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INSIDE

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Preimplantation Genetic Screening Improves IVF Success in Women with Diminished Ovarian Reserve

ABSTRACT AND COMMENTARY

By Michael A. Thomas, MD

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

Synopsis: *Low levels of anti-Müllerian hormone in combination with an elevated day 2-3 follicle-stimulating hormone is associated with a high rate of aneuploid embryos.*

Source: Katz-Jaffe MG, et al. Association of abnormal ovarian reserve parameters with a higher incidence of aneuploid blastocysts. *Obstet Gynecol* 2013;121:71-77.

In a prospective fashion, 372 patients were offered comprehensive chromosome screening because they fell into one or more of the following categories: advanced maternal age (≥ 39 years), history of two or more unsuccessful in vitro fertilization (IVF) cycles with adequate embryo quality, or unexplained recurrent pregnancy loss (two or more). All patients underwent testing for ovarian reserve by assessing serum anti-Müllerian hormone (AMH) at any time during the menstrual cycle and follicle-stimulating hormone (FSH) on cycle day 2 or 3. Also, early follicular estradiol, baseline transvaginal ultrasound for

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antral follicle count, and an endometrial cavity evaluation were performed. Normal values for AMH were defined as > 1 ng/mL and day 2-3 FSH as < 10 mIU/mL. The 279 subjects in group 1 had normal ovarian reserve testing as evidenced by normal values of both AMH and FSH. Group 2 consisted of 93 patients who had evidence of abnormal ovarian reserve testing with group A having a low AMH and elevated FSH (n = 25), group B demonstrating a normal AMH and elevated FSH (n = 34), and group C showing a low AMH and elevated FSH (n = 34). Patients underwent IVF and had their blastocysts biopsied, and 23 chromosomes were analyzed for potential abnormalities. Only euploid embryos were eventually transferred after being frozen by vitrification while awaiting biopsy results. When comparing group 1 (normal ovarian reserve testing) to group 2 (abnormal ovarian reserve testing), group 1 participants were younger (37.5 vs 38.8 yrs), had higher AMH (3.2 vs 1.3 ng/ml) and lower day 2-3 FSH concentrations (6.9 vs 10.5 mIU/mL), higher number of oocytes retrieved (20.8 vs 14.3), and a lower number of aneuploid blastocysts (14.3 vs 35.1). No difference in live birth rate was noted between group 1 or group 2 (58.4 vs 48.4%). Within group 2, the subjects in group A (lower AMH and high FSH) were noted to have a lower number of oocytes retrieved and a higher percentage of aneuploid blastocysts. No difference in live birth rate was noted within the group 2 subgroups. The authors concluded that women with biochemical evidence of diminished ovarian reserve have a higher percentage of aneuploid embryos. However, preimplantation genetic screening (PGS) allows the transfer of euploid embryos, which resulted in live birth rates that were equivalent regardless of their initial ovarian reserve testing.

■ COMMENTARY

Ovarian reserve testing (antral follicle count, early follicular FSH, or AMH) is being used routinely by both reproductive endocrinologists and generalists to forecast a woman's potential stimulation response to clomiphene citrate or gonadotropins, oocyte quality, and subsequent reproductive outcome. Despite poor numbers, some patients conceive. The study by Katz-Jaffe et al helps to demystify ovarian reserve testing as the last word in determining whether couples with a combined low AMH and high day 2-3 FSH should abandon all hopes of conceiving without the use of a donor oocyte.

In this study, PGS was available to those couples if the IVF cycle resulted in embryos that progressed to the blastocyst stage. One of the things that we don't know from this study is how many of the couples with abnormal ovarian reserve testing started the study without going to the blastocyst stage. PGS has been used at IVF centers in patients with recurrent pregnancy losses, advanced maternal age, and those with a number of failed IVF cycles with or without good embryo quality. This current study suggests that, despite prediction of poor reproductive outcome and abnormal ovarian reserve on serum testing, outcomes may be good if PGS is performed. This provides an option to couples who have been routinely directed to donor egg. However, these data demonstrating a beneficial effect of PGS in poor prognostic groups are in contrast to other studies that have transferred euploid embryos with lower birth rates than reported here.[1] In 2007, the Practice Committee of the American Society for Reproductive Medicine (ASRM) stated that they did not support the routine use of PGS to improve live birth rates in patients with recurrent pregnancy loss, previous implantation failure, or advanced maternal age.[2]

One major difference in the Shahine review and the ASRM document is use of fluorescence in situ hybridization or comparative genomic hybridization (CGH) in cleaved embryos, which allows analysis of selected numbers of chromosomes. In the Katz-Jaffe study, the trophectoderm of the blastocyst was biopsied and analyzed using metaphase CGH in subjects from 2007-2008 and single nucleotide polymorphism microarray in those participating from 2009-2011. These improved techniques allow analysis of all 23 chromosomes and therefore enhance accuracy in making a diagnosis of aneuploidy.

The results of the current study are promising for couples who have abnormal ovarian reserve testing despite age or poor outcomes in past ART cycles. However, these results need to be repeated in other centers using these same advanced techniques. ■

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Placenta Previa

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *A new study shows that the vast majority of low-lying placentas or marginal previas noted in second trimester patients resolved by term. However, there was a doubling of the rate of postpartum hemorrhage in these patients even if the placentas had migrated away from the cervix.*

Source: Osmundson SS, et al. Second trimester placental location and postpartum hemorrhage. *J Ultrasound Med* 2013;32:631-636.

With the recent emphasis on early prenatal diagnosis, most patients today are having ultrasound examinations in the first trimester for nuchal translucency testing followed by a second trimester evaluation of fetal anatomy. Although the focus has been predominantly on the fetus, every scan includes an assessment of placental location. Sometimes a low-lying placenta or even a placenta previa is discovered. Since the meaning of the low-lying or marginal previa is unclear, counseling and management have varied widely among clinicians.

A group from Northwestern University recently published a study that primarily dealt with whether a low-lying placenta found between 18 and 24 weeks of gestation carries an increased risk for postpartum hemorrhage.[1] The study also revealed some other spinoff findings that may help to clarify the meaning of this ultrasound finding.

Over a period of 6 months, 282 patients with adequate follow-up data were diagnosed as having low-lying placentas between 18 and 24 weeks of gestation (placental edge was 0.1-2.5 cm from the endocervix). Another 61 patients with marginal previas (touching, but not overlapping the endocervix) and 30 patients with complete previas (covering the cervix) were included. "Resolution" meant that within 28 days of delivery the placental edge was noted to be > 2.5 cm from the endocervix. Persistent low-lying placentas were those that remained < 2.5 cm from the cervical os prior to delivery.

The diagnosis of postpartum hemorrhage was made if the blood loss was estimated to be > 500 cc after vaginal delivery or > 1000 cc after cesarean section. A separate group of 410 women with placentas that were > 2.5 cm from the cervix at 18-24 weeks were used as controls.

Low-lying placentas resolved in 98% of patients, while marginals and complete previas resolved in 89% and 59% of cases, respectively. Antepartum bleeding occurred in 32% vs 0.5% (P = 0.004), postpartum hemorrhage in 12.4% vs 4.9% (P = 0.001), and need for uterotonics 11.0% vs 6.1%, (P = 0.01) compared with controls. Statistically significant differences remained in all categories even if the low-lying, marginal, or complete previas had resolved by late gestation.

■ COMMENTARY

The term "placenta previa" carries a stigma that puts into play lifestyle proscriptions such as no intercourse, no physical exertion, no travel, etc., and the diagnosis often leaves patients with the feeling that they are sitting on a time bomb. Now it should be clear that the second trimester finding of a placenta that is close to, if not just covering, the cervix carries far less meaning than if found toward term. The authors have again uncovered what others have noted: that only a few of these placentas will remain close to the cervix as pregnancy progresses.

Why this happens is still a matter of conjecture but one explanation is that the lower uterine segment lengthens out, pulling the placenta away from the cervix. Another theory is that the lower uterine segment is a less hospitable place for the placenta to implant, and the placenta, in an effort to seek a better environment on higher ground, atrophies near the cervix while proliferating in its upper portion — an activity called "trophotrophism."

Another question that emerges in patients with low-lying placentas at term is whether they can have vaginal deliveries. For years, the definition of a placenta previa included placentas whose lower edge extended down to within 2 cm of the endocervix. Also, placenta previa essentially meant delivery by cesarean section. Now it is quite clear that many of these patients can deliver vaginally. For example, Vergani et al noted that patients with placentas between 1.0-2.0 cm of the cervical os had only a 31% chance of having a cesarean section and a 3% chance of antepartum bleeding.[2] If placentas were between 0.1-1.0 cm from the cervix, the cesarean section rate was 75% and the rate of antepartum bleeding was 29%. These results suggest that more than two-thirds of patients in the 1-2 cm range, previously considered by standard definition to have placenta previas, could actually have a successful vaginal delivery. Even one out of four of those with placentas within 1 cm of the endocervix could have vaginal deliveries, but at a higher rate of antepartum bleeding.

The major thrust of the featured study was to determine how often a finding in the second trimester of a low-lying placenta is associated with postpartum bleeding.[1] There was a clear association, even in patients where there was resolution of the finding in the third trimester. In these cases, the odds ratio for hemorrhage was 2.7 (95% confidence interval [CI], 1.46-5.07) and need for uterotonic agents was 2.1 (95% CI, 1.24-3.84) compared with controls.

Why would this be? We assume that most postpartum bleeding comes from the exposed vascular surface left by the vacated placenta and this is rectified by tamponade created by strong generalized uterine contraction. Unfortunately, the lower segment contracts less well than the upper segment, and often help is needed from oxytocin and other forms of uterine stimulation. This study simply alerts the clinician to this possibility. However, there is no ready explanation as to why the lower uterine segment site, vacated by the long-gone placenta in the "resolved" group, would be involved in the bleeding after delivery.

Below are some suggestions for dealing with the inadvertent finding in the second trimester of a low-lying or marginal placenta:

1. In the first and second trimester, the term "placenta previa" should be rarely used and the diagnosis should be reserved only for those patients with vaginal bleeding and placentas that are clearly overlapping the cervix.

2. If the patient has had no bleeding, there is no evidence to indicate that she should alter her lifestyle.

3. Have the patient return after 32 weeks to document resolution.

4. Apprise motivated patients wishing to avoid cesarean section, whose placental edges are still 1.0-2.0 cm from the cervix by term, that they have about a 70% chance of delivering vaginally.

5. Be prepared for a greater chance of postpartum hemorrhage, even if the placenta is no longer in the vicinity of the cervix before delivery. ■

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LNG-IUS and Nuisance Bleeding

ABSTRACT & COMMENTARY

By Rebecca H. Allen, MD, MPH

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

Synopsis: *In this randomized, controlled trial, tranexamic acid and mefanamic acid were no better than placebo in reducing the number of bleeding or spotting days in the first 3 months after LNG-IUS placement.*

Source: Sordal T, et al. Management of initial bleeding or spotting after levonorgestrel-releasing intrauterine system placement: A randomized controlled trial. *Obstet Gynecol* 2013;121:934-941.

In this double-blind, randomized, placebo-controlled trial, the investigators evaluated two treatments for the "nuisance" bleeding that commonly occurs in the first few months after the levonorgestrel intrauterine system (LNG-IUS) is placed. The first treatment, tranexamic acid, is an anti-fibrinolytic agent approved for the treatment of heavy menstrual bleeding. The second treatment, mefanamic acid, is a non-steroidal anti-inflammatory drug (NSAID) that is approved for the treatment of primary dysmenorrhea. Women aged 18-45 years with regular menstrual cycles using the LNG-IUS for contraception were included. All women received standardized counseling regarding expected bleeding patterns after LNG-IUS placement. The device was placed within 7 days of the onset of menses and women were randomized to tranexamic acid (500 mg three times daily), mefanamic acid (500 mg three times daily), or placebo (three times daily). The women took the study medications only during a spotting or bleeding episode and were followed for 90 days. Women recorded their bleeding pattern on diary cards: 1) spotting, less than associated with normal menstruation with no need for sanitary protection (except for pantyliners), and 2) bleeding, defined as need for sanitary protection.

A total of 187 women were randomized to one of the three treatments and compliance was high in all three arms (> 80%). The women were recruited from Norway, Ireland, and Denmark and were mainly white (> 96%) with an average body mass index (BMI) of 25 kg/m^2. The median number of bleeding or spotting days during the 90-day treatment period was 25 for tranexamic acid, 29 for mefanamic acid, and 33 for placebo. This difference was not statistically significant. There was also no difference between the three groups in the number or length of bleeding or spotting episodes. Age, BMI, and smoking did not influence the results. Overall satisfaction with the LNG-IUS was high in all three groups with 85% or more women reporting being satisfied.

■ COMMENTARY

The majority of women who discontinue the LNG-IUS device do so in the first 6 months of use and irregular bleeding is the number one reason cited.[1] On average,

in the first 90 days after LNG-IUS insertion, women may experience 36 days of bleeding or spotting.[2] However, this pattern improves over time and at the end of 1 year, approximately 20% of women will be amenorrheic.[3] Therefore, women should be counseled on expected bleeding patterns with the LNG-IUS. However, if an effective treatment for "nuisance" or unscheduled bleeding and spotting existed, it may prevent discontinuation and increase satisfaction rates. The purpose of this trial was to evaluate two potential treatments for the "nuisance" bleeding that women may experience in the first few months of LNG-IUS use and compare those to standard counseling about expected bleeding patterns. The authors of this study chose to administer the treatment when the bleeding actually occurred rather than prophylactically. Unfortunately, they were unable to show that mefanamic acid or tranexamic acid decreased bleeding or spotting in the first 3 months of LNG-IUS use. However, the dose of tranexamic acid used was much lower than that typically prescribed for heavy menstrual bleeding (1300 mg three times daily for 5 days).

Most of the research performed on unscheduled bleeding with progestin-only contraceptives has been conducted with contraceptive implants or depot medroxyprogesterone acetate.[4] Agents studied have included NSAIDs, tranexamic acid, mifepristone, estradiol, and doxycycline. Interventions for the LNG-IUS are less studied, perhaps because the evidence shows the bleeding pattern will improve so most providers and women are willing to wait. One previous study mentioned by the authors of this current paper examined naproxen and transdermal estradiol administration for unscheduled bleeding in the first 3 months after insertion.[5] In this randomized, controlled trial, the naproxen was dosed at 500 mg twice daily for the first 5 days of each 4-week period after LNG-IUS insertion and transdermal estradiol was dosed at 0.1 mg continuously regardless of bleeding patterns. The investigators found that transdermal estradiol increased the number of bleeding and spotting days (median 44) while the naproxen arm experienced slightly less bleeding and spotting days (median 27.5) compared to placebo (median 32). None of these differences were statistically significant. However, when the data were analyzed by quartiles, women in the naproxen group were more likely to be in the lowest quartile of bleeding and spotting (2-21 days) than women in the placebo group (43% vs 16%). The authors concluded that use of naproxen prophylactically, as studied, contributed to a small decrease in the number of bleeding and spotting days (10%).

A new lower-dose LNG-IUS is now available that contains 13.5 mg of levonorgestrel and releases 14 mcg per day initially, compared to the 52 mg of levonorgestrel in the larger system that releases 20 mcg per day initially.[2] Now that this lower-dose system is on the market, the issue of "nuisance" bleeding with the LNG-IUS may increase. A comparative study did show that, on average, women using the lower dose LNG-IUS seem to experience slightly more bleeding and spotting days over a 3-year period compared to the full dose LNG-IUS.[2] It remains to be seen in clinical practice whether the bleeding profile of the lower-dose system leads to greater discontinuation rates or dissatisfaction compared to the higher-dose system. Our current practice should include thorough counseling about bleeding patterns post-insertion so that women know what to expect. I tell my patients to anticipate 3-6 months of irregular spotting or bleeding before the LNG-IUS exerts its full effect. As far as interventions to offer for unscheduled bleeding, it seems that a trial of NSAIDs would be reasonable. I think it is worth offering some intervention if it will encourage women to continue with the IUD given the benefits of long-acting reversible contraception. We can also look forward to the upcoming release of the Centers for Disease Control and Prevention's Selected Practice Recommendations for Contraceptive Use that will provide some response as to how to treat irregular vaginal bleeding with progestin-only contraceptives. ■

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Targeted Therapy for LGSOC Shows Promise

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *Selumetinib, a selective MEK1/2 inhibitor, achieved objective responses in 15% of patients with recurrent low-grade serous ovarian cancer (LGSOC). The data are relevant as this uncommon tumor type is associated with general chemoresistance, frequent aberration in the MAPK pathway, and prolonged overall survival compared with its more common high-grade variant. Phase 3 trials are planned.*

Source: Farley J, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: An open-label, single-arm, phase 2 study. *Lancet Oncol* 2013;14:134-140.

Low-grade serous carcinoma of the ovary (LGSOC) is a distinct histological variant characterized by chemoresistance, frequent mutations in the MAPK pathway, and prolonged overall survival. Based on its molecular characterization, a Phase 2, open-label, single-arm trial was conducted by the Gynecologic Oncology Group using selumetinib, an oral, selective inhibitor of MEK1/2. This gene is a downstream target of many growth factors for which the ras and raf oncogenes serve as important substrates. In this trial, women (aged ≥ 18 years) with recurrent low-grade serous ovarian or peritoneal carcinoma were given selumetinib (oral 50 mg twice daily) until progression. The primary endpoint was the proportion of patients who had an objective tumor response. Secondary endpoints were progression-free survival (PFS), duration of response, overall survival (OS), toxicity and tolerance of therapy, and an exploratory analysis of K-ras and B-raf mutation was made to response. In all, 52 patients were enrolled in this flexible, two-stage Phase 2 trial over a 2-year period. All patients were eligible for analyses. Eight (15%) patients had an objective response to treatment — one patient had a complete response and seven had partial responses. The median time to response was 4.8 months and the median duration of response was 10.5 months. Thirty-four (65%) patients had stable disease. The median PFS was 11 months and the median OS has not been reached. Thirty-three (63%) patients had non-progressive disease at 6 months. There were no treatment-related deaths. Grade 4 toxicities were cardiac (1), pain (1), and pulmonary events (1). Grade 3 toxicities that occurred in more than one patient were gastrointestinal (13), dermatological (9), metabolic (7), fatigue (6), anemia (4), pain (4), constitutional (3), and cardiac events (2). No correlation to response based on K-ras/B-raf mutation was seen among the 34 patients who had enough genomic DNA for this analysis. The authors concluded that selumetinib is well tolerated and is active in the treatment of recurrent LGSOC; further investigation is warranted in these patients.

■ COMMENTARY

LGSOC is a distinct subset of serous ovarian cancer characterized morphologically by low-grade nuclear atypia and infrequent mitotic counts.[1] Unlike other histologies classified by the World Health Organization, serous cancer is now considered in two tiers: low grade and high grade. These categories do not strictly follow Grade 1 vs Grade 2/3; in fact, a retrospective review of serous histology in a large Phase 3 chemotherapy adjuvant trial demonstrated that 8 of 21 (38%) low-grade ovarian tumors were initially classified as FIGO grade 2/3.[2] This grading scheme has shown strong intra- and inter-pathological validity and was a strength of the current study, as all pathology was reviewed and confirmed on potential participants before registration.[3] Genomically, LGSOC is more closely aligned with serous tumors of low malignant potential (borderline tumors) than to high-grade serous ovarian cancer, despite the two histology types demonstrating invasion and metastatic and recurrence potential.[4] And, like platinum-resistant high-grade serous cancer, LGSOC is dramatically chemoresistant, demonstrating 4% or less objective response to a number of commonly used, FDA-approved cytotoxic agents for ovarian cancer management.[5] Further, it was the identification of mutations in the MAPK pathway (rare in high-grade serous ovarian cancer) that provided the rationale for using a MEK inhibitor in this disease.[6] MEK is a downstream target of a series of growth factor activation (e.g., IGF1-R, EGFR, VEGFR, etc.) that govern important cellular characteristics such as growth, proliferation, and metastases. As was observed in the trial, mutations in the immediate substrates such as ras and raf are frequent and can lead to MEK activation. The observed response rate of 15% is impressive in the patient population given the low likelihood of objective response based on historical data with chemotherapy and hormonal therapy. Although it was disappointing to not see a direct relationship between mutation in these upstream effectors and objective response, there are several caveats to consider: 1) the test samples were from initial diagnosis in most cases (the median number of chemotherapy regimens before trial entry was 3), 2) only the most common K-ras and B-raf mutations were studied, 3) only a proportion of the original population was tested, and 4) there is likely tumor heterogeneity between the primary and metastatic sites. The trial is important because it provides a clear path to potential registration in randomized trials. In these efforts, physician's choice of therapy can be used as a control arm and toxicity profiles can be extremely relevant, even if there are no response or survival differences. Currently, two randomized trials of a MEK inhibitor vs physician's choice are set to begin this year. It is a unique opportunity to demonstrate targeted therapy in a subset of ovarian cancer patients where effective options, other than more surgery, are limited. ■

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DRSP and Thrombosis: Do Gathering Clouds Imply a Storm or Poor Visability?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *A review of incident cases of venous thrombosis in women using oral contraceptives (OCs) in a U.S. insurance database found that use of drospirenone-containing OCs containing 20 µg of ethinyl estradiol (EE) was associated with a two-fold increase in risk compared to levonorgestrel pills. This risk was not increased with use of 30 µg EE drospirenone pills.*

Source: Bird ST, et al. Drospirenone and non-fatal venous thromboembolism: Is there a risk difference by dosage of Ethinyl-Estradiol? *J Thromb Haemost* 2013; Apr 11 [Epub ahead of print].

Several prior database studies have demonstrated an increased risk of venous thromboembolism (VTE) with third-generation and drospirenone (DRSP)-containing combined oral contraceptive (COC) pills when compared to levonorgestrel (LNG)-containing COCs, but the expected estrogen dose-response relationship has not been consistent. To determine whether DRSP and ethinyl-estradiol 20 µg (DRSP/EE20) had a lower VTE risk than DRSP and ethinyl-estradiol 30 µg (DRSP/EE30), the authors performed a retrospective cohort analysis using the IMS LifeLink Health Plan Claims Database from the United States. The cohorts were assembled using the claims database to identify women aged 18-46 years taking DRSP- or LNG-containing COCs. The diagnosis of VTE was defined using ICD-9-CM coding and required anticoagulation. The VTE relative risk (RR) was calculated using a Cox proportional hazards model comparing DRSP and LNG users, and the cohorts were further stratified by EE dose and user-type (new/prevalent). A propensity score was used to control for baseline comorbidities such as BMI and other potential confounders.

This large database included 238,683 DRSP and 193,495 LNG users. Overall, the incidence of VTE was 18/10,000 women-years (WY) among DRSP users, and 8.9/10,000 WY among women using LNG COCs (relative risk [RR], 1.90; 95% confidence interval [CI], 1.51-2.39). However, when EE dose was considered, the risk was confined to new users of DRSP/EE20 pills (RR, 2.35; 95% CI, 1.44-3.82) compared to new users of LNG/EE20. In contrast, an increased risk for DRSP/EE30 new users relative to LNG/EE30 new users was observed only among women initiating COCs between 2001-2006 (RR, 2.51; 95% CI, 1.12-5.64), with a reversal of the point estimate seen during 2007-2009 (RR 0.76, 95% CI; 0.42-1.39). A decrease in the risk of VTE with a reduction in EE dose was not observed: In direct comparison DRSP/EE20 had an elevated VTE risk relative to DRSP/EE30 (RR, 1.55; 95% CI, 0.99-2.41), but this was not statistically significant.

■ COMMENTARY

The DRSP VTE controversy may seem like old news, and the issue has been extensively covered in previous issues of *OB/GYN Clinical Alert*. Although the issue may seem resolved for those of us in the United States with new product labeling for DRSP-containing pills, the issue is still contentious in Europe. The controversy was recently reignited by highly publicized cases of VTE in young women using the cyproterone acetate (CPA)-containing COC (Diane 35®) in France. Although this pill (not available in the United States) has been on the market for more than 30 years, a cluster of reports of rare VTE events led to public outcry and a national investigation that resulted in the withdrawal of Diane from the French market and to recommendations for further restrictions on COC prescribing. This new firestorm has been powered by the recent publication of case-control and database studies supporting an increased VTE risk associated with use of third-generation progestogens, CPA, and DRSP compared to LNG. Although highly consistent, the risk estimates that come from these studies are controversial, as similar results were not observed in the true prospective study conducted by Dinger et al.[1] The wind that fans the fire blows directly from Denmark in the form of the large Danish database studies published by Lidegaard.[2,3] More about the European story will come in a Special Feature in our next issue, but it seems appropriate to comment on the Bird study now.

Since VTE is a rare (defined as an incidence of < 1/1000) event in otherwise healthy young women using the pill, large numbers of individuals must be studied to obtain statistically valid comparisons. For this reason, it is easy to see the attraction and rationale behind the use of large national insurance claims databases to address rare serious adverse events. Unfortunately, the Achilles' heel of claims database studies is the inability to accurately evaluate the presence of important baseline confounders. Confounders are factors that are associated both with inclusion in a cohort and with the outcome of interest. In modern database studies, complex schemes such as propensity scores are constructed to adjust for the presence of missing confounders that are simply not available in the record. Unfortunately, this is subjective, and the technics used can artificially influence the results. As inconvenient as it may be, there is no substitute for real prospective

data. This makes interpretation of risk estimates smaller than 2-3 extremely hazardous.

Personally, I don't find the evidence convincing that the type of progestogen in a COC modifies the risk of VTE. One of the basic issues I struggle with is the lack of biologic plausibility, as no definitive mechanism for a progestogen-effect on coagulation has been demonstrated. In contrast, the biologic response of the coagulation system to estrogen is well established. This response to estrogen is a physiologic and life-saving evolutionary tactic to prevent hemorrhage during childbirth. A reduction in VTE risk in response to a decrease in EE dose has been observed for more than 40 years.[4] Not surprisingly, the resolution of epidemiologic studies has proven insufficient to determine whether a continued decrease in the dose of EE below 35 µg further reduces VTE risk. In fact, a paradoxical increase in risk with 20 µg compared to 30 µg desogestrel-containing pills was observed in several studies during the third-generation progestogen pill scare of the 1990s.[5-7] Taken together, these observations led many experts to conclude that the third-generation progestogen scare was unwarranted, and the data seemed seriously compromised by preferential prescription of newer pills to high-risk women. Denying this suggests a fantasy world contrary to our current understanding of the coagulation system. The inverse dose-response reported by Bird et al in the current manuscript is consistent with these earlier reports and equally unlikely to be true.

Although at first glance the overall elevated risk associated with DRSP compared to LNG pills reported in the Bird study seems to support the findings of earlier studies, the data actually provide evidence that the increased risk association reported by Lidegaard and others may in fact be spurious. The drop in risk for the 30 µg DRSP pill over time demonstrates both a healthy user effect and a likely shift of high-risk users to both LNG pills and 20 µg DRSP pills.[8] Taken together, this suggests that the observed association of an increased risk associated with DRSP pills in all database studies is an artifact attributable to preferential prescribing to high-risk women. Look for more about this in the August Special Feature. ■

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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. **What is considered an appropriate test to determine ovarian reserve in a reproductive-aged woman?**
   a. Midluteal progesterone
   b. Endometrial biopsy
   c. Anti-Müllerian hormone
   d. LH:FSH ratio

2. **Which of the following is appropriate to the data regarding placental position at term if the placental edge is between 1 and 2 cm from the cervix?**
   a. The rate of antepartum bleeding is about 20%.
   b. The cesarean section rate is 31%.
   c. The chance of vaginal delivery is less than 50%.
   d. There is no evidence to support trying a vaginal delivery.

3. **In which of the following ways are low-grade serous ovarian cancer and high-grade ovarian cancer similar?**
   a. Ability to invade and metastasize
   b. High rate of P53 mutation
   c. Short overall survival
   d. High rate of initial chemosensitivity
   e. Frequent mitotic figures

4. **Which of the following is the most likely explanation for the observed increase in venous thromboembolism risk among 20 µg ethinyl-estradiol drospirenone pills compared to 30 µg drospirenone pills?**
   a. Preferential prescription of the 20 µg pills to high-risk women
   b. Reduced inhibition of hepatic cytochrome pathways activated by drospirenone
   c. Preferential prescription of the 20 µg pills to younger healthy women
   d. Use of the 30 µg pills in women with a family history of breast cancer

In Future Issues:

Another Pill Scare: What Should Be Our Response?

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PHARMACOLOGY WATCH

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

Is Naproxen the Safest NSAID for the Heart?

In this issue: NSAIDs and cardiovascular risk; new antithrombotic guidelines; warfarin during surgery; Pfizer selling Viagra online; azithromycin and cardiovascular risk; and FDA actions.

NSAIDs associated with less vascular risk

Naproxen may be the safest anti-inflammatory — at least when it comes to cardiovascular risk — according to a new study. Researchers from the United Kingdom undertook a meta-analysis of 280 trials of non-steroidal anti-inflammatory drugs (NSAIDs) vs placebo and 474 trials of one NSAID vs another. Main outcomes were major vascular events, major coronary events, stroke, mortality, heart failure, and upper gastrointestinal (GI) complications including bleeding. All NSAIDs and COX-2 inhibitors (coxibs) increased major vascular events except for naproxen (rate ratio [RR], coxibs 1.37 [95% confidence interval (CI), 1.14-1.66; $P = 0.0009$] and diclofenac 1.41 [95% CI, 1.12-1.78; $P = 0.0036$] mostly due to an increase in major coronary events). Ibuprofen also significantly increased the risk of major coronary events (RR 2.22, 95% CI, 1.10-4.48; $P = 0.0253$), but not major vascular events. Naproxen did not significantly increase the risk of major vascular events. Coxibs and diclofenac also significantly increased risk of vascular death, and there was a nonsignificant increase with ibuprofen, while there was no increase with naproxen. Heart failure risk was roughly doubled by all NSAIDs. The risk of upper GI complications was lowest with coxibs and highest with naproxen (coxibs 1.81, 95% CI, 1.17-2.81; $P = 0.0070$; diclofenac 1.89, 95% CI, 1.16-3.09; $P = 0.0106$; ibuprofen 3.97, 95% CI, 2.22-7.10; $P < 0.0001$, and naproxen 4.22, 95% CI, 2.71-6.56; $P < 0.0001$). The authors conclude that the vascular risks of diclofenac and possibly ibuprofen are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk (but higher GI risk) than other NSAIDs (*Lancet* published online May 30, 2013). The authors speculate that high-dose naproxen has fewer cardiovascular effects because it is the strongest inhibitor of COX-1, resulting in near complete suppression of platelet thromboxane biosynthesis (thus blocking platelet aggregation) throughout the 12-hour dosing interval. ■

New antithrombotic guidelines

A new guideline from the American Academy of Neurology gives primary care doctors guidance on periprocedural management of antithrombotic medications in patients with a history of stroke. Among the recommendations is that stroke patients undergoing dental procedures should routinely continue aspirin. Aspirin should also be considered for continuation in stroke patients undergoing invasive ocular anesthesia, cataract surgery, dermatologic procedures, transrectal ultrasound-guided prostate biopsy, spinal/epidural procedures, and carpal tunnel surgery. Aspirin should possibly be continued during other procedures such as virtroretinal surgery, EMG, transbronchial lung biopsy, colonoscopic polypectomy, upper endoscopy and biopsy/sphincterotomy, and abdominal ultrasound-guided biopsies. For stroke patients on warfarin, the guideline recommends continuation of the drug

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during dental procedures and probably during most dermatologic procedures. Other more invasive procedures should warrant discussion. The guideline states there is insufficient evidence to support or refute periprocedural heparin-bridging therapy to reduce thromboembolic events in chronically anticoagulated patients. Bridging therapy is probably associated with increased bleeding risk as compared with warfarin cessation, but the risk difference compared with continuing warfarin is unknown (*Neurology* 2013;22:2065-2069). ■

Continuing warfarin for surgery

In related news, a new study suggests that continuing warfarin for pacemaker or defibrillator surgery is safer than heparin bridging. Nearly 700 patients with an annual risk of thromboembolic events of ≥ 5% who required pacemaker or defibrillator surgery were randomized to continued-warfarin treatment or bridging therapy with heparin. The primary outcome was clinically significant device-pocket hematoma, which occurred in 12 of 343 patients (3.5%) in the continued-warfarin group as compared with 54 of 338 (16.0%) in the heparin-bridging group. There was one episode of cardiac tamponade and one myocardial infarction in the heparin-bridging group and one stroke and one TIA in the continued warfarin group. This study was stopped early after interim analysis found that the primary outcome occurred four times as often in the heparin-bridging group. These findings suggest that a strategy of continued warfarin therapy at the time of pacemaker or defibrillator surgery markedly reduced incidence of clinically significant device pocket hematoma as compared with heparin bridging (*N Engl J Med* 2013;368:2084-2093). ■

Pfizer launches own Viagra website

Pfizer is aggressively pursuing the online market for sildenafil (Viagra) by launching its own "Viagra home delivery" website. The drug will be available online directly from Pfizer but will still require a doctor's prescription. This move is also designed to counter online marketing of counterfeit Viagra, the most commonly counterfeited drug in the world. Pfizer plans to make Viagra available online at approximately $25 a pill. Meanwhile, the company has lost patent protection for its other version of sildenafil citrate marketed for pulmonary hypertension under the trade name Revatio. This version of the drug is only available in 20 mg strength, but is otherwise identical to Viagra, which is available in 25, 50, and 100 mg strengths. It is yet to be seen whether physicians will prescribe generic 20 mg sildenafil off label for erectile dysfunction. ■

Azithromycin and cardiovascular risk

Does azithromycin increase cardiovascular (CV) risk? A recent observational study showed that azithromycin was associated with a 2-3 times higher risk of death from CV disease in patients at high risk for CV disease (*N Engl J Med* 2012;366:1881-1890). A new study looks at the risk of the drug vs placebo and a comparator antibiotic (penicillin V) in Danish adults ages 18-64. As compared with no use of antibiotics, use of azithromycin was associated with a significantly increased risk of CV death (rate ratio 2.85; 95% CI, 1.13-7.24); however, when compared to penicillin V, there was no increased risk (crude rate CV death 1.1/1000 person years azithromycin vs 1.5/1000 penicillin V). With adjustment for CV risk, current azithromycin use was not associated with increased risk of CV death compared with penicillin V in a general population of young and middle-aged adults. (*N Engl J Med* 2013;368:1704-1712). This study is reassuring, suggesting that the increased risk of death is probably due to the illness rather than the drug, especially in low-risk populations. However, the risk of the macrolides still should be considered among patients with a high baseline risk of CV disease. ■

FDA actions

The FDA has approved a new once-daily combination inhaler for the treatment of chronic obstructive pulmonary disease (COPD). The product combines the long-acting beta-agonist (LABA) vilanterol with the steroid fluticasone furoate. Vilanterol is a new LABA and fluticasone furoate is reported to have longer lung retention time compared to the proprionate allowing for once-daily dosing. The product is a dry powder that is delivered via the Ellipta device. The new inhaler was evaluated in 7700 patients with COPD and showed improved lung function and reduced exacerbations compared to placebo. Vilanterol/fluticasone furoate is marketed by GlaxoSmithKline in collaboration with Theravance as Breo Ellipta.

The FDA has approved a new cholesterol combination drug, combining ezetimibe and atorvastatin. The drug is indicated for lowering cholesterol in patients with primary or mixed hyperlipidemia and in those with homozygous hypercholesterolemia. It is approved in four strengths, each containing 10 mg of ezetimibe with 10, 20, 40, or 80 mg of atorvastatin. The combination reduces LDL cholesterol levels up to 61% in clinical trials. Like the previously marketed simvastatin/ezetimibe, there is no evidence that the combination improves cardiovascular outcomes over a statin alone. The combination will be marketed by Merck as Liptruzet. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

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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Food Allergy in IBS: Patch Testing

Source: Stierstorfer MB, et al. Food patch testing for irritable bowel syndrome. *J Am Acad Dermatol* 2013;68:377-384.

We have, as yet, no fully satisfactory etiologic explanation for the symptom complex recognized as irritable bowel syndrome (IBS). Yet, demonstration of various derangements — hypersensitivity to neurogenic stimuli, altered bowel flora, dysregulation of serotonin — has been seen in subgroups of persons with typical IBS. Results from IBS trials of non-systemic antibiotics (e.g., rifaximin) demonstrate improvements in IBS symptoms and support bacterial flora imbalance in some, but not all, IBS subjects.

IBS patients commonly report foods that exacerbate symptoms. Could these food sensitivities represent actual food allergy, and contribute etiologically to IBS? A variety of commonplace foods and food additives have been documented to cause allergic *cutaneous* contact dermatitis (type-4 hypersensitivity). Could similar responses lead to inflammatory changes in the gut and symptoms of IBS?

Stierstorfer et al performed patch testing in IBS subjects (n = 51) using up to 40 different foods or food additives that have been previously recognized as implicated in food hypersensitivity. Fifty-eight percent of subjects had one or more patch test results indicating possible food sensitivity, and when the "offending" food was eliminated from the diet, about two-thirds of subjects reported symptomatic improvement. Food allergy may play a more important role in IBS than previously recognized. ■

A Relationship Between Atrial Flutter and Sleep Apnea

Source: Bazan V, et al. Obstructive sleep apnea in patients with typical atrial flutter: Prevalence and impact on arrhythmia control outcome. *Chest* 2013;143:1277-1283.

Commonly recognized consequences of obstructive sleep apnea (OSA) include increased risk for hypertension, cardiovascular events, and arrhythmias, the most common of which is atrial fibrillation (AFib). Less well understood is the relationship between atrial flutter (AF) and OSA. Even though invasive treatment through catheter ablation is highly effective for AF, over the long term, as many as one-third of AF ablation patients develop postoperative AFib, which of course has its own toxicities.

Bazan et al evaluated a preoperative population of AF patients with polysomnography, none of whom had previously been diagnosed with or suspected of OSA. Overall, 82% of subjects were diagnosed with OSA, almost half of whom were graded as severe OSA.

Over the ensuing 12 months, use of continuous positive airway pressure (CPAP) in OSA patients who had received catheter ablation for AF resulted in a dramatic reduction in new postoperative AFib: from 46% (untreated) to 6% (treated).

OSA appears to be more commonplace in AF than previously recognized. Although a much larger randomized clinical trial will be necessary for confirmation, this small study suggests that for AF patients with OSA who are undergoing catheter ablation, CPAP substantially reduces the likelihood of postoperative AFib. ■

Beyond Hypertension: Metabolic Effects of Telmisartan

Source: Takagi H, et al. Telmisartan as a metabolic sartan: The first meta-analysis of randomized controlled trials in metabolic syndrome. *J Am Soc Hypertens* 2013;7:229-235.

It has not gone unnoticed that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) can sometimes have a favorable effect on glucose metabolism in diabetics and prediabetics. Experts have opined that it is perhaps vascular dilation in the skeletal muscle compartment from renin-angiotensin-aldosterone system blockade that produces increased glucose utilization. One of the ARBs, telmisartan, in addition to its blood pressure-lowering effect, has been noted to have peroxisome proliferator-activated receptor (PPAR)-gamma activation activity, distinct from the other members of this drug class. PPAR-gamma activation could favorably impact metabolic syndrome, but individual clinical trials of telmisartan have been inconclusive in this regard.

Takagi et al performed a meta-analysis of clinical trials (n = 10) of telmisartan in patients (n = 546) with metabolic syndrome. Favorable effects were seen for

fasting glucose, insulin, and A1c. Of the 10 trials analyzed, only three included data on adiponectin, but results were also favorable for this metric.

Large clinical trials of telmisartan in patients with established vascular disease (e.g., TRANSCEND, n = 5926) have shown a nonsignificant trend toward less new onset diabetes, but the number of metabolic syndrome subjects in this trial was not specified.

Whether favorable changes seen in metabolic syndrome patients treated with telmisartan are sufficient to improve "hard" outcomes (myocardial infarction, cerebral vascular accident, diabetes mellitus) would require a very large clinical trial. ■

Risk of New Onset Diabetes with Statins

Source: Danaei G, et al. Statins and risk of diabetes: An analysis of electronic medical records to evaluate possible bias due to differential survival. *Diabetes Care* 2013;36:1236-1240.

The oft-quoted "9% increase in new onset diabetes (NODM) due to statins" sounds pretty scary. What is left out of the aforementioned quote, however, is that the increased risk is a *relative*, not *absolute*, increase. To make the issue more concrete: In one of the largest meta-analyses (n = 91,000), we learned that statins increase risk for diabetes. Among 45,521 statin-treated patients, there were 2226 NODM cases (compared to 2052 of 45,619 placebo recipients); the incidence of NODM then was 4.89% in the statin group, compared to 4.5% in the placebo group, for an underwhelming risk increase of 0.39%. This would translate into a number needed to treat of 250 patients receiving a statin to induce one new case of diabetes. Not nearly so scary, huh?

The most recent analysis of NODM compiled data from the electronic medical records of 500 United Kingdom general practices (n = 285,864). Similar to the above mentioned meta-analysis, the absolute annual incidence in the United Kingdom dataset was 1.59% in statin users compared to 1.13% in nonusers.

Statins can cause NODM, but in trials of secondary prevention, risk of NODM is far outweighed by risk reduction for cardiovascular events. ■

Perimenstrual Asthma: A High-Risk Phenotype

Source: Rao CK, et al. Characteristics of perimenstrual asthma and its relation to asthma severity and control: Data from the severe asthma research program. *Chest* 2013;143:984-992.

Some women with asthma note a worsening of asthma related to onset of menses. In the National Heart, Lung, and Blood Institute Severe Asthma Research Program (SARP), 17% of women (92/483) reported that menses were a trigger for their asthma symptoms. Exploration of perimenstrual asthma (PMA) as a distinct phenotype has been prompted by the recognition of an association between PMA and asthma acuity. Indeed, near-fatal and fatal asthmatic events have been linked to PMA.

Evaluation of women identified with PMA from SARP found that nearly twice as many PMA subjects met criteria for classification as severe asthma than women without PMA. In addition, levels of asthma control were worse in PMA subjects, and they experienced greater urgent health care utilization. Aspirin sensitivity was found three times more often in PMA patients (30% vs 10%), as were nasal polyps (16% vs 5%).

At the current time, PMA is not a widely appreciated entity. In the United States, there are still approximately 5000 asthma deaths per year. Any phenotypic prototype that can help to identify an asthma population at greater risk of fatal or near-fatal asthma might be a step toward reducing the mortality burden of asthma. ■

What's the Durability of Lifestyle Change in Type 2 Diabetes?

Source: Jakicic JM, et al. Four-year change in cardiorespiratory fitness and influence on glycemic control in adults with type 2 diabetes in a randomized trial: The Look AHEAD trial. *Diabetes Care* 2013; 36:1297-1303.

Embarking on lifestyle change is widely reinforced early on by numerous incidental happenstances. First, response to diet is most prominent in the early weeks of dieting. Second, relative gains in fitness and strength are most obvious in the early weeks of dieting. Third, most support programs providing advisors for diet, exercise, and psychological aspects are "front-loaded" (greater frequency/intensity at first) to try and establish optimum patterns early on. Fourth, as one gains positive initial steps, observers and friends tend to be avid supportive "cheerleaders," a response that diminishes as the going gets tougher, occasional ground is lost, or ground gained is less visible.

Jakicic et al report on the outcome at 4 years in the Look AHEAD Research Group trial. Overweight or obese type 2 diabetics (n = 3942) were randomized to intensive lifestyle intervention (ILI) or standard care. ILI included weekly instructional/support sessions × 24, continuing with lesser (but still frequent) support on diet and exercise throughout 4 years time. Goal exercise time was 175 minutes a week of brisk walking or the equivalent. As perhaps is intuitive, the intervention group achieved and maintained better fitness levels, better A1c, and better weight control. Structured ILI programs can provide sustained benefits in overweight and obese type 2 diabetics. ■

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