Providing Evidence-based Clinical Information for 25 Years

OB/GYN CLINICAL ALERT®

A monthly update of developments in female reproductive medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure: *OB/GYN Clinical Alert*'s editor, Jeffrey T. Jensen, MD, MPH, receives research support from, is a consultant to, and serves on the speakers bureau of Bayer Healthcare/ Bayer Schering; he also receives research support from Wyeth and Warner-Chilcott and is a consultant to Schering Plough. Peer reviewer Catherine LeClair, MD, reports no financial relationship to this field of study.

Placenta Previa: Distance to Internal Os and Mode of Delivery

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor and Chief of Obstetrics,
University of Colorado Health Sciences Center, Denver

Dr. Hobbins reports no financial relationship to this field of study.

Synopsis: *The authors of this large Italian study showed that two-thirds of patients with placentas 10-20 mm from the cervix and one-third of those between 1-10 mm can safely deliver vaginally, and explored the concept that patients with placental edges within 2 cm of the endocervix should be defined as having placenta previa.*

Source: Vergani P, et al. Placenta previa: Distance to internal os and mode of delivery. *Am J Obstet Gynecol* 2009;201:266.e1-5.

IT IS UNCLEAR WHERE THE IDEA ORIGINATED THAT THE DEFINITION OF placenta previa would include placentas that are within 2 cm of the endocervix. However, this concept has been so heavily ingrained in today's practice that it is rare now for a patient to escape a planned cesarean section once this diagnosis is made late in pregnancy.

A group from Italy recently published a study that dealt with outcomes of pregnancies where the placental edges were within 2 cm of the endocervix. Vergani and colleagues evaluated 120 patients diagnosed to have placenta previa by vaginal ultrasound examinations, which were done within 28 days of delivery. Since the study involved 14,973 patients delivering over a 5-year period, the incidence of placenta previa was 8/1000.

The brave management protocol included attempting vaginal deliveries for those whose placentas were less than 2 cm from the endocervix and, obviously, sectioning all those at 37-39 weeks whose placentas were overlapping the cervix.

VOLUME 26 • NUMBER 7 • NOVEMBER 2009 • PAGES 49-56

OB/GYN CLINICAL ALERT IS AVAILABLE ONLINE
www.ahcmedia.com

Forty-two patients had planned cesarean sections for overlapping placentas. After excluding those patients whose placentas had moved away from the cervix by more than 2 cm before delivery and those whose last ultrasound examinations were more than 28 days prior to delivery, 53 patients remained. They were all given a trial of labor.

The results were divided into 2 categories. Group 1 included 24 patients with placentas that were 1-10 mm from the cervix; group 2 had 29 patients whose placentas were between 10-20 mm away. The rates of cesarean section were 75% for group 1 vs 31% for group 2 (odds ratio [OR], 6.7; 95% confidence interval [CI], 2-26). The incidence of bleeding before labor was 29% vs 3%, respectively (OR, 11.5; 95% CI, 1.5-76). Blood loss during delivery and postpartum hemorrhage were essentially the same between groups.

■ COMMENTARY

This study strongly suggests that 2 of 3 patients with low-lying placentas (10-20 mm from the cervix) can deliver safely by the vaginal route, and, surprisingly, even 1 of 3 highly motivated patients with placental edges that are within 10 mm from the cervix can deliver vaginally without major increased risk of intrapartum or postpartum hemorrhage.

There are clearly some limitations in the study such as bias in the management of these patients, since the providers were not blind to the ultrasound results. Another factor that may make the 10-20 mm group look better is that in some cases the last scans were performed up to 28 days prior to the scan in delivery — time enough for the placentas, through relative placental migration, to move into "non-previa" land.

Nevertheless, the authors of the study imply, Oppenheimer and Farine in a companion editorial state,[1] and I wholeheartedly agree, that the old definition of placenta previa, whose origin has been nebulous from the start, should be scrapped. Patients with ultrasound information within a week of delivery (and preferably performed on the labor and delivery floor on admission), indicating that their placentas are within 2 cm of the endocervix, now can be counseled with the above data in mind. ■

Reference

1. Oppenheimer LW, Farine D. A new classification of placenta previa: Measuring progress in obstetrics. *Am J Obstet Gynecol* 2009;201;227-229.

OB/GYN Clinical Alert, ISSN 0743-8354, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen
DIRECTOR OF MARKETING: Schandale Kornegay
SENIOR MANAGING EDITOR: Paula Cousins

Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to **OB/GYN Clinical Alert**, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421
Editorial E-Mail: paula.cousins@ahcmedia.com
Customer Service E-Mail: customerservice@ahcmedia.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
Add $17.95 for shipping & handling
(Resident/Student rate: $125).

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482

Canada
Add GST and $30 shipping

Elsewhere
Add $30 shipping

Accreditation

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the OB/ GYN. It is in effect for 36 months from the date of the publication.

AHC Media LLC

Questions & Comments
Call **Paula Cousins**, Senior Managing Editor, at (404) 262-5468.

Advocating Vaginal Hysterectomy

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

Clinical Professor, Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine, Nashville

Dr. Ling reports no financial relationship to this field of study.

Synopsis: *The stated goal of describing "… some of the advantages of the vaginal route in order to help vaginal surgery schools to re-establish the leading role of this approach as part of the minimally invasive gynecological surgery trend" is addressed in a systemic review of key findings in the literature.*

Source: Salcedo F. Vaginal hysterectomy in non-prolapsed uteruses: "No scar hysterectomy." *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20:1009-1012.

THIS IS AN ALMOST BLATANT ADVERTISEMENT FOR vaginal hysterectomy. So the astute reader would

logically ask, "Why is this being reviewed in this newsletter? Aren't we supposed to be getting the cutting edge literature to help us advance our practice?" Fair questions, and there is actually a logical answer. Since the newest literature is being generated on the most recent advances in gynecologic surgery, the old standbys don't often get attention in a fashion that encourages the physician or patient to view the entire surgical landscape. It's a bit like the nightly news in that rarely does one hear a story about how things are going well.

As more clinical emphasis and research endeavors point toward minimally invasive surgery, the author points out in this "Current Opinion/Update" piece that vaginal hysterectomy is, in fact, also minimally invasive. It just doesn't happen to be "new." The author also correctly points out that since the advent of laparoscopic hysterectomy (be it laparoscopic-assisted or total laparoscopic), the commercial interests behind the laparoscopic approach should not be ignored. Of note, he refers to the recent reports of use of the vaginal route for laparoscopic cholecystectomies and nephrectomies as an indication that the gynecologist as vaginal surgeon can be in charge of the destiny of this surgical technique.

The primary reasons for not performing vaginal hysterectomy are listed and literature is cited for each one that refutes these common misconceptions. He describes these as "myths" and focuses on the key point, "In the end, it is actually the surgeon's experience and skills that will play the decisive role … ." How many of the 5 contraindications to vaginal hysterectomy *(see Table, below)* have you heard used to justify an alternative approach?

Just as he is able to refute the contraindications, he points out the advantages of the vaginal approach over both the abdominal and laparoscopic approaches. As compared with the abdominal approach, the literature shows that there is less surgical time, less post-operative ileus, less pain, fewer hospital days, less time to return to full function, fewer scar complications, and less risk for those with medical problems.

Comparing the vaginal approach with the laparoscopic approach, he notes that the recovery time is similar, the vaginal approach can be learned faster, there are no trocar/pneumoperitoneum risks, general anesthesia is not mandatory, and the cost for instrumentation is less.

Table

Common contraindications to vaginal hysterectomy

- No prolapse
- Uterus is too big
- History of cesarean or abdominopelvic surgery
- No previous vaginal delivery
- Oophorectomy needed

■ COMMENTARY

The author recommends that the vaginal hysterectomy be advocated for in medical schools and training programs. Those are indeed places where the basics are taught and the role of various surgical approaches are learned. I would add, however, that the readers of this publication are the real keys to success in that how an individual practices is a reflection of the environment that he/she finds himself/herself in. I refer to my own practice in which we have both senior gynecologists who use vaginal surgery extensively, as well as younger, less experienced surgeons who have trained relatively recently and whose numbers of cases are limited.

You are, by definition, in one of those two groups, i.e., either you are comfortable performing vaginal hysterectomy, often in the face of the "contraindications" listed in the Table or you tend to accept those contraindications and lean toward either abdominal or laparoscopic approaches. May I suggest that if you are in the first group, that you make yourself available to junior partners or colleagues at your hospital to assist in surgery to show them the "tricks of the trade." Alternatively, you can be part of the local teaching program in which you can teach those still in training. As fewer faculty are extensively experienced in vaginal surgery (similar to the problem of operative vaginal delivery), having input from part-time or volunteer clinicians will be increasingly important.

Alternatively, if you are in the second group, I encourage you to link up with a surgical mentor who can enhance your surgical training from residency with different approaches or thought processes. Attending meetings that focus on surgical technique (even without hands-on opportunities) can often aid in addressing your surgical questions.

I totally agree with the author of this review. The future of vaginal surgery is in the hands of those who are able to both perform as well as advocate it. Newer is not always better, it's just newer. Therein lies the challenge for all of us: How do we best serve our patients who need a hysterectomy? You can be the best judge, one patient at a time. ■

Risk of VTE with Oral Contraceptives

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *The risk of venous thrombosis associated with oral contraceptive use correlated with ethinyl estradiol dose and was lowest in users of levonorgestrel combination pills.*

Source: van Hylckama Vlieg A, et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: Results of the MEGA case-control study. *BMJ* 2009;339:b2921.

In a population-based case-control study from the Netherlands, combined oral contraceptives increased the risk of venous thrombosis (VTE) fivefold compared with non-use (odds ratio [OR], 5.0; 95% confidence interval [CI], 4.2-5.8). The risk of VTE was lowest in users of oral contraceptives containing levonorgestrel (OR, 3.6; 95% CI, 2.9-4.6), and highest in users of products containing gestodene (OR, 5.6; 95% CI, 3.7-8.4), desogestrel (OR, 7.3; 95% CI, 5.3-10.0), cyproterone acetate (OR, 6.8; 95% CI, 4.7-10.0), and drospirenone (OR, 6.3; 95% CI, 2.9-13.7). The highest risk was seen in the first 3 months of use and risk was positively correlated with estrogen dose.

Synopsis: *Combination oral contraceptives containing desogestrel, gestodene, or drospirenone were associated with a significantly higher risk of venous thrombosis than oral contraceptives containing levonorgestrel.*

Source: Lidegaard O, et al. Hormonal contraception and risk of venous thromboembolism: National follow-up study. *BMJ* 2009;339:b2890.

A cohort study using the population-based Danish National Registry showed that the risk of venous thrombosis in current users of combined oral contraceptives decreases with increasing duration of use and decreasing estrogen dose. The overall absolute risk of venous thrombosis per 10,000 woman-years in non-users of oral contraceptives was 3.01 and in current users was 6.29. Compared with non-users of combined oral contraceptives the rate ratio of venous thromboembolism in current users decreased with duration of use (< 1 year, 4.17 [95% CI, 3.73-4.66]; 1-4 years, 2.98 [95% CI, 2.73-3.26]; and > 4 years, 2.76 [95% CI, 2.53-3.02]) and with decreasing dose of estrogen. Compared with oral contraceptives containing levonorgestrel (LNG; RR = 1), an increased risk was seen with products containing desogestrel: 1.82 (95% CI, 1.49-2.22); gestodene: 1.86 (95% CI, 1.59-2.18); drospirenone: 1.64 (95% CI, 1.27-2.10); and cyproterone acetate: 1.88 (95% CI, 1.47-2.42). Compared with non-users of oral contraceptives, the rate ratio for venous thromboembolism was not increased in users of progestogen-only oral contraceptives (levonorgestrel or norethisterone: RR 0.59 [95% CI, 0.33-1.03]; 75 μg desogestrel: RR, 1.12 [95% CI, 0.36-3.49]; and for users of the LNG-intrauterine system [IUS]: RR, 0.90 [95% CI, 0.64-1.26]).

■ COMMENTARY

The simultaneous publication of these 2 epidemiologic studies of the risk of venous thrombosis in oral contraceptive users in a leading general European medical journal, received considerable press in the United Kingdom but less notice here. The results deserve scrutiny as we review this important topic once again.

Oral contraceptives (OCs) will celebrate 50 years of market approval in the United States next year, and arguably represent one of the most important breakthroughs in human social biology. While a variety of excellent contraceptive choices currently exist, the availability and acceptance of oral contraception paved the path toward the improved status and equality of opportunity that women enjoy today. OCs represent the gold standard by which other highly effective reversible methods are measured. Combined OCs also provide a myriad of non-contraceptive health benefits and are broadly useful in female heath care.

Decisions in clinical medicine (as in life) require consideration of both benefit and risk. One of the important risks of combined OCs is thrombosis. Consistent evidence over the last 40 years has established that the risk of venous and arterial thrombosis is increased among users of combined OCs compared to non-pregnant non-users. Most of us probably quote the textbook statistic that the baseline risk is about 2 cases of VTE/10,000 women, with 4 cases/10,000 among users of OCs and 6 cases/10,000 in pregnant women. However, the literature reviewed by Heinemann and Dinger shows 2 levels of VTE incidence rates: one for community/cohort studies and one for database studies.[1] The estimated overall VTE incidence rates for women of reproductive age ranges between 5.5-13.5 and 3.8-12.2 per 10,000 women-years in community and cohort stud-

ies, respectively, but only 0.7-3.8/10,000 in database studies. This difference is probably attributable to methodological problems associated with some database studies; principally exclusions and selection of controls and verification of disease. Combined oral contraceptives increase the risk whatever baseline is used. OC use also provides significant protection against pregnancy, a condition associated with a substantially higher risk of thrombosis. So as always, we must consider risks, benefits, and alternatives.

The van Hylckama Vlieg analysis was performed using data from the MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) database, a large, population-based, case-control study on risk factors for venous thrombosis that includes data from 6 participating anticoagulation clinics in the Netherlands (Amersfoort, Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht) collected between March 1999 and September 2004.[2] Cases had a confirmed first episode of deep venous thrombosis (leg or arm) or pulmonary embolism. Controls were age-matched individuals without history of malignancy or cardiovascular disease. Women up to age 50 were studied, and the long period of data collection allowed the authors to collect information concerning length of exposure to oral contraceptives in large numbers of women.

Overall, compared to non-users current oral contraceptive use was associated with a crude fivefold increased risk of venous thrombosis (OR, 5.0; 95% CI, 4.2-5.8), with the highest risk during the first 3 months of use (OR, 12.6; 95% CI, 7.1-22.4) The risk estimate was lowest for levonorgestrel (OR, 3.6; 95% CI, 2.9-4.6) products, and highest for products containing desogestrel (OR, 7.3; 95% CI, 5.3-10.0), cyproterone acetate (OR, 6.8; 95% CI, 4.7-10.0), and drospirenone (OR, 6.3; 95% CI, 2.9-13.7). As can be noted by the confidence intervals, relative to levonorgestrel, the risk of VTE was significantly increased only for desogestrel (OR, 2.0; 95% CI, 1.4-2.8) and cyproterone acetate (OR, 2.0; 95% CI, 1.3-3.0), but not drospirenone (OR, 1.7; 95% CI, 0.7-3.9). Restricting the analysis to monophasic preparations with levonorgestrel, gestodene, or desogestrel demonstrated a nonsignificant trend toward a reduced thrombotic risk with ethinyl estradiol (EE) doses of 20 μg (OR, 0.8; 95% CI, 0.5-1.2) and increased risk (OR, 1.9; 95% CI, 1.1-3.4) for 50 μg pills relative to 30-35 μg. Based upon these data, the authors conclude that levonorgestrel products containing the lowest dose of estrogen should be the preferred product.

The Danish study made use of outstanding national databases that link to the Central Person Registry (information on address and vital status that is updated daily) using the personal identification number of all Danish citizens given at birth or immigration.[3] The National Registry of Medicinal Products Statistics has recorded all redeemed prescriptions on Danish citizens since 1994, and the National Registry of Patients has collected discharge diagnoses and surgical codes from all Danish hospitals since 1997. Use of the registry eliminates recall bias for OC type. The study looked at incidence rates of VTE in users of combined OCs, progestin-only pills, and the LNG-IUS.

The analysis included an impressive 3.4 million woman-years of current use, 2.3 million woman-years of former use, 4.8 million woman-years of never use, or a total of 10.4 million woman-years of observation. The crude incidence of venous thromboembolism among non-users (never or former use) of hormonal contraceptives was 3.01/10,000 woman-years, and among current users of oral contraceptives was 6.29/10,000 woman-years. Consistent with other studies, the risk among women using combined OCs decreased with duration of use, from 4.17 (95% CI, 3.73-4.66) during the first year of use to 2.76 (95% CI, 2.53-3.02) after more than 4 years of use. The study also confirmed the trend toward a nonsignificant reduction in risk with lower EE dose to 20 μg. As was reported in the Dutch study, using levonorgestrel-containing products as a reference, the risk of VTE was significantly higher in OCs containing desogestrel (1.82; 95% CI, 1.49-2.22), cyproterone acetate (1.88; 95% CI, 1.47-2.42), and drospirenone (1.64; 95% CI, 1.27-2.10). An important contribution of this study was the lack of any apparent increased risk of thrombosis in women using the progestin-only pill and the LNG-IUS (adjusted rate ratio, 0.89; 95% CI, 0.64-1.26).

So how should clinicians view these new studies? Following the "pill scare" in the 1990s that came after an apparent increased risk of VTE with third generation progestogens was widely reported, the importance of selective prescription of new OCs to high-risk women, and the healthy user effect seen in women continuing use of existing products, has been discussed. Both of the studies reported here have the advantage of data collection occurring after the "pill scare," and the authors assume that selective prescription is an unlikely source of bias in the results, at least for desogestrel. However, important differences in users and non-users of oral contraceptives make up sources of bias due to confounding factors not easily adjusted for in epidemiologic studies.

Two large scale population-based phase IV postmarketing studies of drosperinone were commissioned by Schering AG (now Bayer Healthcare) after the introduc-

tion of the novel progestogen in the United States and Europe, to avoid a comparable "pill scare" situation to what occurred with the introduction of the third generation progestogens in the 1990s. Both used a prospective cohort design, and utilized independent research organizations, data safety monitoring boards, and data analysis teams that created a wall between corporate and public health interests in the data.

The American study was performed using cohorts established to investigate potential hyperkalemic complications possibly related to the potassium-sparing diuretic effects of drospirenone (DRSP), an agreed upon postmarketing study required for FDA approval of Yasmin® (30 µg EE, 3 mg DRSP).[4] Women initiating Yasmin and medically similar initiators of other oral contraceptives were identified using a HIPAA-compliant proprietary research database built from electronically captured provider, facility, and pharmacy claims at United Healthcare-affiliated health plans and large employer groups, with follow-up in the written medical records. All initiators of Yasmin were successfully matched in the database to 2 initiators of comparable OCs. There were 18 confirmed instances of thromboembolism among the Yasmin initiators, for an incidence rate of 13/10,000 woman-years, and 39 among other oral contraceptive initiators, for an incidence rate of 14/10,000 woman-years (RR, 0.9; 95% CI, 0.5-1.6). The authors calculated absolute incidence rates. Based upon their data, a clinician can expect to observe similar numbers of cases of thromboembolism (1/769 drospirenone users, 1/714 other OC users) over the course of 1 year of use. But, since both of these estimates (about 14/10,000) sound higher than what we commonly quote patients (e.g., 4/10,000 for OC users), should we be concerned? Also, this study simply compared drospirenone to other OCs, and we have no data as to what these OCs were (how many contained desogestrel?), so what do we know about relative safety with respect to levonorgestrel?

The EURAS study provides some of these answers.[5] The European Active Surveillance study (EURAS) was a multinational, prospective, non-interventional cohort study of new users of DRSP, levonorgestrel, and other progestin-containing OCs. The Center for Epidemiology and Health Research in Berlin performed the study, which was supervised by an independent advisory board.

The objectives of the study were to characterize and compare the risks of short- and long-term use of DRSP-containing OCs and established OCs in a study population representative of actual OC users. In other words, since only real world OC users were studied, incidence rates between preparations are directly comparable. The main clinical outcome of interest was to document the occurrence of uncommon cardiovascular events (e.g., arrhythmias, myocardial infarction, stroke, VTE, and sudden death) and compare the incidence rates between users of DRSP-containing OCs and users of established OCs. Based on the fact that European regulatory authorities considered the progestogen LNG to have the least impact on VTE risk, it was decided that the primary cardiovascular outcome of interest should be the VTE hazard ratio (HR) between users of DRSP-containing OCs and users of LNG-containing OCs. To study these events, large numbers of subjects were needed, so the study planned to enroll 50,000 women at multiple sites in Europe. Recruitment of the cohort members was conducted via a network of physicians who prescribed OCs in 7 European countries: Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom. At the participating centers, all women who received a prescription for a new OC were asked by their physicians whether they were willing to participate. All subjects who were either OC starters (first ever users) or OC switchers were eligible for enrollment in the study provided that they signed the informed consent and data privacy form. Importantly, more specific inclusion or exclusion criteria were not applied because of the non-interference approach of the study design. Cardiovascular outcomes were adjudicated by 3 independent medical experts specializing in radiology/nuclear medicine, cardiology, and internal medicine/phlebology who were blind to treatment group.

After baseline assessments and data collection, follow-up was scheduled every 6 months to assess adverse events or discontinuation. A total of 58,674 study participants were followed for 142,475 woman-years of observation. An array of comprehensive multi-tiered follow-up interventions kept loss-to-follow-up for the entire cohort to an impressively low 2.4% and did not differ between groups. Since some subjects were followed for as long as 4 years, many switched to another OC, to a non-oral hormonal method, or became non-users during the follow-up interval, providing data for these additional groups. Both intention-to-treat and as-treated analyses were performed, but since the groups were not randomized at enrollment, the distinction is not important, and the results were not affected.

The investigators found no difference in the overall incidence of serious adverse events (SAEs) between users of any of the oral contraceptive groups. Underlying the health benefits of contraception, the highest rate of SAEs occurred among non-users, primarily due to pregnancy-related events. The EURAS study was powered to

show non-inferiority of DRSP-containing OCs regarding VTE risk in comparison to LNG and other OCs. A similar incidence of VTE (per 10,000 women-years of exposure) was found in all cohorts: DRSP 9.1 (95% CI, 5.9-13.3); LNG 8.0 (95% CI, 5.2-11.7); and other OCs 9.9 (95% CI, 7.4-13). Note the precise confidence intervals around the point estimates produced due to the large numbers of women studied. The adjusted HRs for DRSP vs LNG was 1.0 with a CI of 0.6-1.8. Thus, a twofold higher risk of VTE during DRSP use compared to LNG use was excluded, and non-inferiority according to the study objectives was demonstrated. All other outcomes were similar.

Like the American study, the big surprise of the EURAS study was the higher incidence of VTE seen in all groups. In the no-use cohort, 12 VTEs were observed. This corresponds to an overall incidence of 4.7/10,000 woman-years. Seven of these occurred in the course of pregnancy (19.4/10,000 woman-years) and 5 (2.3/10,000 woman-years) among non-pregnant non-users. The authors were careful to point out that these results are not necessarily representative for non-users who have never used OCs, and must be considered tentative.

So has the incidence of VTE gone up? Risk of VTE in the EURAS study was highest in the first 3 months of use. Another finding was that obese women (BMI > 30.0 kg/m^2) had an approximately threefold higher VTE risk compared to women with normal weight (BMI, 20.0-24.9 kg/m^2). This may explain the higher incidence seen in the American cohorts. The diagnosis of VTE is considerably easier and more precise today than it was 20 years ago, and no one can pass through an emergency room without the opportunity for advanced imaging. We are able to see more and smaller clots. It is controversial whether all of these diagnoses are significant.

Taking all of this evidence together, I think we can safely put the results of the *BMJ* articles in perspective. VTE risk is greatest during the early months of use of a new product, so stick with a winner. Obesity increases health risks, and magnifies the risk of VTE threefold. Use of lower-dose estrogen pills may increase safety, and evidence is beginning to accumulate that there may be additional safety as we reduce to 20 µg. The Danish study also provides epidemiologic data to support the safety of the LNG-IUS. Prospective trumps epidemiology in most cases, so the differences between type of progestogen appear to be less robust, and we can base

CME Objectives

The objectives of *OB/GYN Clinical Alert* are:

- To present the latest data regarding diagnosis and treatment of various diseases affecting women, including cancer, sexually transmitted diseases, and osteoporosis;
- To present new data concerning prenatal care and complications, as well as neonatal health; and
- To discuss the pros, cons, and cost-effectiveness of new testing procedures.

CME Questions

29. Which of the following is *correct* regarding the results of the above placenta previa study?

a. If the placenta is 10-20 mm from the endocervix, two-thirds will end up having a cesarean section.
b. If the placenta was within 10 mm of the endocervix, no patient had a vaginal delivery.
c. Not all patients with placentas touching the endocervix had cesarean sections.
d. Only one-third of patients with placentas 10-20 mm from the cervix needed cesarean sections.

30. The incidence of "placenta previa" in the above study was 8/1000.

a. True
b. False

31. Which statement does *not* fit regarding the data in the placenta previa study?

a. The study validates the dictum that any patient with a placenta that is within 2 cm of the endocervix should have a cesarean section.
b. The managing physicians were not blind to the ultrasound findings.
c. There were no differences in the rates of postpartum hemorrhage and blood loss during delivery between those with placentas 10-20 mm and 1-10 mm from the endocervix.
d. It makes sense to have ultrasound information regarding placental location as close as possible to the time of delivery.

32. Among current users of oral contraceptives, risk of VTE appears to be greatest during which time period?

a. With use longer than 2 year
b. With use longer than 1 year
c. Within the first 3 months
d. Duration of use does not appear to affect risk.

Answers: 29. d, 30. a, 31. a, 32. c.

our decisions for oral contraceptive prescriptions on other features besides VTE risk. Price and side-effect profiles matter most. Drospirenone has recently joined the ranks of generic progestogens, and this increases consumer choice. As we know that the highest risk of VTE exists with pregnancy, we need to do whatever we can to make sure our patients tolerate their pills well, comply with the regimen, and continue with the method. That's the bottom line. ■

References

1. Heinemann LA, Dinger JC. Range of published estimates of venous thromboembolism incidence in young women. *Contraception* 2007;75:328-336.
2. van Hylckama Vlieg A, et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: Results of the MEGA case-control study. *BMJ* 2009;339:b2921.
3. Lidegaard O, et al. Hormonal contraception and risk of venous thromboembolism: National follow-up study. *BMJ* 2009;339:b2890.
4. Seeger JD, et al. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;110:587-593.
5. Dinger JC, et al. The safety of a drospirenone-containing oral contraceptive: Final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344-354.

Statement of Financial Ownership

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
OB/GYN Clinical Alert	0 7 4 3 - 8 3 5 4	10/01/09
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta,
Fulton County, GA 30305

Contact Person: Robin Saleh
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Robert Mate, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
Paula Cousins, same as above
Managing Editor *(Name and Complete Mailing Address)*
Coles McKagen, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor
	Washington, D.C. 20005

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: OB/GYN Clinical Alert
14. Issue Date for Circulation Data Below: September 2009

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			651	580
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	407	377
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	33	31
	(4)	Other Classes Mailed Through the USPS	38	31
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			478	439
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	16	17
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			20	20
f. Total Free Distribution *(Sum of 15d and 15e)*			36	37
g. Total Distribution *(Sum of 15c and 15f)*			514	476
h. Copies Not Distributed			137	104
i. Total *(Sum of 15g, and h.*			651	580
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			93%	92%

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2009 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: President and CEO — Date: 9/27/09

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

PHARMACOLOGY WATCH

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

SSRIs and Pregnancy: Increase in Septal Heart Defects

In this issue: Depression and pregnancy, new vaccine recommendations from the CDC, corticosteroids and/or antivirals for Bell's palsy, rasagiline and Parkinson's disease, and FDA Actions.

Use of SSRIs during pregnancy

Depression is common in pregnancy, affecting up to 20% of women, with about 13% taking an antidepressant during pregnancy. A new study from Denmark suggests that use of sertraline (Zoloft®) and citalopram (Celexa®) by mothers during pregnancy is associated with an increased risk of septal heart defects in their children. Researchers utilized the Danish nationwide registry to review nearly 500,000 births from 1996 to 2003. Selective serotonin reuptake inhibitors (SSRIs) in general were not associated with major malformations, but were associated with septal heart defects. Among the individual drugs, sertraline conveyed the highest risk (odds ratio [OR], 3.25; confidence interval [CI], 1.21-8.75), followed by citalopram (OR, 2.52; CI, 1.04-6.10). Use of more than one SSRI was associated with an OR of 4.70 (CI, 1.74-12.7). The absolute prevalence of septal heart defects was 0.5% among unexposed children, 0.9% among children whose mothers received any SSRI, and 2.1% among children whose mother were prescribed more than one SSRI (*BMJ* 2009:339:b3569; Epub ahead of print 23 Sept 2009). Significant in this study was the low overall rate of heart defects and the lack of association of heart defects with paroxetine (Paxil®) or fluoxetine (Prozac®), although the authors consider this a "class effect," and the greatest risk was noted if more than one drug was used during pregnancy. ■

CDC issues new vaccine recommendations

The Centers for Disease Control and Prevention has recently revised several vaccine recommendations:

Quadravalent meningococcal conjugate vaccine. The Advisory Committee on Immunization Practices (ACIP) is recommending revaccination of persons at prolonged increased risk for meningococcal disease. In a statement in the September 25th *Morbidity and Mortality Weekly* Report, ACIP is recommending that persons with increased susceptibility to meningococcal disease, such as those with persistent complement component deficiencies, functional asplenia, prolonged exposure such as those traveling to or living in nations where the disease is epidemic or hyperendemic, should receive a booster with the quadravalent meningococcal conjugate vaccine 5 years after their previous vaccination if they received it at age 7 or older. Children who received the first vaccine between ages 2 and 6 should be revaccinated after 3 years. Those who remain at high risk should continue to be revaccinated every 5 years. The recommended booster vaccine is the MCV4 vaccine (Menactra®).

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Haemophilus influenzae *type b vaccine.* The FDA recently approved Hiberix® for *Haemophilus influenzae* type b (Hib) ending a prolonged shortage of the Hib vaccine. Hiberix is approved as a booster for children ages 15 months to 4 years who have received a primary series of shots. The Centers for Disease Control and Prevention has now issued recommendations that the vaccine can be given as early as age 12 months to facilitate timely booster vaccination. Children who missed a booster because of the recent shortage should receive a booster with any of the Hib vaccines, including Hiberix, at the earliest opportunity.

Hepatitis A vaccine. Hepatitis A vaccine is now recommended for all close household contacts and international adoptees when the children are from intermediate-risk or high-risk areas, with an initial dose being given at least 2 weeks before the child's arrival.

Quadravalent human papilloma virus vaccine. In related news, an FDA advisory panel is recommending that the quadravalent human papilloma virus vaccine (Gardasil®) be approved for males ages 9-26 to prevent genital warts. The vaccine is currently approved only for females in that age group. Meanwhile, the same FDA advisory panel has endorsed the approval of GlaxoSmithKline's Cervarix®, a bivalent HPV vaccine which targets HPV 16 and HPV 18, leading causes of cervical cancer. If approved it would also be recommended in women ages 10-25. The new vaccine protects against 2 of the HPV strains covered by Gardasil, but also contains an adjuvant, which is designed to enhance the immune system's response to these HPV strains. Whether this imparts clinical difference is yet to be seen. The FDA is yet to act on the advisory committee's recommendations. ■

Bell's palsy: Corticosteroids and/or antivirals?

For treatment of Bell's palsy, corticosteroids with or without antivirals have been the subject of much debate. A new meta-analysis suggests that combination therapy may lead to better outcomes. The review included 18 trials with 2786 patients. The outcomes were unsatisfactory facial recovery at 4 months, unsatisfactory short-term recovery, synkinesis and autonomic dysfunction, or adverse effects. Combination therapy with corticosteroids and antivirals resulted in slightly better outcome than steroids alone ($P = 0.05$). Antiviral agents alone did not show a benefit (*JAMA* 2009;302:985-993). At least one source (UpToDate) recommends a typical treatment regimen for Bell's palsy of prednisone 60-80 mg per day along with valacyclovir 1000 mg three times a day for 1 week. ■

Rasagiline and Parkinson's disease

Does rasagiline slow the progression of Parkinson's disease? A recent study suggests lower doses of the drug may be beneficial. In this multinational study, 1176 subjects with untreated Parkinson's disease were randomized to rasagiline 1 mg or 2 mg per day for 72 weeks or placebo for 36 weeks followed by rasagiline for 36 weeks. Disease progression was rated on a standard rating scale. Patients who were started at baseline on rasagiline 1 mg met all endpoints in the primary analysis: a slower rate of worsening between weeks 12 and 36 ($P = 0.01$), less worsening of the score between baseline and week 72 ($P = 0.02$), and non-inferiority between weeks 48 and 72 ($P \leq 0.001$). Interestingly, all 3 endpoints were not met with the higher dose of 2 mg per day. The authors conclude that early treatment with rasagiline at a dose of 1 mg per day provided a possible disease-modifying effect, but suggested the results must be interpreted with caution (*N Engl J Med* 2009;361: 1268-1278). Although the findings of this paper are somewhat confusing, it offers some hope since there is currently no effective therapy to slow or stop disease progression in Parkinson's disease. ■

FDA Actions

The FDA has approved asenapine (Saphris®) for the treatment of schizophrenia and bipolar I disorder in adults. The drug is approved for first-line treatment of both conditions. Schering-Plough provided the agency with safety data in 4500 patients, some of whom were treated for more than 2 years. Like other antipsychotics, asenapine will carry a warning regarding increased mortality in elderly patients with dementia-related psychosis. The drug is expected to be available in the fourth quarter of 2009.

The FDA has lowered the approved age limit for levocetirizine (Xyzal®) to 6 months for children with chronic hives and perennial allergic rhinitis and 2 years for children with seasonal allergic rhinitis. Previously the drug had been approved for children 6 years and older. Levocetirizine is marketed by UCB and Sanofi Aventis. ■