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.

Ulipristal Acetate Extends the Emergency Contraception Window

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Ulipristal acetate is an effective and well-tolerated agent for emergency contraception given up to 120 hours after unprotected intercourse.*

Source: Fine P, et al. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. *Obstet Gynecol* 2010;115:257-263.

In this open-label study, women ages 18 years or older with regular cycles who presented for emergency contraception 48-120 hours after unprotected intercourse at 45 Planned Parenthood clinics throughout the United States were treated with a single oral dose of 30 mg ulipristal acetate. Pregnancy status was determined by high-sensitivity urinary human chorionic gonadotropin testing and return of menses. Of the 1241 women evaluated for efficacy, 26 were found to be pregnant at follow-up, yielding a pregnancy rate of 2.1% (95% confidence interval [CI], 1.4%-3.1%). Significantly, the efficacy did not decrease when dosing occurred after 72 hours: Pregnancy rates were 2.3% (95% CI, 1.4%-3.8%) when given between 48-72 hours, 2.1% (95% CI, 1.0%-4.1%) between 73-96 hours, and 1.3% (95% CI, 0.1%-4.8%) for more than 96-120 hours. The treatment was well tolerated, but did increase cycle length by an average of 2.8 days. The duration of menstrual bleeding did not change.

Synopsis: *Ulipristal acetate is at least as effective as levonorgestrel for emergency contraception up to 72 hours after unprotected intercourse and, unlike levonorgestrel, continues to be highly effective up to at least 120 hours.*

Source: Glasier AF, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: A randomised non-inferiority trial and meta-analysis. *Lancet* 2010;375:555-562.

In this randomized, single-blind multicenter, non-inferiority trial, more than 2200 women with regular menstrual cycles who

VOLUME 26 • NUMBER 12 • APRIL 2010 • PAGES 89-96

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

presented to one of 35 family planning clinics located in the United Kingdom, Ireland, and the United States requesting emergency contraception within 5 days of unprotected sexual intercourse received a single supervised oral dose of either 30 mg ulipristal acetate or 1.5 mg levonorgestrel. Follow-up was done 5-7 days after expected onset of next menses. The primary endpoint was pregnancy rate in women who received emergency contraception within 72 hours of unprotected intercourse using a non-inferiority design. Overall, there were 15 pregnancies in the ulipristal acetate group (1.8%; 95% CI, 1.0%-3.0%) and 22 in the levonorgestrel group (2.6%; 95% CI, 1.7%-3.9%), with an odds ratio (OR) of 0.68 (95% CI, 0.35-1.31). In 203 women who received emergency contraception between 72 and 120 hours after sexual intercourse, there were 3 pregnancies, all of which were in the levonorgestrel group.

■ COMMENTARY

These two papers report the results with ulipristal acetate 30 mg as a single-dose agent for emergency contraception. This dose was recently approved (May 2009) by European regulatory authorities as an emergency contraceptive pill, and is marketed under the brand name EllaOne™ (HRA Pharma). Ulipristal acetate, also known as CDB-2914, is a progesterone receptor antagonist that is derived from 19-norprogesterone. It was developed for use in a variety of gynecologic applications including treatment of uterine fibroids, endometriosis, heavy or prolonged uterine bleeding, and cancer. It has also been tested as a daily contraceptive. Much of the early development and testing was done through the National Institutes of Health. In vitro and in vivo comparisons indicate that the progesterone antagonist activity of CDB-2914 is similar to that of mifepristone, but CDB-2914 exhibits lower antiglucocorticoid activity.[1] It is important to point out that ulipristal has never been tested as an abortifacient.

In a 2006 study, Creinin and the other investigators in the NICHD-funded Contraceptive Clinical Trials Network reported the first results comparing the efficacy and adverse effects of CDB-2914 to levonorgestrel for emergency contraception. In this randomized, double-blind non-inferiority trial, women seeking emergency contraception within 72 hours of unprotected intercourse received either a single 50 mg dose of CDB-2914 plus a placebo 12 hours later or two doses of 0.75 mg of levonorgestrel taken 12 hours apart (the standard dosing regimen for Plan B at that time). Although fewer pregnancies occurred in the CDB-2914 group (0.9%; 95% CI, 0.2%-1.6%) this was statistically equivalent to the results obtained using levonorgestrel (1.7%; 95% CI, 0.8%-2.6%).[2]

Now we have two new well-designed studies that provide additional evidence to support the efficacy of ulipristal acetate. There are a few things to point out. First, although the design of the two randomized trials was a non-inferiority analysis, the direction of the effect in both studies suggests that ulipristal may be more effective than levonorgestrel. In fact, the Glasier paper included a secondary meta-analysis that combined the results with the randomized trial by Creinin. The combined analysis provided a sample with sufficient size to show that, compared to levonorgestrel, ulipristal acetate reduced the risk of pregnancy by almost half (OR 0.55; 95% CI, 0.32-0.93) if used within 120 hours of unprotected intercourse, and by almost two-thirds (OR 0.35; 95% CI, 0.11-0.93) if used within 24 hours.

Second, while the effectiveness of levonorgestrel becomes lower when taken more than 72 hours after unprotected intercourse, ulipristal provides protection when taken up to 120 hours after sex. A broader time window should allow for greater use.

The new studies also demonstrated that efficacy was maintained even with a dose reduction from 50 mg to 30 mg. Although side effects are typically mild, significantly more women treated with ulipristal (29%) than levonorgestrel (24%) reported nausea in the Creinin study. In contrast, with a 30 mg dose, the incidence of nausea

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.

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.

was 13% in the randomized study by Glasier, and only 9% in the Planned Parenthood study by Fine et al (similar patient population to the Creinin study). While the reported pregnancy rates with the 30 mg dose were slightly higher, they were statistically equivalent to that seen with 50 mg. The lower pregnancy rate with the 50 mg dose is probably an artifact reflective of an overall low pregnancy rate for both treatments in the Creinin study.

The increase in cycle length (about 2-3 days longer) appears to be the same with either dose of ulipristal, and occurs in most users regardless of whether the drug is taken in the follicular or luteal phase. In contrast, women using levonorgestrel emergency contraception typically experience an earlier onset of bleeding if they use the product in the follicular phase of the cycle, and only have a delay in menses if they take levonorgestrel in the luteal phase. Since almost all women who use ulipristal for emergency contraception will experience an increase in cycle length regardless of the timing in the cycle, this is a key counseling point. Any delay in the onset of menstruation in a sexually active woman who does not wish to become pregnant is likely to provoke anxiety. Reassuring your patient that she will be late by 2-3 days after using ulipristal may reduce stress during the wait.

The biggest advantage of ulipristal will be the longer window for treatment. Both drugs work by inhibiting ovulation. Although levonorgestrel inhibits ovulation in 83% of menstrual cycles when the follicle measures up to 12-14 mm, it blocks ovulation in only 12% of cycles (placebo 13%) when the follicle reaches 18-20 mm, a size that typically occurs within 48 hours of ovulation.[3,4] By contrast, ulipristal acetate prevents ovulation in 60% of cycles when the follicle measures 18-20 mm. Thus, ulipristal can block follicle rupture even when given after the LH surge shortly before an expected ovulation. This explains the greater efficacy and longer treatment window (up to 120 hours) after unprotected intercourse.

When will we see ulipristal acetate in the United States? Ulipristal will likely be a prescription medication, and therefore be more expensive than behind-the-counter levonorgestrel. The fact that women needing emergency contraception will have up to 5 days to obtain ulipristal is a plus, but taking the product as soon as possible after unprotected intercourse should always be advised. Remember, like levonorgestrel, this is still contraception and not an abortifacient. We have no evidence that the drug will prevent pregnancy if taken after ovulation, so the sooner the better. Same goes for FDA approval, the sooner the better please. ■

References

1. Blithe DL, et al. Development of the selective progesterone receptor modulator CDB-2914 for clinical indications. *Steroids* 2003;68:1013-1017.
2. Creinin MD, et al. Progesterone receptor modulator for emergency contraception: A randomized controlled trial. *Obstet Gynecol* 2006;108:1089-1097.
3. Wilcox AJ, et al. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med* 1995;333:1517-1521.
4. Croxatto HB, et al. The effects of immediate pre-ovulatory administration of 30 mg ulipristal acetate on follicular rupture. Rome, Italy: 8th Congress of the European Society of Gynecology; Sept. 10-13, 2009.

Delivery of a Second Twin

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: *By using an "active" approach to the second stage of labor in second twins, many motivated patients can avoid the need for cesarean section without increased neonatal morbidity.*

Source: Fox NS, et al. Active second-stage management in twin pregnancies undergoing planned vaginal delivery in a U.S. population. *Obstet Gynecol* 2010;115(2 Pt 1): 229-233.

IN A RECENT ISSUE OF *OB/GYN CLINICAL ALERT (SEE THE November 2009 issue)*, a special feature was devoted to the contemporary antepartum management of twin pregnancies. However, conspicuously absent in this piece was the intrapartum management of twin deliveries. This month's issue of *Obstetrics & Gynecology* contained a paper that deals with the sometimes troublesome problem of delivering second twins, a discussion of which should now complete the job.

Fox et al undertook a retrospective analysis of 4 years worth of experience of offering an attempted vaginal delivery for a second twin, rather than empirically doing a cesarean section for both, if the second twin was not in

a vertex position. The technique of "active management" of the second stage involved adhering to a strict protocol, which included the following types of patients:

1. Only those whose first twin presented as a vertex.
2. Those whose second twin weighed less than 20% more than the first twin (by ultrasound).
3. Those where the estimated fetal weight of the second twin was more than 1500 g.

The method involved having an epidural in place in the operating room with anesthesia on-site and an operative team poised for a possible cesarean section. The operators were all attendings trained in the techniques to be described. If the second twin settled well into the pelvis, then an amniotomy was performed, and this baby was delivered as a vertex. If the second twin was in a breech presentation, then a breech extraction was undertaken immediately after the first was delivered, with an amniotomy being performed, preferably, after the feet were grasped. If the second twin's head was floating, then a two-handed internal podalic version was attempted with one hand in the vagina/uterus and the other on the abdomen, and the breech was extracted.

Of the 287 patients studied, 157 (54.7%) chose to have an elective cesarean section, and of the remaining 130 patients (43.5%), 85% were successfully delivered by the vaginal route. Interestingly, in the 15% who had to be sectioned, the reasons for an abdominal delivery were based on circumstances presenting prior to delivery of their first twin. In other words, of those who delivered the first twin vaginally, none had to have a cesarean section for the second twin. This also included six patients who had prior cesarean sections.

Most importantly, the ones delivered vaginally had no differences in Apgar scores or cord pH values compared with those delivered by cesarean section.

■ COMMENTARY

To underscore the study findings, about half of all patients with twins chose simply to have cesarean sections, rather than to attempt a vaginal delivery for both. The remaining half was clearly motivated to try for vaginal deliveries, and all but 15% of them had their wish. It is interesting that there were no vaginal/cesarean sections in any of these patients — and those babies born via the vaginal route had no evidence that the route of delivery was associated with an increase in short-term morbidity.

The results of the study are similar to those of another single-center study,[1] but two other studies,[2,3] involving pooled data and operators with varying experience, showed a higher perinatal morbidity with this approach. These latter studies led one respected obstetrician to write that internal version is contraindicated since "no one trained after about 1970 has any idea how to perform the maneuver."[4] In a way, I agree, since, although some younger obstetricians have been trained to deliver breeches vaginally and could pass the skill on to others (as the authors of the Fox study were and did), the maneuver of moving an unengaged head out of the way and then doing a combined external/internal version is not something with which many obstetricians have had experience. Yet, how is this much different than doing an internal podalic version for a fetus in a transverse lie, followed by an immediate breech extraction?

The authors used the term "second-stage active management" for the second twin, which simply means "Do something right away after the first twin is delivered." In this case, either one would immediately rupture membranes of the second twin if the vertex comes down into the pelvis or, if it does not, go for the feet anyway you can, followed by an extraction. Another option, not addressed in the study for a vertex with a high station, would be to quickly make sure with ultrasound that there is no cord in front of the head, and then to needle the membranes so the head can settle into the pelvis. I would assume that in most cases the second twin could be delivered as a vertex under these circumstances.

Whatever the technique, this paper suggests that with the Fox study's experienced operators, the vast majority of patients with twins wanting vaginal deliveries attained their goal, without apparent neonatal morbidity. However, the "skilled operator" part is extremely important, as pointed out in a companion editorial by Mary D'Alton,[5] and, based on contemporary trends, those with this experience are a dying breed. ■

References

1. Schmitz T, et al. Neonatal outcomes of twin pregnancy according to the planned move of delivery. *Obstet Gynecol* 2008;111:695-703.
2. Armson BA, et al. Determinants of perinatal mortality and serious neonatal morbidity in the second twin. *Obstet Gynecol* 2006;108(3 Pt 1):556-564.
3. Smith GC, et al. Mode of delivery and the risk of delivery-related perinatal death among twins at term: A retrospective cohort study of 8073 births. *BJOG* 2005;112:1139-1144.
4. Cruikshank DP. Intrapartum management of twin gestations. *Obstet Gynecol* 2007;109:1167-1176.
5. D'Alton M. Delivery of the second twin: Revisiting the age-old dilemma. *Obstet Gynecol* 2010;115(2 Pt 1): 221-222.

Decreasing Surgical Site Infections

ABSTRACT & COMMENTARY

By Alison Edelman, MD, MPH

Associate Professor, Assistant Director of the Family Planning Fellowship Department of Obstetrics & Gynecology, Oregon Health & Sciences University, Portland

Dr. Edelman is a consultant to Schering-Plough and receives grant/research support from the Society for Family Planning.

Synopsis: *Chlorhexidine-alcohol scrub decreases surgical site infections in clean-contaminated surgical procedures (i.e., hysterectomies).*

Source: Darouiche RO, et al. Chlorhexidine-alcohol versus povidone-iodine for surgical site antisepsis. *N Engl J Med* 2010;362:18-26.

DAROUICHE AND COLLEAGUES PERFORMED A U.S. MULTICENTER randomized clinical trial of 849 patients undergoing clean-contaminated surgical procedures. Patients were randomized to chlorhexidine-alcohol scrub or povidone-iodine scrub and paint. Intent-to-treat analysis was used. Primary outcome was surgical site infections within 30 days of the procedure. Demographics of the study population included: 10% in each group underwent gynecologic procedures, average age was 53 years, and a little under half of the study subjects in each group were female. In addition, approximately 25% of patients in each group underwent some sort of preoperative shower with chlorhexidine gluconate, povidone-iodine, or triclocarban, and 100% of patients received preoperative antibiotics. Surgical site infection was significantly lower in the chlorhexidine-alcohol scrub group (9.5% vs 16.1%; $P = 0.004$; relative risk, 0.59; 95% confidence interval, 0.41-0.85).

■ COMMENTARY

As more attention is placed on health care reform, including lower costs while improving performance, clinicians need lower tech tools to improve clinical outcomes. Surgical site infections account for approximately 15% of all nosocomial infections.[1] In turn, these infections increase health care costs by lengthening hospital stays, increasing clinical costs, and increasing hospital readmissions.[2] Darouiche et al provides us with one of the only randomized controlled trials comparing two commonly used surgical site preparations, chlorhexidine-alcohol scrub (Chloraprep®) and povidone-iodine scrub and paint (Scrub Care Skin Prep Tray®). Who knew that skin preparations for surgical site antisepsis, something that we use every day, has been so little studied?

The advantages of this study, besides its prospective randomized design, include that it was performed free of pharmaceutical support at six university-affiliated hospitals across the United States in both men and women undergoing a variety of clean-contaminated surgeries (colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynecologic, and urologic). In addition, 100% of patients had antibiotics initiated preoperatively (Wow!). Its limitations include that comorbidities such as obesity or diabetes were not specifically reported but stated to be equal between groups (it would still be nice to know the numbers), approximately 50% of patients in each group received antibiotics postoperatively but it was not noted for how long, and 25% of patients underwent some sort of preoperative antisepsis shower. However, their randomization worked well with equal amounts of these adjunctive but not evidence-based antiinfection practices in both groups.[3,4] Often, the results of studies are not easily generalizable for the practicing clinician, but this study did a good job of incorporating "gold-standard" study techniques while maintaining "real-life" practices.

The Centers for Disease Control and Prevention classifies surgical site infections into three different categories: superficial or deep incisional and organ space.[5] Chlorhexidine-alcohol scrub (Chloraprep) was more protective against superficial and deep incisional infections (superficial: 4.2% vs 8.6%; $P = 0.008$; deep: 1% vs 3%; $P = 0.05$). There was no difference in rates of organ space infections between the two groups (4.4% vs 4.5%). One could speculate that skin antisepsis has little to do with organ space antisepsis, and with 100% compliance of systemic antibiotics in this study, this rate is as low as it can go.

This study provides us with high-level evidence to support a change in practice to start using chlorhexidine-alcohol scrub for surgical site antisepsis. Interestingly, there is emerging evidence that the increased effectiveness is due to the alcohol component and it may not matter if it is combined with chlorhexidine or iodine.[6] If you do decide to use an alcohol-based preparation, a note of warning, adequate drying must be allowed prior to use to eliminate the risk of fire when using electrocautery. Copious amounts of hair can impede/delay the drying

process (something to think about when you are near the vulva).[6,7] ■

References

1. CDC Surgical Site Infections: Data and Statistics. Available at: www.cdc.gov/ncidod/dhqp/dpac_ssi_data.html. Accessed Feb. 15, 2010.
2. Urban JA. Cost analysis of surgical site infections. *Surg Infect (Larchmt)* 2006;7(Suppl 1):S19-22.
3. Webster J, Osborne S. Preoperative bathing or showering with skin antiseptics to prevent surgical site infection. *Cochrane Database Syst Rev* 2007;2: CD004985.
4. Edwards P, et al. Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. *Cochrane Database Syst Rev* 2004;3:CD003949.
5. Mangram AJ, et al. Guideline for prevention of surgical site infection 1999. *Am J Infect Control* 1999; 27:97-132.
6. Reichman D, Greenberg J. Reducing surgical site infections: A review. *Rev Obstet Gynecol* 2009;2: 212-221.
7. Weber S, et al. DuraPrep and the risk of fire during tracheostomy. *Head Neck* 2006:28:649-652.

Pessary Management of Incontinence

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: *Two-thirds of patients with genuine stress incontinence with minimal pelvic organ prolapse can be successfully fitted with an incontinence pessary or dish.*

Source: Nager CW, et al. Incontinence pessaries: Size, POPQ measures, and successful fitting. *Int Urogynecol J Pelvic Floor Dysfunct* 2009;20:1023-1028.

IN THIS MULTICENTER TRIAL, PATIENTS WITH DOCUMENTed stress urinary incontinence (SUI) with a pelvic organ prolapse quantification (POPQ) score < 2 were randomized to groups that received an incontinence pessary or an incontinence pessary along with behavioral therapy. Ninety-two percent of the 235 patients were successfully fitted with an incontinence pessary or dish. A history of hysterectomy, the genital hiatus, and the genital hiatus/total vaginal length ratio did not predict unsuccessful fitting. No specific POPQ measurement was helpful in determining incontinence pessary size.

■ COMMENTARY

This is a publication from the Pelvic Floor Disorders Network with involvement of excellent investigators from the United States. Just as the subspecialty of urogynecology (a.k.a., female pelvic medicine and reconstructive surgery) is becoming established, the authors sought to bring some standardization to the art of pessary fitting. If the size of the pessary can be predicted using standard measures, then an office could more easily target which pessaries to have in stock and available to patients. It would also aid the novice in fitting pessaries, an experience that is not extensively found during residency training in many locations.

Of clinical relevance for the busy practitioner, during the study, successful fitting of the incontinence ring or dish was accomplished by trained nurse practitioners, RNs, or physical therapists. Two-thirds of the patients were successfully fitted with a No. 2, No. 3, or No. 4 incontinence ring or a 65-, 70-, or 75-mm dish.

The authors note that a weakness of the study is that the patients had minimal prolapse and all had SUI. Patients with more prolapse or with different POPQ measures may well fare differently. A strength, however, is that it was shown that pessaries can be successfully fitted by interested providers other than just physicians. Because no specific POPQ measurements guided the fitting of the pessary, the authors conclude that the state of the art is just that … fitting an incontinence pessary remains an art.

This certainly opens our eyes to another aspect of conservative management of incontinence. I wonder how "lost" this lost art is, i.e., how many readers are actively using pessaries in their practice. Can a patient who is considering surgical and nonsurgical options for incontinence be considered fully informed if a pessary has not been mentioned? Even though pessary use is not extensive in our practice, we certainly do have them available. The Milex web site is the best place to go to look for these supplies. Was this an unsolicited advertisement for them? Not really. Consider it more of a helpful office management cost-efficiency tip. ■

Laparoscopy vs Laparotomy for Endometrial Cancer Staging: The Lap2 Report

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor, University of Texas;
M.D. Anderson Cancer Center, Houston

Dr. Coleman is a consultant to GlaxoSmithKline, Eli Lilly Co., Abbott Laboratories, Sanofi-Aventis, and Pfizer, and serves on the speakers bureau for GlaxoSmithKline, Eli Lilly Co., and OrthoBiotech.

Synopsis: *Laparoscopic surgical staging for clinical stage I-IIA uterine cancer is feasible and safe, providing staging information on par with laparotomy and a superior profile relative to complications and hospital stay.*

Source: Walker JL, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study Lap 2. *J Clin Oncol* 2009;27:5331-5336.

ENDOMETRIAL CANCER IS THE MOST COMMON GYNECOlogic malignancy and most often presents with corpus-limited disease. The principle aspect of initial care is organ removal, which may be approached surgically via the vagina or abdomen, or endoscopically. The latter two are preferred given the ability also to evaluate for extra-uterine disease in the abdomen and pelvis, as well as the retroperitoneum (surgical staging).

A formal phase III randomized surgical trial was conducted by the Gynecologic Oncology Group to assess the safety and feasibility of laparoscopic surgical staging relative to laparotomy. Eligible patients had clinical stage I-IIA uterine cancer and were randomly assigned 2:1 to laparoscopy vs laparotomy. The main study endpoints were 6-week morbidity and mortality, hospital length of stay, conversion from laparoscopy to laparotomy, recurrence-free survival, site of recurrence, and patient-reported quality-of-life outcomes.

In the current report, the latter 3 variables are not discussed due to immature data (survival and recurrence patterns) or are reported elsewhere (quality of life). Overall, 1248 of 1682 patients randomized to laparoscopy had the procedure completed without conversion to laparotomy (74%). The primary reason for conversion was poor visibility (54% of the 246 conversions). Laparoscopy was associated with significantly fewer moderate-to-severe postoperative adverse events (14% vs 21%; $P < 0.0001$), including ileus, and fewer hospital days (percentage greater than 2 days: 52% vs 94%; $P < 0.0001$), but was associated with a higher rate of noncompliance in removing paraortic lymph nodes (8% vs 4%; $P < 0.0001$) and longer operative times (204 vs 130 minutes; $P < 0.001$). However, there were similar rates of intraoperative complications, percentage of patients identified with positive nodes, and stage distribution. The authors conclude the laparoscopic approach is safe and feasible with noted improvements in short-term outcomes. Survival data are pending.

■ COMMENTARY

While endoscopic removal of the uterus has been performed for some time, the ability and utility of endoscopic surgical staging for endometrial cancer was launched when surgical dissection of the retroperitoneum became feasible. In the two decades since these initial reports, hundreds of papers have appeared in the literature highlighting improvements in surgical technique; patient selection; new, improved, or modified instrumentation; short- and long-term outcomes; and most recently, the introduction of robotics. Nearly all of these reports have come from a relatively limited number of highly skilled surgeons, developing referral or speciality practices and providing education to trainees and novices, who continually push the surgical envelope. Since the majority of endometrial surgical staging cases in this country are not reported in research studies, metrics of safety and feasibility of the laparoscopic approach are difficult to quantify.

Recognizing this important limitation, the Gynecologic Oncology Group launched a randomized clinical trial to initially describe the complications of the endoscopic route in members of this cooperative group without formal restrictions on surgical skill. Later, the protocol was expanded to describe outcomes as a non-inferiority design; these data are still maturing. However, for those who routinely offer the endoscopic approach for disease-limited endometrial cancer, the results of this initial summary are not surprising, and are validating — with the exception of conversion rates. While it would be expected that case volume increases would reduce conversion to laparotomy due to surgical skill, it is likely that this acquired acumen also stretched patient selection to older, more obese, and more medically diverse patients, keeping the conversion rate higher than expected. Indeed, over half of the conversion cases were due to surgical field

exposure. The recent introduction of robotics will likely have a positive effect on these issues as optics, motility degrees of freedom, and surgeon comfort are all substantially improved with these machines. Ultimately, long-term survival data for the two approaches must be equivalent or better to cement this surgical approach, despite the obvious bias to preferentially offer the procedure. Fortunately, those data will be available in the coming years. ■

Additional Readings

1. Kornblith AB, et al. Quality of life of patients with endometrial cancer undergoing laparoscopic international federation of gynecology and obstetrics staging compared with laparotomy: A Gynecologic Oncology Group study. *J Clin Oncol* 2009;27:5337-5342.
2. Gehrig PA, et al. What is the optimal minimally invasive surgical procedure for endometrial cancer staging in the obese and morbidly obese woman? *Gynecol Oncol* 2008;111:41-45.
3. Veljovich DS, et al. Robotic surgery in gynecologic oncology: Program initiation and outcomes after the first year with comparison with laparotomy for endometrial cancer staging. *Am J Obstet Gynecol* 2008;198:e1-e9.

CME Questions

47. According to be recent study, which of the following does not represent an exclusion for trying for a vaginal delivery for a second twin?
a. The first twin is a breech.
b. The second twin weighs < 1500 g.
c. The second twin is in a breech presentation.
d. The estimated fetal weight of the first twin is > 30% of the second.

48. Some studies have shown an increase in perinatal mortality and morbidity in second twins delivered vaginally.
a. True
b. False

49. According to the information above, which of the following options is preferred if the second twin's head is floating?
a. Do an immediate cesarean section.
b. Try an internal version and extraction immediately after the delivery of the first baby.
c. Grasp the head and pull it down for a vertex delivery.
d. None of the above

50. The use of chlorhexidine-alcohol scrub improved the overall rate of surgical site infections as compared to povidone-iodine scrub and paint.
a. True
b. False

51. Which of the following were improved for the laparotomy cohort?
a. Length of hospitalization
b. Intraoperative complications
c. Post-operative ileus
d. Total node count
e. Length of procedure

Answers: 47. d, 48. a, 49. b, 50. a, 51. e.

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.

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*.

Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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.

of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■