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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.

Rivaroxaban: A Fixed-dose Regimen for Anticoagulation

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Rivaroxaban, a novel oral factor Xa inhibitor, provided a highly effective simple, fixed-dose regimen for treatment of acute deep vein thromboembolism without the need for laboratory monitoring and reduced the risk of recurrent clot during continued treatment.*

Source: The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-2510.

This paper presents two parallel studies that evaluate the safety and efficacy of oral rivaroxaban in the treatment of acute deep venous thrombosis (DVT) and in continuing prophylaxis for recurrence. The authors compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT in an open-label, randomized, event-driven, non-inferiority study. They also studied patients who had completed 6-12 months of initial treatment for DVT (either from the acute phase study or from usual care) in a double-blind, randomized, event-driven superiority study comparing rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months. The primary efficacy outcome for both studies was recurrent venous thromboembolism. The principal safety outcome was major bleeding (or clinically relevant non-major bleeding) in the initial treatment study and major bleeding in the continued treatment study.

In the acute protocol, 1731 patients were given rivaroxaban and 1718 were treated with enoxaparin plus a vitamin K antagonist. The number of recurrent DVTs in rivaroxaban-treated subjects (36 events [2.1%]) was statistically non-inferior to that observed in the enoxaparin-vitamin K antagonist group (51 events, [3.0%]; hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04). Safety was similar with identical numbers of bleeding events (8.1%) in each group. In the continued

VOLUME 27 • NUMBER 10 • FEBRUARY 2011 • PAGES 73-80

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treatment study, 602 patients received rivaroxaban and 594 placebo. The rivaroxaban-treated subjects had significantly fewer recurrent DVTs (8 events [1.3%] vs 42 [7.1%] with placebo; HR, 0.18; 95% CI, 0.09-0.39). While significantly more of the rivaroxaban-treated subjects experienced clinically relevant non-major bleeding, only four experienced non-fatal major bleeding vs none in the placebo group ($P = 0.11$). The authors concluded that rivaroxaban offers a simple, single-drug approach that simplifies the care of patients requiring anticoagulation for DVT.

■ COMMENTARY

One pleasure of working in a university environment is collaboration and contact with colleagues from other specialties. My favorite hematologist has an office just down the hallway from me, and when he becomes excited about a new medication I listen. Rivaroxaban is a factor Xa inhibitor. In addition to the present study investigating acute and chronic venous thromboembolism, the clinical trial development program has included randomized trials of DVT prevention following elective orthopedic procedures, DVT prevention in hospitalized medically ill patients, and stroke prevention in patients with atrial fibrillation.[1-3]

Obstetrician gynecologists deal with pregnant women and women using hormonal contraception and menopausal hormonal therapies. Since estrogen increases the risk of both DVT and arterial thromboembolism, these conditions are important concerns for our practice.

One of the medications that most physicians love to hate is warfarin. The major headache in dealing with patients on warfarin is the need for frequent blood monitoring and dose adjustment. The major advantage of rivaroxaban is that it is dosed orally in a fixed dose that does not require blood monitoring for adjustment. It also is unnecessary to switch drugs after initial treatment. For acute treatment, the drug is dosed twice per day. For longer-term prophylaxis, once daily treatment is all that's required. The current study adds to a body of literature demonstrating that rivaroxaban may improve the risk-benefit ratio of both short- and long-term anticoagulation therapy for a variety of conditions. During the acute phase of treatment, there were similar numbers of recurrent DVTs reported among patients treated with rivaroxaban and conventional therapy. Since it is no surprise that any anticoagulation therapy would reduce recurrent DVTs during prolonged treatment, the powerful reduction in risk of recurrent clot with rivaroxaban therapy is less important than the impressive safety data. The risk of non-fatal major bleeding was less than 1%. While minor bleeding (primarily mucosal bleeding) was higher with treatment, few subjects discontinued because of this.

This important new drug is likely to change our practice in a manner similar to the introduction of low molecular weight heparin. By eliminating the cost and complexity of monitoring anticoagulation therapy, more gynecologists will feel comfortable prescribing this medication. While not yet approved by the FDA, rivaroxaban (Xarelto®) will likely join dabigatran (Pradaxa®) as an oral alternative to warfarin. Dabigatran was approved by the FDA in October 2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. An 18,000-person, randomized, non-inferiority trial called RE-LY (Randomized Evaluation of Long-term anticoagulation therapY) found that a 150 mg dose of dabigatran twice daily was more effective in preventing strokes in high-risk patients than warfarin, while a lower dose (110 mg) was comparable, but with a lower bleeding risk than warfarin (the risk is similar with the approved dose of 150 mg twice daily).[4] This drug is not approved for DVT prophylaxis or treatment, but is being used off-label by some hematologists as it does not require blood monitoring.

All this is good news for women. It is also good for news for health care providers. ■

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

EXECUTIVE EDITOR: Coles McKagen
SENIOR MANAGING EDITOR: Paula Cousins

GST 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.

AHC Media LLC

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The IUD: An Upstream Battle to Clear Its Name

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

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Dr. Edelman has no financial relationship to this field of study.

Synopsis: *The levonorgestrel-releasing intrauterine device prevents sperm penetration at mid-cycle, more evidence to support a mechanism of action.*

Source: Lewis RA, et al. Effects of the levonorgestrel-releasing intrauterine system on cervical mucus quality and sperm penetrability. *Contraception* 2010;82:491-496.

Lewis and colleagues performed an investigator-blinded study of sperm penetrability and quality of mid-cycle cervical mucus between levonorgestrel-releasing intrauterine device (LNG-IUD) users (n = 14) and hormone-free controls (n = 16). Cervical mucus was graded using a standardized analysis from the World Health Organization (WHO). Sperm penetrability was tested using two different testing methods (WHO simplified slide test and Kremer sperm cervical mucus penetration test), which basically monitored for sperm penetration (yes/no) over time and, if penetration, to what depth. Only 14% of LNG-IUD users had favorable cervical mucus at mid-cycle compared to 69% of the control group. None of the LNG-IUD users demonstrated sperm penetration by either test at any time point vs the control group that had 64% (WHO test), 85% at 2 hours (Kremer test), and 79% at 6 hours (Kremer test).

■ COMMENTARY

Although studies continue to demonstrate the contrary,[1] the IUD continues to be plagued by the belief that it is an abortifacient. However, most of these studies have focused on older IUD models (i.e., copper IUD) and not the LNG-IUD. Several mechanisms of action are thought to play a role in the contraceptive effect of the LNG-IUD including endometrial suppression and cervical mucus viscosity similar to other progestin-only contraceptives.[2,3] Lewis et al set out to prove the LNG-IUD effects on cervical mucus. This elegant study found that LNG-IUD users had no sperm penetration at the most fertile time point in their cycles (the authors included a picture of this phenomenon that is well worth a look).

So what happens if sperm manages to navigate the impenetrable mucus of a LNG-IUD user? Obviously, this would have to occur around mid-cycle for it to be a potential concern. There is a consistent body of evidence across different IUD types (inert, copper, and LNG-releasing) that demonstrate a non-abortifacient effect. These experiments have shown that the sterile inflammatory environment created by an IUD inactivates and destroys sperm.[4] In fact, no sperm were found in the fallopian tubes of IUD users vs almost half of the control group.[5] So what if sperm survives these obstacles? Well, IUDs also have an adverse effect on ova with lower numbers of ova recovered in IUD users (39% vs 59%).[6] So what if the sperm and egg do manage to meet up? IUD users had either no embryos at all (64%) or abnormal embryos (36%) vs 50% of controls with normal embryos, 35% abnormal embryos, or 15% with none.[6] [Please note that these studies were performed in users of copper IUDs.] While I understand that this will probably always be a contentious issue due to socio-cultural-political interests, the scientific evidence continues to chip away at the persistent belief that IUDs are abortifacients.

Now let's switch our focus away from the more arcane deliberations regarding LNG-IUD mechanism of action to a very clinically relevant topic. When does this effect on cervical mucus occur? Many of us, including me, tell women that they should use a backup method or avoid sex for 7 days after LNG-IUD placement, theorizing that if they are mid-cycle, then this will be enough time to make sure they do not put themselves at risk for pregnancy. This same group of investigators looked at how rapidly the LNG-IUD effect on cervical mucus appears.[7] They placed LNG-IUDs mid-cycle with documentation of good quality (fertile) cervical mucus. Five of 6 subjects had poor quality mucus within 1 day. The remaining subject had poor quality mucus documented by day 3. Although very preliminary in nature, this incredibly detailed work might help us to better counsel women and allow women to return to their normal activities earlier without feeling guilty that they are going against our advice. ■

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Early Delivery: Neonatal Outcomes After Demonstrated Fetal Lung Maturity Before 39 Weeks of Gestation

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Despite tests documenting fetal pulmonary maturity, delivering patients between 36 and 38 weeks gestation is associated with a greater chance of combined neonatal morbidity than if patients are delivered at 39-40 weeks without these tests.*

Source: Bates E, et al. Neonatal outcomes after demonstrated fetal lung maturity before 39 weeks of gestation. *Obstet Gynecol* 2010;116:1288-1295.

THE PENDULUM HAS BEEN SWINGING AWAY FROM DOING early deliveries without indications, but the question remains: What is early? From this discussion emerges another question: Is it legitimate to justify delivering patients before, let's say, 39 weeks because there is amniotic fluid documentation of fetal pulmonary maturity?

A paper in the December 2010 issue of *Obstetrics & Gynecology* addresses these issues. The authors reviewed data from one center in Alabama from 1999 through 2008. They concentrated on patients who were between 36/0 and 38/6 weeks and were delivered after an L/S ratio (> 2) or a positive phosphatidyl glycerol (PG) suggested the fetuses were pulmonically mature (group 1). Outcomes of these infants were compared with those who were delivered without amniocentesis at 39 or 40 weeks (group 2). In both groups, gestational age was assessed using ACOG clinical guidelines. Exclusions were applied to both groups, which included fetal or maternal indications/complications that might skew the neonatal outcomes. The authors were interested in comparing various indicators of neonatal morbidity between the two groups.

In group 1 they found statistically increased risks for RDS (odds ratio [OR] = 7.6), need for "respiratory support" (OR = 2.0), surfactant use (OR = 6.5), hyperbilirubinemia requiring treatment (OR = 11.2), suspected or proven sepsis (OR = 1.7), NICU admissions (OR = 1.7), and hypoglycemia (OR = 5.8). The composite morbidity was two times higher for those delivered before 39 weeks, compared with those delivered after that time.

■ COMMENTARY

This paper contains some important messages. Messing with Mother Nature can have unwanted consequences. Also, if infants are born between 36 and 38 weeks, a "positive" L/S ratio, PG, or, undoubtedly, fluorescent polarization does not afford complete immunity to common neonatal morbidities — including those involving the respiratory system. The L/S ratio and other indices of fetal lung maturity continue to be important tools in obstetrical management, especially in high-risk pregnancies. However, how old the fetus/infant is at the time of delivery seems to be more important than documentation of pulmonary maturity. Here the emphasis should be on early, precise dating of pregnancy, and amniocentesis, a procedure that is inconvenient, uncomfortable, expensive, and definitely not innocuous, should be reserved for clinical problems where there has been demonstrated benefit. ■

Are Procedural Complications Related to Sleep Pattern the Night Before?

ABSTRACT & COMMENTARY

By Frank W. Ling, MD

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

Synopsis: *The complication rate for procedures performed by attending surgeons and obstetricians was not greater among those who worked overnight.*

Source: Rothschild JM, et al. Risks of complications by attending physicians after performing nighttime procedures, *JAMA* 2009;302:1565-1572.

Conducted in a 700+ bed tertiary care, urban academic teaching hospital with a trauma center and referral center for high-risk obstetrics, this retrospective cohort study involved the procedures of 86 surgeons and 134 OB/GYNs between 1999 and 2008. Cases performed between midnight and 6 am were considered "overnight" and "sleep opportunity" was defined as the time between the end of the overnight procedure and the start of the first scheduled morning procedure. The study was conducted to see if sleep opportunities correlated with surgical complications among attending surgeons and OB/GYNs. The complication rates among post-nighttime procedures were compared with those of controls. Also, complication rates in post-nighttime procedures performed by physicians with more than 6-hour sleep opportunities were compared to those performed by physicians who had sleep opportunities of 6 hours or less. Nearly a thousand obstetrical and more than 900 surgical cases were identified as post-nighttime, and these were compared to almost 4000 obstetrical and more than 3500 surgical control cases.

There were complications in 101 post-nighttime cases (5.4%) and 365 control procedures (4.9%; odds ratio [OR], 1.09; 98% confidence interval [CI], 0.84-1.41). Among the post-nighttime complications, they occurred in 6.2% of cases in which the sleep opportunity was 6 hours or less compared to 3.4% of cases where the sleep opportunity exceeded 6 hours (OR, 1.72; 95% CI, 1.02-2.89). In addition, complication rates in post-nighttime procedures performed after working more than 12 hours was higher, but not significantly, than after working 12 hours or less (6.5% vs 4.3%; OR, 1.47; 95% CI, 0.96-2.27).

■ COMMENTARY

The conclusions of this article, from one single study site, are that there were not higher complication rates for surgeons and gynecologic surgeons who had worked overnight, although the complication rates were slightly higher among the post-nighttime procedures done if sleep opportunities were less than 6 hours. Surgeons did have a higher complication rate if sleep opportunities were limited, though the rate was not increased for OB/GYN attendings.

Is that reassuring? It can be, particularly if you're one of those surgeons who works inconsistent and unpredictable hours. Throughout our training, the issue of long hours and sleep deprivation has always been there, particularly with the implied concern that daytime activity could be adversely affected by nighttime emergencies/unscheduled procedures. On the other hand, if you are someone looking to debunk these data, one can simply (and correctly) point out that this was only one study site, it was retrospective in nature, and the outcome measures were not defined appropriately. It was also done at a tertiary care facility, which certainly could be very different from community hospitals that most people utilize in their respective practices. Nevertheless, there is not a statistical difference in the surgical complication rates whether or not the surgeon had done other procedures the night before.

Likewise, much more study is needed for anyone to be able to determine the critical amount of rest/sleep that a surgeon needs to avoid increasing the complication rates after a nighttime procedure. Prospective data are needed. There may not, in fact, be a specific number of hours of rest that is needed. That is unlikely to stop boards, commissions, governmental agencies, etc., from declaring that certain guidelines must be in place to protect the welfare of patients. In fact, who can argue with regulations that protect the patient? We're all practicing this business called medicine for that primary reason, i.e., the patient. The controversy arises when the good intentions of those making the rules run into the good intentions of those trying to render quality health care.

The results of the 2003 ACGME decision to limit resident duty hours to 80 hours per week have yet to be fully appreciated. Since that time, further tweaking has occurred, with more refinements to defining how those hours may be counted. Even greater reductions are in play, with first year residents being limited differently than upper level trainees. On the other hand, the topic of hours of attending physicians has not been addressed, with this article being one attempt to take part in that discussion. I raise the topic of resident duty hours because it is germane to practitioners as they look at their newly graduated younger colleagues and how they practice. Some may adapt well to an unregulated practice pattern with unlimited practice hours. Others may either choose not to adapt or find that the rigors of such a schedule are stressful and/or difficult to manage.

Of greater importance are patient safety topics that we can all do something about. First, we can all have back-up plans for what we currently do. Self-awareness of fatigue also plays a critical role. It's OK to be tired and admit to it. It has been reported that fatigue played a role in up to 16% of preventable adverse events in one study.[1] Another study came to different conclusions for cardiac surgeons who performed procedures within a 24-hour period after an overnight case. In that study, there was no difference between surgeons who were or were not sleep-deprived.[2]

Perhaps a series of questions could stimulate each of us to determine how we fit into this controversy:

1. Are older, more experienced physicians more or less susceptible than residents to the effects of fatigue?

2. Are we taking full advantage of "hospitalists" to minimize the risk of overnight emergency procedures adversely affecting the surgeon the next morning?

3. Does the practice routinely avoid scheduling elective surgery the day after someone has been on call the night before?

4. Do we have back-up providers available to step in should surgeons find that fatigue is affecting them?

5. Have we adequately educated ourselves on the topics related to sleep deprivation?

6. Do we use caffeine appropriately (as opposed to inappropriately) as a stimulant to combat fatigue?

7. Is the possibility of delaying elective surgery appropriately utilized (recognizing the inconvenience and stress on the patient and families)?

8. Do attending physicians factor in monetary reward (i.e., surgical fees) as they decide if an elective procedure should be rescheduled?

The topic of patient safety in the operating room would not be complete without touching on a couple of other topics. What effect has the surgical "time out" made? You can be your own judge. Maybe it's not a bad thing, even if it seems as though it shouldn't be necessary.

What about patient safety elsewhere? I'd like for each of you to think about your practice. Answer these questions to see how things stack up within an environment that you, as the practitioner, have a greater degree of control:

1. Do we have a fool-proof tracking mechanisms for all lab tests drawn?

2. Do we have a system to notify patient of all abnormal results?

3. Are providers responsible for signing off on all test results?

4. Are phone calls logged and answered in a timely fashion?

5. Does the office have appropriate protocols in place in case of cardiac arrest or adverse patient outcomes?

6. If procedures such as hysteroscopy or LEEP are done in the office, are the same safety measures taken in the hospital operating rooms utilized in the office?

What we do in our respective daily activities should be based on good medicine first, but with a healthy dose of patient safety in mind at every turn. Let's lead the way and show the government, insurers, and anyone who wants to watch us that physicians take this topic seriously. ■

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Single Umbilical Artery: Need for Specialist Fetal Echocardiography

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Synopsis: *A large study involving fetuses with single umbilical artery shows that few serious cardiac anomalies are missed with standard four-chamber and outflow tract views, when no extra cardiac abnormalities are noted.*

Source: DeFigueiredo D, et al. Isolated single umbilical artery: Need for specialist fetal echocardiography? *Ultrasound Obstet Gynecol* 2010;36:553-555.

A SINGLE UMBILICAL ARTERY (SUA) IS FOUND IN ABOUT 1 IN 200 fetuses in the second trimester. Since the finding is associated with an increase in fetal anomalies, it alerts clinicians to search for any of the possible abnormalities linked with this finding. However, opinions vary as to how this search should be conducted.

In an effort to help develop a common diagnostic approach, investigators from London tackled one option — the need for a full fetal echocardiogram. They reviewed data from 46,272 patients who had routine second trimester ultrasound evaluations, which included a four-chamber view of the fetal heart, along with an attempt to image the outflow tracts. Each patient in the study had a fetal anatomic survey between 18 and 25 weeks, at which time an SUA was found in 264 cases (0.5%). In 233 patients, no cardiac defects or other anomalies were noted, but two of the "cleared" fetuses were found later to have ventricular septal defects (VSD). In the second group of 10 patients, isolated cardiac abnormalities were identified in utero, and in the third group of 13, in whom extra cardiac anomalies were diagnosed, six also had cardiac defects. In total, the incidence of cardiac defects was 6.5%, which included 10 cases (4.3%) from the 233 patients in groups 1 and 2. Six of the 13 (46.2%) with extra cardiac anomalies also had cardiac defects. Most importantly, in 11 of the 16 patients delivering fetuses with cardiac defects, the diagnosis was made in utero with four-chamber and outflow views alone. The ones that slipped through were small VSDs and a persistent superior vena cava, anomalies that are of lesser consequence.

The authors' conclusion was that if four-chamber and outflow tracts appear normal, "it may not be necessary to refer patients (with SUA) for specialist fetal echocardiography." However, if extra cardiac anomalies are found

with SUA, there is about a 50% chance for an associated cardiac abnormality, and this would warrant a detailed cardiac examination.

■ **COMMENTARY**

Our impression is that SUA is more common than the 0.5% incidence noted in the above paper. However, referral centers are often dealt loaded decks for obvious reasons. In fact, one center doing high-risk screening at 11-14 weeks noted an incidence of SUA in 5.9%,[1] which undoubtedly reflects a mixture of structurally anomalous and chromosomally abnormal fetuses that do not make it to the second trimester sonogram because of spontaneous loss or termination of pregnancy. From data pooled from the literature involving 1038 patients with SUA and cited in the DeFigueiredo study, it is certainly clear that this finding is associated with a higher rate of fetal anomalies (33%) and, specifically, cardiac anomalies (11%). Hua et al found an incidence of SUA in the overall population of 0.6% and, in those with SUA, there was a 20-fold increased risk for cardiac anomalies, a three times greater chance of renal anomalies, and a two-fold risk of IUGR.[2] Another important anomaly syndrome to be ruled out is trisomy 18, since about 50% of fetuses with this abnormality have SUAs.

Here are some suggestions for patients whose fetuses have SUA:

1. When performing a second trimester anatomy scan, particular attention should be paid to the fetal spine, posterior fossa, and kidneys (pelvic kidneys are not an uncommon accompaniment to SUA).
2. The four-chamber and outflow tracts should get the most attention.
3. If quad screen results are available, the pattern of very low analytes should trigger a "marker" search for trisomy 18.
4. If everything appears normal, there is no need for a full fetal echocardiogram.
5. Another scan should be scheduled for after 30 weeks to check interval fetal growth.

Most importantly, normal results from steps 1-4 should be very reassuring for patients with a fetus with SUA, as the first thing they will do after learning of an SUA, will be to go online. There they will find a wealth of scary information. ■

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Complications of Products Developed to Prevent Complications

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *HA-CMC barrier placement at the time of optimal cytoreduction was not associated with increased postoperative complications, but may be associated with an increased incidence of pelvic abscess.*

Source: Krill LS, et al. Analysis of postoperative complications associated with the use of anti-adhesion sodium hyaluronate-carboxymethylcellulose (HA-CMC) barrier after cytoreductive surgery for ovarian, fallopian tube and peritoneal cancers. *Gynecol Oncol* 2010 Dec 7; Epub ahead of print.

Intraoperative placement of adhesion barriers has been a long-practiced adjuvant to major abdominal/pelvic surgery in an attempt to reduce postoperative complications such as bowel obstruction and infertility. Most available evidence suggests HA-CMC barriers are safe and effective in reducing postoperative adhesions, particularly in patients undergoing bowel surgery for non-cancer indications. However, the nature of ovarian cytoreduction involves performing many of these same types of procedures in potentially riskier and more compromised patients. The authors of the current retrospective report investigated whether patients undergoing optimal cytoreduction experienced higher postoperative morbidity when HA-CMC barriers were placed. Over a 14-year period, 375 patients underwent optimal surgical cytoreduction, in whom HA-CMC barriers were placed in 168 (45%). Institutional practice patterns left placement to the discretion of the primary surgeon; however, placement was not utilized in those in whom a suboptimal resection was achieved. The sheets were placed more often in patients in whom complete cytoreduction (no visible postoperative residuum) was achieved.

Univariate analysis of procedures performed demonstrated that HA-CMC barriers were utilized more frequently in patients undergoing hysterectomy, rectosigmoid resection, splenectomy, nodal dissection, diaphragm stripping, and placement of a pelvic drain. Despite these variances, major morbidity was similar between the two cohorts; pelvic abscess, however, was observed in 12% of

patients with HA-CMC barriers vs 5% in those without ($P < 0.01$). Independent factors associated with pelvic abscess formation following HA-CMC barrier use were performance of a hysterectomy and primary (vs secondary) cytoreduction. Interestingly, placement of a pelvic drain was independently associated with risk of pelvic abscess (odds ratio [OR], 3.42; $P = 0.04$) and was accentuated by use of HA-CMC barriers (OR, 10.1; $P = 0.005$); however, use of HA-CMC barriers was only marginally associated with pelvic abscess risk (OR, 2.7; 95% confidence interval, 1.00-5.82; $P = 0.05$). The authors concluded that their data support others in the literature, but suggested that in their more homogenous population HA-CMC barriers may be associated with an increased risk of pelvic abscess.

■ COMMENTARY

The quest to prevent adhesions is driven by the morbidity observed when they do occur. Even though there may be no overt morbidity following the index surgical procedure, reoperation, which occurs frequently in patients with ovarian malignancy, can be hazardous, particularly if intraperitoneal chemotherapy has been administered. Other frequent events following aggressive cytoreduction, such as infection, hematoma, ileus, wound complications, and lymphocele, add to the potential for "abdominal catastrophe" when subsequent exploration is indicated. Since secondary cytoreduction for recurrent disease and surgical exploration for complications due to progressive disease are not uncommon, anything to reduce competing factors exacerbating an already tenuous situation is welcomed.

The current report draws attention to a potential complication that can indeed promote that which we sought to avoid, adhesions. While the literature to support the safety of HA-CMC barrier use is fairly consistent, their use in gynecologic oncology patients has been associated with an increase in postoperative fluid collections. This concern is very difficult to attribute solely to the barriers, as pelvic peritoneal stripping, ascites, and use of blood hemostatics/coagulants intraoperatively all contribute to these "anomalies" on postoperative imaging. However, in the current trial all of the events recorded as abscesses were confirmed infected by clinical criteria and/or microbiology assessment. In the package insert for this product, abscess is listed to be about 4 times higher (8% vs 2%) in patients randomized to HA-CMC while undergoing colectomy/ileal pouch anastomosis. However, power to detect a difference in that study (as in the current trial) was insufficient to adequately assess this risk. The current trials' retrospective nature, as well as its lack of description of where the sheets were placed, potential imbalance of patient comorbidities, and lack of consistent criteria for percutaneous assessment limit definitive interpretation. However, the hypothesis that pelvic drain use may augment pelvic abscess formation when HA-CMC barriers are used should be addressed in future study, particularly since these drains are often placed to combat hematoma formation or complications from anastamotic leak. ■

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

35. What percentage of LNG-IUD users had sperm penetration at mid-cycle?
a. 20%
b. 0%
c. 65%
d. 10%

36. Early delivery is associated with statistically increased risk for which of the following outcomes?
a. RDS
b. NICU admissions
c. Hyperbilirubinemia
d. Hypoglycemia
e. All of the above

37. Which of the following is *not* appropriate regarding the types of anomalies most commonly found with SUA?
a. Cardiac anomalies
b. Skeletal dysplasias
c. Renal anomalies
d. Trisomy 18
e. IUGR

Answers: 35. b, 36. e, 37. b.

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, Travel Medicine Advisor.*

Statin Use in Patients with Abnormal Liver Function

In this issue: Statins and liver function; dosing timing for thyroxine; rivaroxaban for VTE, DVT, and stroke; echinacea and the common cold; and FDA actions.

Statins and liver function

Most physicians are hesitant to use statins in patients with abnormal liver function tests (ALT or AST less than three times the upper limit of normal). A new study suggests that not only are statins safe and effective, they may improve liver abnormalities in patients with fatty liver. In a study recently published in the *Lancet*, 437 patients enrolled in the Greek Atorvastatin and Coronary Heart Disease Evaluation study population were noted to have moderately abnormal liver tests at baseline, which were possibly associated with non-alcoholic fatty liver disease. Of that group, 227 were treated with a statin (atorvastatin) and 210 were not. Patients treated with a statin had substantial improvement in liver tests ($P < 0.0001$), whereas the group not treated with a statin had further increases in liver enzyme concentrations. Cardiovascular events occurred in 10% of atorvastatin-treated patients vs 30% of the non-statin group (60% relative risk reduction; $P > 0.0001$). This was a greater improvement in benefit than seen in patients with normal liver function tests. Fewer than 1% of the participants who received a statin had to discontinue statin treatment because of transaminase concentrations more than three times the upper limit of normal. The authors concluded that "statin treatment is safe and can improve liver tests and reduce cardiovascular morbidity in patients with mild to moderately abnormal liver tests that are potentially attributable to nonalcoholic fatty liver disease" (*Lancet* 2010;376:1916-1922). ■

Dosing timing for thyroxine

When is the best time to take thyroxine? Patients are generally told to take it on an empty stomach in the morning and wait at least 30 minutes before eating. A new study suggests that taking thyroxine at bedtime might be a better option. Over 6 months, 105 patients were randomized to take 1 capsule in the morning and 1 capsule at bedtime (one containing levothyroxine and the other a placebo), with a switch after 3 months. Taking levothyroxine at bedtime lowered thyrotropin levels and increased free thyroxine and total triiodothyronine levels (the primary outcome). Treatment did not change secondary outcomes including quality of life. The authors concluded that taking levothyroxine at bedtime is a good alternative to morning intake (*Arch Intern Med* 2010;170:1996-2003). This would likely benefit patients who find it difficult to wait 30 minutes to eat after taking their thyroxine each morning. ■

Rivaroxaban: an oral, factor Xa inhibitor

Rivaroxaban is an oral, direct factor Xa inhibitor that is approved in several countries for the prevention of venous thromboembolism (VTE) after orthopedic surgery. It is currently being evaluated by the FDA for this indication. Based on the findings of the EINSTEIN study, it appears the drug is also effective for the treatment of acute deep vein thrombosis (DVT). EINSTEIN consists of three randomized trials of rivaroxaban, one for the treatment of acute DVT, one for treatment of acute pulmo-

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nary embolism, and one for continued, long-term treatment in patients who have received treatment for acute DVT or pulmonary emboli. The results of the first and third wings of the study were recently reported in the *New England Journal of Medicine*.

In the DVT treatment arm, 3449 patients with acute DVT were randomized to rivaroxaban (50 mg twice daily for 3 weeks, followed by 20 mg once daily) or subcutaneous enoxaparin followed by a vitamin K antagonist (either warfarin or acenocoumarol) for 3, 6, or 12 months. In the continued treatment wing of the study, patients were randomized in a double-blind fashion to rivaroxaban 20 mg once daily or placebo for additional 6 or 12 months after completion of 6-12 months of treatment for VTE. The primary outcome for both studies was recurrent DVT. For the treatment of acute DVT, rivaroxaban was non-inferior to enoxaparin-vitamin K antagonist (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.44-1.04; $P < 0.001$). In the continued treatment study, rivaroxaban had superior efficacy compared to placebo (8 events [1.3%] vs 42 events [7.1%] with placebo; HR 0.18; 95% CI, 0.09-0.39; $P < 0.001$). There were four patients in the rivaroxaban group with non-fatal major bleeding vs none in the placebo group. The EINSTEIN authors concluded that "Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation" (*N Engl J Med* 2010;363:2499-2510).

Rivaroxaban is also being evaluated for the prevention of stroke in patients with nonvalvular atrial fibrillation based on the ROCKET AF study, which was presented at the American Heart Association meetings in November 2010. If approved, it will join the recently approved direct thrombin inhibitor dabigatran (Pradaxa®) for this indication. Both drugs have the advantage over warfarin of not requiring ongoing lab monitoring. ■

Echinacea and the common cold

The National Center for Complementary and Alternative Medicine (NCCAM), a division of NIH, has been in existence for nearly 20 years, much of the time under the intense scrutiny of the mainstream medical community. Despite NCCAM's attempts to verify the effectiveness of alternative healing practices, most if not all rigorously studied modalities have been shown to be ineffective. The benefit of another alternative staple, echinacea, is questioned with the publication of a NCCAM-sponsored study testing the benefit of the herbal remedy for treating the common cold. More than 700 patients in Wisconsin with new-onset common cold were assigned to one of four groups: no pills, placebo pills (blinded), echinacea pills (blinded), or echinacea pills (unblinded). The primary outcome was severity of the cold by self reporting with secondary outcomes of interleukin-8 levels and neutrophil counts from nasal washes. The comparison of the two blinded groups showed a trend toward benefit for the echinacea group (an average decrease in duration of cold of 7-10 hours out of 1 week; $P = 0.089$), but no difference in mean illness duration. There were no differences in the secondary outcomes. The authors concluded that the differences in illness duration and severity were not statistically significant with echinacea compared to placebo (*Ann Intern Med* 2010;153:769-777). ■

FDA Actions

The FDA is removing the breast cancer indication for bevacizumab (Avastin-Genentech). The somewhat unusual move was made after an FDA advisory panel suggested last summer that the drug did not provide a survival benefit for patients with breast cancer and at the same time caused serious side effects. The drug is still approved for treating cancer of the brain, colon, kidney, and lung.

The **FDA advisory panel is recommending approval for the first new diet pill in a decade. Orexigen Therapeutics' Contrave® is a combination of the antidepressant bupropion and the opioid antagonist naltrexone.** The drug was recommended for approval by a vote of 13-7, with some committee members voicing concern about potential side effects of the drug and recommending close post-marketing follow-up and studies to assess the risk of major cardiac events. The recommendation to approve the drug was based on studies that show an average weight loss 4.2% greater than placebo.

The **FDA has approved denosumab for the prevention of skeletal related events (fracture and bone pain) in patients with bone metastases from solid tumors.** The drug, which is given as a once monthly injection, was approved after a 6-month priority review. Denosumab is a monoclonal antibody to RANKL, a protein essential for the formation, function, and survival of osteoclasts. Denosumab in a lower-dose formulation was recently approved for the treatment of osteoporosis under the trade name Prolia™. Amgen Inc. will market the drug for this new indication under the trade name Xgeva™. It is expected to compete strongly with Novartis Pharmaceutical's zoledronic acid (Zometa®), which is approved for the same indication. ■