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# Alcohol in Pregnancy

ABSTRACT & COMMENTARY


***By John C. Hobbins, MD***

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*Dr. Hobbins reports no financial relationships relevant to this field of study.*


***Synopsis:*** *Data collected from a large study involving four countries show no effect of alcohol exposure in varying degrees on the rate of preterm birth, low birth weight, average birth weight, and preeclampsia.*


**Source:** McCarthy FP, et al. Association between maternal alcohol consumption in early pregnancy and pregnancy outcomes. *Obstet Gynecol* 2013;122:830-837.

A 2011 AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG) Committee Opinion gave "compelling and clear advice to avoid alcohol" in pregnancy and prior to pregnancy.[1] Yet the Centers for Disease Control and Prevention (CDC) indicates that about 50% of women in the United States admit to some intake of alcohol in pregnancy.[2] Since the data are inconsistent regarding how much alcohol affects the fetus, even in higher dosage, the Royal College of Obstetrics and Gynecology has taken a less conservative approach by saying that harm is unlikely to occur from one to two units of alcohol consumed once or twice per week.[3] However, the Royal College strongly advises against binge drinking.

In an effort to see if alcohol consumption in varying amounts has an effect on some easy-to-track outcomes, a multicenter study was undertaken in four countries: Great Britain, Ireland, New Zealand, and Australia — the Screening for Pregnancy Endpoints (SCOPE) study.[4] Outcome data were available on 5628 patients who were enrolled between 2006 and 2011. Patients were screened for alcohol consumption immediately prior to, and/or during, the first 15 weeks of pregnancy. The amount of exposure was quantified as follows: one unit of alcohol


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represented 10 mL of pure alcohol, which was equivalent to one shot of whiskey, a half a glass of wine, or one small glass of beer. Bottled mixed drinks each contained two units. Binge drinking meant that more than six units were consumed per drinking session.

The timing of alcohol exposure was broken up into four groups: 1) abstinent throughout this period, 2) none prior to conception, 3) quitting before 15 weeks, and 4) drinking throughout this window of time. Binge drinking was tracked according to these time intervals.

Based on the CDC data, the alcohol consumption statistics were not surprising. For example, 40% reported no alcohol consumption in pregnancy, 19% admitted to "occasional" intake (1-2 units per week), 25% were in the "low" category (3-7 units per week), 11% were "moderate" drinkers (8-14 units per week), and 5% were in the "heavy" group (> 14 units per week). Thirty-four percent said there was exposure to alcohol during the first 3 months and 23% admitted to at least one episode of binge drinking. It is important that the authors attempted to account for the many confounding variables, including smoking, when evaluating the results.

The authors studied four outcomes: birth weight, small for gestational age (SGA), spontaneous preterm birth, and preeclampsia. After adjusting for confounding variables there were no differences between groups regarding average birth weight, low birth weight, or the rates of SGA or preeclampsia. Even binge drinkers did not display differences in these categories and the timing of alcohol exposure had no effect on any of these endpoints.

Simply put, the timing and amount of alcohol consumption before and during early pregnancy seemed to have no effect on any of the four outcomes evaluated.

## ■ COMMENTARY

Often patients have been referred to us for ultrasound evaluations because they consumed alcohol in varying amounts early in pregnancy. The majority have not been hard-core drinkers and many were in the restaurant business where it is common for employees to gather at the bar for a few pops (or more) before heading home. Since the admonition to abstain from alcohol in pregnancy is well entrenched in the United States, these women were frightened out of their wits when they suddenly found themselves pregnant. This study suggests that their possible concerns, at least for preterm birth, growth restriction, and preeclampsia, can be allayed. On one hand, since alcohol consumption in large amounts during organogenesis can be a teratogen (the face and heart) and has the capability later in pregnancy to affect the central nervous system (as in fetal alcohol spectrum disorders), it would not be advisable to advocate a carte blanche approach to drinking in pregnancy, and obviously avoiding any alcohol is the best way to avoid any effect. On the other hand, since thus far there are no conclusive data to link modest intake with fetal effect, it is very unlikely that an occasional drink would have an adverse effect.

Many years ago, we tried to correlate alcohol intake in pregnancy with in utero brain findings on ultrasound, as well as with one specific measure of neurological performance in infants.[5] We found that abnormal neurological results correlated with frontal lobe size, which, in turn, correlated with alcohol intake. However, this relationship was significant only when there was heavy consumption (six drinks or more per day). Interestingly, no infant in the study, even in the high consumption group, displayed the constellation of stigmata necessary to document alcohol's most devastating effect — fetal alcohol syndrome.

The story gets more complicated on the maternal side when one delves into the genetics of vulnerability to alcohol addiction and the varying abilities of individuals to metabolize alcohol, and, obviously, on the fetal side there is much more to learn about alcohol's variable effects. Not surprisingly, the topic of alcohol in pregnancy is controversial and has brought out a full spectrum of hawks and doves (and last time I wrote about this I got flack from both sides). As indicated in the ACOG committee opinion, abstaining is a foolproof way to ensure that a fetus will not be affected. However, it also seems reasonable to tell women who have had some inadvertent exposure to alcohol in early pregnancy that it is unlikely to have had a major effect on their fetuses — with the caveat that it is time to either stop or keep their consumption to an occasional glass of an alcoholic beverage once

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or twice a week from that point on, as articulated by the British College. ■


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# Redefining the Natural History of Borderline Ovarian Tumors

ABSTRACT & COMMENTARY


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*Dr. Coleman reports no financial relationships relevant to this field of study.*


***Synopsis:*** *Borderline ovarian tumors present in early stage, infrequently relapse, are generally cured with surgical resection, and may be conservatively treated in women desiring continued fertility. However, nearly a third of recurrences are malignant and pursue an aggressive course like their invasive primary counterparts.*


**Source:** du Bois A, et al. Borderline tumours of the ovary: A cohort study of the Arbeitsgmeinschaft Gynakologische Onkologie (AGO) Study Group. *Eur J Cancer* 2013;49:1905-1914.

Borderline ovarian tumors are unique ovarian neoplasms that demonstrate proliferation without infiltrative destructive growth or stromal invasion. Clinically, they carry a much more favorable prognosis compared to invasive epithelial ovarian cancer. However, their rarity has limited clear information regarding prognostic factors and no prospective studies exist that evaluate therapeutic strategies. To provide clarity into these important clinical parameters, the AGO study group carried out a retrospective cohort study, collecting data from consecutive patients with ovarian borderline tumors treated between 1998 and 2008 in 24 German centers. All tumors underwent central pathological review, and case patients were prospectively followed for outcomes of recurrence, therapy, and death. Of 1042 patients undergoing independent pathological review, borderline ovarian tumor was confirmed in 950 patients; of the 92 patients excluded, 43% had primary invasive disease and the remaining benign disease. The histology of the borderline tumors was serous (67%) and mucinous (31%). Most were diagnosed in stage I (82%); 8% and 10% were stage II and III, respectively. Overall, 74 patients (8%) experienced relapse and 43 (5%) died within the observation period. Multivariate analysis revealed higher stage, incomplete staging, tumor residuals, and organ preservation as independent prognostic factors for disease recurrence. While the presence of implants was prognostic, neither microinvasion nor micropapillary growth pattern impacted progression-free survival (PFS). Of 74 relapsed patients, 30% had malignant transformation to invasive ovarian cancer with 5-year PFS and overall survival of 12% and 50%, respectively. Prognosis of ovarian borderline tumors correlates with tumor-related as well as surgery-related factors. The balance between recurrence risk and organ preservation and fertility-sparing surgery is an important issue deserving further research.

## ■ COMMENTARY

It has been well described that, in general, ovarian borderline tumors are uncommon and of good prognosis.[1] However, the natural history of the disease is not well understood, particularly in regard to recurrence, due to the rarity of the condition and of these events. This paper represents the largest collection of cases with central path review and provides better clarity to prognostic factors previously intimated from retrospective work. The most surprising outcomes in this review were the lower than expected recurrence risk (8% vs historically 11-15%) and invasive recurrence risk (2% vs historically 4%).[2] Also of note were the recurrence risks in patients undergoing conservative surgery (organ preserved) and incomplete staging. Fortunately, neither of these factors increasing the risk for recurrence (by up to 5-fold) led to poorer survival. This was largely due to "in organ" recurrence for those undergoing fertility-sparing surgery and the frequency of non-invasive recurrent disease (70% of recurrences). However, somewhat surprising was their identification of high-grade invasive disease (34%) in the 22 patients who recurred with invasive disease.[3] The outcomes of these patients was no different than expected from invasive ovarian cancer in general. Finally, a good take-home message from the study was the utility of expert pathology review. In this trial, all cases were independently re-reviewed. In nearly one in eight cases, a different opinion was reached with a 60:40 split on benign and malignant diagnoses.

Since this was a retrospective re-review of the original histology, intervention was carried out locally based on the original histology (read locally as borderline ovarian cancer). However, when the outcomes of these discrepant groups were analyzed, the outcomes were vastly different than expected; median PFS in the borderline re-read as invasive was 6 years, and median PFS in the group re-read as benign was not reached (greater than 12.5 years). Overall for the confirmed borderline tumors the median PFS was 12.5 years. This differential strengthens the validity of the revised histological assessment. ■


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# A Final Word on Safety of Vaginal Ring Contraception?

ABSTRACT & COMMENTARY

***By Jeffrey T. Jensen, MD, MPH***

***Synopsis:*** *A large prospective study from the United States and Europe confirms that the risk of venous and arterial thromboembolism associated with use of the contraceptive vaginal ring is similar to that seen with use of combined pills.*

**Source:** Dinger J, et al. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. *Obstet Gynecol* 2013;122:800-808.

The transatlantic active surveillance on cardiovascular Safety (TASC) of Nuvaring® study was a large, multinational, controlled, prospective, observational, active surveillance study designed to assess the cardiovascular safety of the ethinyl estradiol/etonogestrel releasing contraceptive vaginal ring (CVR). The study was performed at 1661 study sites in the United States and five European countries. These sites enrolled a total of 33,295 subjects who were new users (new starters, switchers, or restarters) of the CVR or of a combined oral contraceptive (OC) pill. The choice of method was made by the woman and/or her doctor. After the choice of method was completed, the subject was invited to join the study. This required the subject to complete a health history and provide contact information to the central monitoring site. Follow-up occurred for 2 to 4 years with an impressively low loss to follow-up of only 2.9%. Altogether, a total of 66,489 woman-years of exposure to the hormonal methods were recorded. The primary clinical outcomes of interest (venous and arterial thromboembolism) were validated by attending physicians and further adjudicated by an independent board. The venous thromboembolic hazard ratio (HR) for the vaginal ring compared with combined OCs was the primary statistical variable.

The crude venous thromboembolism incidence rates for the vaginal ring users and combined OC users were 8.3 and 9.2 per 10,000 woman-years, respectively. Cox regression analysis for the vaginal ring users compared with combined OCs yielded adjusted hazard ratios (HRs) of 0.8 (95% confidence interval [CI], 0.5-1.6) for venous and 0.7 (95% CI, 0.2-2.3) for arterial thromboembolism. When the analysis was restricted to compare the CVR to levonorgestrel pills only, the adjusted HR was 1.0 (95% CI, 0.3-3.3). The authors concluded that the CVR is associated with a risk of venous and arterial thromboembolic similar to that of the combined pill during routine clinical use.

## ■ COMMENTARY

Over the last year, I have written extensively about the ongoing controversy regarding safety of hormonal contraceptives. This paper provides another excellent example of how to perform a good Phase 4 study. The methodology of the TASC study is essentially the same as that of the European Active Surveillance (EURAS) study of drospirenone-containing OCs.[1] Both studies were mandated by regulatory authorities, paid for by industry (EURAS Bayer, TASC Merck), and conducted by Jürgen Dinger of the ZEG institute in Berlin. The planning, conduct, and evaluation of the study were supervised by an independent Safety Monitoring and Advisory Council, ethical approval was obtained through an independent agency, and the study was registered in the public clinical trials registry of the United States National Library of Medicine. This transparency makes it easy to follow the logic of the methods.

The results demonstrate no difference in the risk of venous thromboemolism and arterial thrombotic events associated with use of the CVR when compared to combined pills. Since the design of prospective Phase 4 studies permits the collection and analysis of important baseline confounders, these studies provide the highest quality of evidence on uncommon and rare side effects associated with hormonal contraception. I have written extensively about the limitations of database studies in assessing these same outcomes. While the series of manuscripts by Lidegaard[2,3] using data from the Danish National Database show a consistent increase in risk with newer progestins such as desogestrel (and its metabolites such as etonogestrel) and drospirenone when compared with le-

vonorgestrel, the inability to adjust for baseline confounding represents a significant limitation.[4] I encourage each of you to read the excellent discussion by Dinger in the TASC paper.

Although we have high acceptance of the CVR in my area, the use of long-acting reversible contraception methods continues to challenge the market for combined hormonal methods. For our residents, the prescription of a combined method is now a "teachable moment." Combined hormonal methods provide a number of important nonhormonal benefits, and are of particular value for women who experience symptoms due to persistent ovarian follicles, ovulation events, or cycle-related hormonal symptoms. The CVR can provide the benefits of a combined method and the convenience of once per month dosing. I believe in providing many options and allowing women to make an informed choice of what is right for them. This requires accurate information of risks, so I encourage you to take the time to teach. ■

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# Urodynamic Testing before Stress Incontinence Surgery

ABSTRACT & COMMENTARY


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*Dr. Ghetti reports no financial relationships relevant to this field of study.*



***Synopsis:*** *For women with uncomplicated, demonstrable stress urinary incontinence, preoperative office evaluation alone was not inferior to evaluation with urodynamic testing for incontinence outcomes at 1 year.*



**Source:** Nager C, et al. A randomized trial of urodynamic testing before stress-incontinence surgery. *N Engl J Med* 2012;366:1987-1997.


Up to 50% of U.S. women are affected by urinary incontinence, and of those[1] 15-80% have stress incontinence symptoms.[1,2] Stress incontinence is the complaint of involuntary leakage of urine on effort, physical exertion, sneezing, or coughing.[3] Based on industry estimates reported by the FDA, approximately 260,000 mesh sling procedures were performed in 2010 for the treatment of stress incontinence.[4] Urodynamics studies are often performed prior to surgery to assess incontinence symptoms and guide management decisions. Urodynamic testing involves evaluation of voiding uroflowmetry, post-void residual urine volume measurement, and pressure-flow studies with a catheter in place and storage function through cystometry and leak point pressure testing.[3]

The current study addresses the question of whether performing preoperative urodynamic testing improves incontinence treatment outcomes. This 11-center, randomized, noninferiority trial compared results of women who underwent office incontinence evaluation-only with results of women who underwent office evaluation and urodynamic testing prior to a planned surgery for uncomplicated stress urinary incontinence. Patients eligible for this trial were ≥ 21 years of age, had symptoms of stress urinary incontinence for a minimum of 3 months, had greater stress urinary incontinence scores vs urgency incontinence scores on the Medical, Epidemiological, and Social Aspects of Aging (MESA) questionnaire, had a postvoid residual urine volume < 150 mL, had negative urine analysis or culture, had visible urethral mobility, had a desire for surgery, and had observed transurethral loss of urine with cough or valsalva. Patients with prior incontinence surgery, pelvic irradiation, pelvic surgery within the prior 3 months, and anterior or apical pelvic organ prolapse of 1 cm or more distal to the hymen were excluded from the trial. Basic office evaluation consisted of: provocative stress test (performed at any volume and defined as visible transurethral loss of urine at time of cough or Valsalva), assessment of postvoiding residual, assessment of urethral mobility, and urine analysis or culture. The primary outcome was treatment success as measured by two validated instruments, the Urogenital Distress Inventory (UDI) and the Patient Global Impression of Improvement (PGII). Treatment success was defined as a reduction in UDI score from baseline to 12 months of ≥ 70% and a PGII response of "very much better" or "much better" at 12 months. A planned subgroup analysis was performed comparing surgical outcomes only among women in the study who ultimately underwent surgical treatment. For this subgroup analysis, successful treatment included a negative standard-volume stress test at 12 months in addition to the above definition.

A total of 630 women were randomized. Primary outcome data were available for 264 women in the urodynamic group and 259 in the office evaluation-only for the per-protocol analysis. Treatment success was 76.9% in the urodynamic group compared to 77.2% in the office evaluation-only group. The between-group difference was -0.3

percentage points (95% confidence interval, -7.5 to 6.9) and met the authors' predetermined criterion for noninferiority of office evaluation alone. In the subgroup analysis of 443 women undergoing treatment, there was not a difference in the number of women who ultimately did not undergo surgery 17 (5.4%) in the urodynamic group vs 27 (8.6%) in the evaluation-only group ($P$ = 0.12). Surgical treatment was successful in 154/222 (69.4%) in the urodynamic group vs 161/221 (72.9%) in the evaluation-only group ($P$ = 0.42). The rate of successful treatment with office evaluation alone was not inferior to the rate among women who underwent urodynamic testing. The authors therefore conclude that in women with uncomplicated stress urinary incontinence, a basic office evaluation is sufficient for preoperative evaluation.

**■ COMMENTARY**

Urodynamic testing is invasive and uncomfortable for patients. It poses a risk of urinary tract infection and is very costly to the health care system. The role of urodynamic evaluation in the preoperative evaluation of stress incontinence remains controversial.[5] In the UK, the National Institute for Health and Clinical Excellence published its 2006 guidelines on the management of urinary incontinence in women stating "the use of multichannel cystometry is not routinely recommended before surgery in women with a clearly defined clinical diagnosis of pure stress urinary incontinence."[6] The Cochrane review published in 2009 prior to this trial concluded, "a larger definitive trial is needed, in which people are randomly allocated to management according to urodynamic findings or to standard management based on history and clinical examination."[7] In a time of rising health care costs, this trial fills this critical gap in information.

This randomized noninferiority trial follows the modified CONSORT checklist for reporting noninferiority and equivalence randomized trials.[8] For clarification, I will briefly review trial types as outlined in the CONSORT statement. Let's assume two hypothetical interventions: A and B. A randomized controlled trial is designed to determine whether A is superior to B. An equivalence trial is designed to ascertain whether A is similar to B, while a non-inferiority trial is designed to determine whether A is no worse than B. In other words, "non-inferiority trials intend to show that one treatment has at least as much efficacy as another or is worse by a certain amount."[8]

This trial found that 1-year postoperative outcomes in women evaluated by basic office evaluation alone were not inferior to those of women who underwent formal urodynamic testing. To measure the possible benefits of urodynamic testing, this study used a general measure of postoperative lower urinary tract function that included urinary symptoms as well as patient perception of improvement. While this study does not address the role of urodynamic testing in more complicated patients, such as women with urge predominant incontinence, a history of prior incontinence surgery and pelvic organ prolapse, this study is very pertinent to a large number of our patients. Any woman with the complaint of urinary incontinence was assessed for eligibility. Eligibility criteria allowed for the inclusion of women with symptoms of both stress urinary incontinence and stress-predominant mixed urinary incontinence aiding the generalizability of the results to a large proportion of women with stress incontinence similar to what we see in everyday practice. ■

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*Special Feature*

# Early Pregnancy Failure: How Can We Confidently Diagnose Nonviable Pregnancies?


***By Rebecca H. Allen, MD, MPH***

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*Dr. Allen reports no financial relationships relevant to this field of study.*



***Synopsis:*** *According to new guidelines from the Society of Radiologists in Ultrasound, more conservative cutoffs are recommended for diagnosing early pregnancy failure. For example, a crown-rump length of ≥ 7 mm without a heartbeat or a mean sac diameter of ≥ 25*

*mm and no embryo are required before the diagnosis of pregnancy failure with 100% confidence can be made.*

**Source:** Doubilet PM, et al. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med* 2013;369:1443-1451.

The diagnosis of early pregnancy failure is an important call to make as a provider. The consequences of inaccurate diagnosis in the setting of a desired pregnancy are extreme — namely, possible interruption of a normal pregnancy. Diagnosing pregnancy early in gestation is now more common, yet managing equivocal findings of viability on transvaginal ultrasound are also challenging. Many practices routinely obtain an early dating ultrasound on their obstetric patients. In addition, first-trimester bleeding is a common presentation to medical offices and emergency departments. In an area where radiology, obstetrics and gynecology, emergency medicine, and family medicine intersect, recommendations from various specialty societies on the diagnosis of early pregnancy failure have differed in the past. When I was a resident, we learned the 5-10-20 rule. In this mnemonic, one should expect to see a heartbeat by the time the crown-rump length measured 5 mm, a yolk sac if the mean gestational sac diameter was 10 mm, and an embryo if the mean gestational sac diameter was 20 mm. If these structures were not seen, then the diagnosis of miscarriage was made.

In early pregnancy, there is a predetermined and predictable order of development: the gestational sac appears at 5 weeks, the yolk sac at 5.5 weeks, and the embryo can be seen at 6 weeks with a variation of ± half a week.[1] When pregnancies deviate from these expected findings, the diagnosis is suspicious for early pregnancy failure. But how can one be absolutely certain? It turns out that the evidence behind the guidelines or "rules of thumb" promulgated by various subspecialty organizations is not robust.[2] It is surprising that for a diagnosis of such importance, we have failed to conduct appropriately powered studies. Many of these standard guidelines were based on older studies with small numbers of patients. For example, the American College of Radiologists' guideline from 2009 states that an embryo should be seen by a mean gestational sac diameter of 16 mm and a heartbeat should be seen in an embryo > 5 mm.[1] The studies behind these criteria had a total combined subject number of 47 women!

Fortunately, several systematic reviews published in 2011 in the journal *Ultrasound in Obstetrics and Gynecology* have clarified what we know and what we don't know.[3,4,5,6] In response to these articles, the Society of Radiologists in Ultrasound (SRU) convened a multispecialty panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy in October 2012. This group reviewed the literature and issued more conservative recommendations to avoid falsely diagnosing a miscarriage when the pregnancy could be viable. These are similar to new guidelines issued by the American College of Radiologists and the Royal College of Obstetricians and Gynaecologists.[7,8] The American College of Obstetricians and Gynecologists has yet to weigh in on this issue.

First, the authors reviewed the cutoff for cardiac activity detection in an embryo. Although cardiac activity is usually seen in an embryo of any crown rump length, the old criteria of 5 mm was based on such small numbers of patients that the 95% confidence intervals for the specificity of this finding are very large. In fact, several studies have documented subsequent viable pregnancies in embryos of 5 mm and 6 mm that did not have a heartbeat visualized. Furthermore, the inter-observer variation in the measurement of crown-rump length is ± 15% even among experienced sonographers.[6] Therefore, the SRU concluded that a cutoff of 7 mm is more appropriate and would yield a specificity and positive predictive value of 100%. When the crown-rump length is less than 7 mm and there is no heartbeat, this is considered suspicious, but not diagnostic, of pregnancy failure.

Second, the authors looked at mean gestational sac diameter (the average of the sagittal, transverse, and anteroposterior diameters of the sac). Older studies suggested cutoffs of 16 mm or 20 mm for failed pregnancy if there was no embryo present. These, too, are based on a small number of subjects and have wide confidence intervals. In addition, the issue of interobserver variability comes into play.[6] Therefore, the SRU recommends that a mean sac diameter of ≥ 25 mm and no embryo is diagnostic of miscarriage while a mean sac diameter of 16-24 mm and no embryo is suspicious.

The SRU document then outlines time-based criteria with which miscarriage can be diagnosed. They state that the absence of an embryo with a heartbeat ≥ 14 days after a scan that showed a gestational sac without a yolk sac is diagnostic of pregnancy failure. In addition, the absence of an embryo with a heartbeat ≥ 11 days after a scan that showed a gestational sac with a yolk sac is diagnostic of a pregnancy failure. Other findings that are suspicious for, but not diagnostic of, pregnancy failure include enlarged yolk sac (> 7 mm), empty amnion, and small gestational sac in relation to the size of the embryo (< 5 mm) difference between mean sac diameter and crown-rump length. For any suspicious findings, the authors recommend follow-up ultrasound in 7-10 days.

In essence, this article is a plea for clinicians to be more stringent in their diagnosis of miscarriage. The misdiagnosis of miscarriage has been the subject of national health system review in the United Kingdom and Ireland.[1] Early Pregnancy Assessment Units, dedicated to the care

of women in early pregnancy, are very common in those countries as well as Canada.[9] Even with those specialized units, reviews found that improvements in diagnosis could be made. If the diagnosis of miscarriage is unsure and/or the woman requests a repeat ultrasound, this should be ordered. It is rare that the diagnosis of miscarriage by ultrasound is taking place in an emergency situation. Therefore, with a stable patient, there is plenty of time to be sure of the diagnosis before intervening medically or surgically.[2] As clinicians, we should first "do no harm," as the Hippocratic Oath says. ■

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## CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

## CME Questions

1. **Which of the following is true based on the findings in the SCOPE study?**
   a. There was an increase in preterm birth in those with moderate-to-heavy consumption of alcohol.
   b. There was an increase in low birth weight in those exposed to alcohol.
   c. Binge drinking had an effect on fetal growth.
   d. There was an effect of alcohol on the incidence of preeclampsia.
   e. None of the above

2. **Alcohol has been shown to have a teratogenic effect, but not on the central nervous system.**
   a. True
   b. False

3. **Which of the following was an independent prognostic factor for recurrence in the study of borderline ovarian tumors?**
   a. Incomplete surgical staging
   b. Histology
   c. Ascites
   d. Micropapillary architecture

4. **Results from the Transatlantic Active Surveillance on Cardiovascular safety of Nuvaring® study support that the risk of venous and arterial thrombosis seen in contraceptive vaginal ring users is:**
   a. significantly higher than that observed in users of levonorgestrel pills.
   b. significantly lower than that observed in users of all combined pill users.
   c. no different from the risk seen in copper IUD users.
   d. not significantly different than that observed in users of oral contraceptives.
   e. lower than a general population of nonusers of the pill.

5. **Based on findings of the reported Urinary Incontinence Treatment Network randomized controlled trial, which of the following is least required in the initial evaluation of a woman with uncomplicated stress urinary incontinence?**
   a. Assessment of postvoid residual
   b. Evaluation for urinary tract infection
   c. Formal urodynamic testing
   d. Positive provocative stress test

6. **According to Society of Radiologists in Ultrasound guidelines, which of the following is true?**
   a. A pregnancy with an embryo measuring 5 mm and no heartbeat can be diagnosed a miscarriage.
   b. An anembryonic pregnancy with a mean sac diameter of 25 mm can be called a failed pregnancy with 100% specificity.
   c. An enlarged yolk sac (> 7 mm) is diagnostic of pregnancy failure.
   d. Seven days after a scan showed a gestational sac with a yolk sac, a repeat ultrasound is performed and does not show an embryo with a heartbeat; therefore, miscarriage can be diagnosed.

Clinical Briefs in Primary Care™

Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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## Goldilocks Unable to Find Amount of Antioxidants That's Just Right

**Source:** Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldiloks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

## Antipsychotics Are Associated with Increased VTE Risk

**Source:** Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

## Physician Visits for Itching

**Source:** Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

## Consequences of Non-Adherence in Treated Hypertensives

**Source:** Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

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## Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

**Source:** Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

## *Clinical Briefs in Primary Care* is going digital!

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## Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

**Source:** Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

# Reglan Safe in Pregnant Women for Nausea and Vomiting

***In this issue:*** Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

## Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

## Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

## FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

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Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■