasovagal syncope, elevate the passenger’s legs. Consider checking his or her blood sugar and giving glucose orally or dextrose by IV, because hypoglycemia may be the cause.

If the passenger is unconscious, give oxygen and establish an IV. Check his or her blood sugar or give 50 mL of 50% dextrose solution (for children, give 2.4 mL/kg of 25% dextrose). Give naloxone 0.1 mg to 0.2 mg IV or IM. Consider using the AED to view the cardiac rhythm.

Preventing in-flight emergencies
Airlines are forbidden to discriminate against those with disabilities, but they have the right to refuse passengers who are not medically fit to fly. If a physician provides advice to patients before a flight, some medical events can be avoided. For example, air travel is contraindicated between 36 weeks’
gestation to 7 days postpartum and in complicated pregnancies, and physician certification is needed after 28 weeks’ gestation. According to the Aerospace Medical Association, those in uncompensated heart failure should not fly. A good rule is that the passenger should be able to walk 150 feet (1 flight of stairs) without severe dyspnea or angina to be safe in the air.

Plaster casts applied within 48 hours of flight should be bivalved to reduce the chance of in-flight circulatory problems. Feeding tubes and other catheters may be affected by the expansion of air or gas up in the air. Likewise, pneumatic splints should not be used in flight. Passengers should not fly within 14 days of a major surgical procedure because they are at increased risk of problems related to gas expansion. Those with contagious diseases should not fly.

Fliers should be encouraged to stand and stretch their legs, especially on long flights, to reduce the chance of pulmonary embolism. Medications should be stowed in carry-on bags, not in checked luggage.

Finally, physicians should remain current about recommendations for airline travel and ask families about plans for travel in their patient and family interviews.

**REFERENCES**

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CONTACT: http://www.uncg.edu/hhs/cwhw/symposium/index.html

APRIL
19-21: North American Society for Pediatric and Adolescent Gynecology (NASPAG) 26th Annual Meeting
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CONTACT: http://www.naspag.org

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CONTACT: http://www.classic.acog.org/acm/

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CONTACT: http://www.aagl.org/annual-meeting

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CONTACT: http://www.obesity.org/meetings-and-events/annual-meeting.htm

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CONTACT: http://www.menopause.org/

3-6: American Urogynecologic Society 33rd Annual Scientific Meeting
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iLipo ........................................................... 7
FUJIREBIO DIAGNOSTICS
HE4 .......................................................... 45

GYRUS ACMI
Innovate .................................................. 41
LACLEDE INC
Luvena ..................................................... 31
PACIFIC WORLD
Bio-Oil ................................................... 37
PFIZER
Premarin .................................................. 56-CV4
Toviaz ....................................................... 24-25
TEXAS CHILDREN’S HOSPITAL
Fetal Center ............................................. 11
VERMILLION INC
OVA1 ..................................................... 19

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SNAPSHOT

Protocol 50—Preeclampsia

AUTHOR: BAHÄ M. SIBAI, MD
UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, OHIO

SYNOPSIS: In this protocol, Dr. Sibai reviews the pathophysiology, diagnosis, and management of preeclampsia. Included are algorithms for management of mild hypertension-preeclampsia and severe preeclampsia.

As the author notes, women who develop preeclampsia in their first pregnancy are at increased risk (20%) for development of preeclampsia in subsequent pregnancies. With severe disease in a first pregnancy, the risk of recurrence is about 30%. With severe disease presenting in the second trimester, the risk of recurrent preeclampsia is 50%. There is an increased risk of chronic hypertension and undiagnosed renal disease, especially in patients with two episodes of severe preeclampsia in the second trimester. These patients should have adequate medical evaluation postpartum. There is also increased risk of intrauterine growth restriction in a subsequent pregnancy.

KEY MESSAGES:

- Hypertension complicates 7% to 10% of pregnancies, of which 70% are due to gestational hypertension-preeclampsia and 30% to chronic essential hypertension.
- Risk factors include nulliparity, obesity, multiple gestation, family history, preexisting hypertension/renal disease, and previous preeclampsia or eclampsia.
- Preeclampsia rarely develops before 20 weeks. In this early stage, rule out underlying renal disease, antiphospholipid antibody syndrome, higher-order multiple gestation, or molar pregnancy.
- Pathogenesis unknown; evidence suggests an endothelial disorder caused by placental antiangiogenic agents.
- Preeclampsia diagnosis is defined by new onset of hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg) and proteinuria (≥ 0.3 g in a 24-hour urine collection or 2+ on a dipstick).
- The first sign of potential development of preeclampsia may be weight gain of >4 lb/week in the third trimester.
- Systolic blood pressure 160 mmHg and diastolic blood pressure 110 mmHg on two occasions at least 6 hours apart in a patient at bed rest signals severe preeclampsia. Other hallmarks include proteinuria ≥ 5 g on 24-hour urine collection and oliguria (<500 mL in 24 hours).
- Delivery is the only definitive cure for preeclampsia and is recommended at 37 weeks’ gestation. The ultimate goals of the management plan must be the safety of the mother first and then delivery of a live, mature newborn who will not require intensive and prolonged neonatal care.
- At ≥37 weeks’ gestation, outpatient management may be possible, depending on the maternal and fetal condition. At least weekly non-stress testing is necessary, measurement of amniotic fluid volume, and U/S assessment of fetal growth every 3 weeks. Prompt hospitalization is necessary if disease progresses.
- Management of severe preeclampsia varies, depending on fetal maturity. Induction and delivery indicated at >34 weeks; termination recommended at <23 weeks.
- Conservative management of severe preeclampsia should be limited to tertiary-care centers.
- Postpartum management requires observation of the mother in the recovery room for 12 to 24 hours under MgSO4 coverage. Note: 25% to 30% of eclamptic and 30% of HELLP syndrome cases occur postpartum.

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

ESTROGEN-ALONE THERAPY

ENDOMETRIAL CANCER

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia and carcinoma in women taking estrogen alone for the first time [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHI estrogen-alone substudy reported increased risk of endometrial cancer among postmenopausal women 50 to 79 years of age during 5.6 years of treatment with topical estradiol (0.05%) or conjugated estrogens (0.625 mg per day, relative to placebo [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

The WHIMS estrogen-alone ancillary study of the WHI reported an increased risk of developing probable endometrial cancer in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Clinical Studies (14.2) in full prescribing information].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

ESTROGEN PLUS PROGESTIN THERAPY

CARDIOVASCULAR DISORDERS AND PROBABLE DEMENTIA

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

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

The WHI estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable deep vein thrombosis in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see Warnings and Precautions (5.2), and Clinical Studies (14.2) in full prescribing information].

In a 52-week clinical trial using PREMARIN Vaginal Cream alone (0.5% inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

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

Cardiovascular Disorders

An increased risk of stroke and deep vein thrombosis (DVT) has been reported with estrogen-alone therapy. An increased risk of pulmonary embolism (PE), DVT, stroke and myocardial infarction (MI) has been reported with estrogen plus progestin therapy [see Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.2) in full prescribing information].

The relative risk of stroke was increased with estrogen plus progestin therapy compared to placebo. In this setting, the absolute risk of stroke was lower in women assigned to estrogen plus progestin therapy compared to those assigned to placebo. In the WHI estrogen plus progestin substudy, there was a statistically significant 2.4-fold greater risk of stroke in CE plus MP (2.5 mg) compared to CE plus placebo (2.5 mg and placebo [see Warnings and Precautions (5.4), and Clinical Studies (14.3) in full prescribing information].

The reported absolute risk of stroke for those women taking estrogen plus progestin was 0.7 per 10,000 women-years, which is similar to the risk of stroke for hormone therapy users in the general population than in the placebo group in year 1, but not during subsequent years. Two thousand women lived more than 300 days but were censored at the time of open-label extension of HERS, HERS II, Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years of follow-up. Rates of CVD events were substantially higher among women in the CE (0.625 mg) plus MP (2.5 mg) group compared to the placebo group in HERS, II and overall.

Antithrombotic therapy is recommended in women with a risk of thrombosis. The reported absolute risk of deep vein thrombosis in postmenopausal women with less than 10 years of estrogen therapy was 1 per 10,000 women-years. Use of estrogen therapy in women with a history of thrombosis is contraindicated. In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

In a 52 week clinical trial using PREMARIN Vaginal Cream alone (0.5% inserted twice weekly or daily for 21 days, then off for 7 days), there was no evidence of endometrial hyperplasia or endometrial carcinoma.

The relative risk of stroke was increased with estrogen plus progestin therapy compared to placebo. In this setting, the absolute risk of stroke was lower in women assigned to estrogen plus progestin therapy compared to those assigned to placebo. In the WHI estrogen plus progestin substudy, there was a statistically significant 2.4-fold greater risk of stroke in CE plus MP (2.5 mg) compared to CE plus placebo (2.5 mg and placebo [see Warnings and Precautions (5.4), and Clinical Studies (14.3) in full prescribing information].

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Adverse Reactions

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders
- Hypersensitivity
- Neoplasms

Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

In a 12-week, randomized, double-blind, placebo-controlled trial of PREMARIN Vaginal Cream (PVC), a total of 423 postmenopausal women received at least 1 dose of study medication and were included in all safety analyses: 143 women in the PVC-21/7 treatment group (0.5 g PVC daily for 21 days, then 7 days off), 72 women in the matching placebo treatment group. A 40 week open-label treatment group (0.5 g PVC daily for 40 weeks), 68 women in the matching placebo treatment group. A 40-week, open-label extension followed, in which 234 women received treatment with PVC, including subjects randomized at baseline to placebo. In this study, the most common adverse reactions 5 percent are shown below (Table 1).

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Number (%) of Patients with Adverse Event</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>PVC (n=143)</td>
<td>Placebo (n=72)</td>
<td>PVC Placebo (n=140)</td>
</tr>
<tr>
<td>Any Adverse Event</td>
<td>95 (66.4)</td>
<td>65 (52.6)</td>
<td>97 (69.3)</td>
</tr>
<tr>
<td>Body As A Whole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11 (7.7)</td>
<td>2 (2.8)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>6 (4.2)</td>
<td>5 (6.9)</td>
<td>9 (6.4)</td>
</tr>
<tr>
<td>Abdominal涨气</td>
<td>8 (5.6)</td>
<td>0</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>7 (4.9)</td>
<td>3 (4.2)</td>
<td>13 (9.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (11.2)</td>
<td>9 (12.5)</td>
<td>25 (17.9)</td>
</tr>
<tr>
<td>Infection</td>
<td>7 (4.9)</td>
<td>5 (6.9)</td>
<td>16 (11.4)</td>
</tr>
<tr>
<td>Pain</td>
<td>10 (7.0)</td>
<td>3 (4.2)</td>
<td>4 (2.8)</td>
</tr>
</tbody>
</table>

Cardiovascular System

- Vasodilatation 5 (3.5) 4 (5.6) 7 (5.0) 1 (1.5)

Table 1: Number (%) of Patients Reporting Treatment Emergent Adverse Events 5 Percent Only

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Diarrhea</th>
<th>Nausea</th>
<th>Pharyngitis</th>
<th>Sore Muscles</th>
<th>Sinusitis</th>
<th>Back Pain</th>
<th>Leukorrhea</th>
<th>Vaginitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVC-21/7</td>
<td>2 (2.8)</td>
<td>3 (4.2)</td>
<td>2 (2.8)</td>
<td>7 (7.1)</td>
<td>3 (4.2)</td>
<td>2 (2.8)</td>
<td>4 (2.8)</td>
<td>6 (8.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2 (2.8)</td>
<td>3 (4.2)</td>
<td>2 (2.8)</td>
<td>7 (7.1)</td>
<td>3 (4.2)</td>
<td>2 (2.8)</td>
<td>4 (2.8)</td>
<td>6 (8.8)</td>
</tr>
</tbody>
</table>

OVERDOSAGE

Overdosage of estrogen may cause nausea and vomiting, breast tenderness, diarrhea, abdominal pain, drowsiness/fatigue, and withdrawal bleeding in women. Treatment of overdose consists of discontinuation of PREMARIN Vaginal Cream and administration of appropriate symptomatic care.

This brief summary is based on PREMARIN Vaginal Cream Prescribing Information W0143C0032 ET01, Rev 05/10.
For your menopausal patient

IS PAINFUL INTERCOURSE GETTING IN THE WAY?

PREMARIN Vaginal Cream provides relief from moderate to severe painful intercourse by treating the underlying source of the problem. By restoring estrogen, PREMARIN Vaginal Cream rebuilds vaginal tissue during treatment, which may help to make intercourse more comfortable.¹

Ease the pain, start treating with PREMARIN Vaginal Cream.¹

Indication
PREMARIN Vaginal Cream is indicated for the treatment of atrophic vaginitis and kraurosis vulvae and for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Important Safety Information
There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease or dementia.

The Women’s Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) (0.625 mg), relative to placebo.

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) (2.5 mg), relative to placebo.

The WHIMS estrogen plus progestin ancillary study of the WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

PREMARIN Vaginal Cream therapy should not be used in women with any of the following conditions: undiagnosed abnormal genital bleeding; known, suspected, or a history of breast cancer; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism or a history of these conditions; active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions; known liver dysfunction or disease; known thrombophilic disorders; known or suspected pregnancy.

In a prospective, randomized, placebo-controlled, double-blind study, the most common adverse reactions (<5%) were headache, infection, abdominal pain, back pain, accidental injury, and vaginitis.


Please see brief summary of Full Prescribing Information, including boxed warning, on the following pages.

premarin™
(conjugated estrogens) vaginal cream
www.PremarinVaginalCreamHCP.com