OB/GYN CLINICAL ALERT®

Providing Evidence-based Clinical Information for 25 Years

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.

New Insights into VBACs and Maternal and Neonatal Outcomes

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: *A recent review of the literature shows, and an NIH consensus panel concludes, that a trial of labor, when compared with a repeat cesarean section, is associated with a lower risk of maternal death and morbidity, but with a slightly higher risk of perinatal mortality and uterine rupture.*

Sources: Guise JM, et al. Vaginal birth after cesarean. New insights on maternal and neonatal outcomes. *Obstet Gynecol* 2010;115:1267-1278; National Institutes of Health Consensus Development Conference Statement: Vaginal birth after cesarean: New insights March 8-10, 2010. *Obstet Gynecol* 2010;115:1279-1295.

ALTHOUGH SOME ASPECTS OF VAGINAL BIRTH AFTER CESAREAN DELIVERY (VBAC) have been covered in previous *OB/GYN Clinical Alert* issues, I cannot pass up an opportunity to comment on two papers appearing in the June issue of *Obstetrics & Gynecology*. One was a critical review of the literature on a trial of labor (TOL) in patients who had previous cesarean deliveries and the other was a consensus statement from a National Institutes of Health (NIH) Development Conference Panel on VBAC.

Guise et al sifted through data from 203 articles that satisfied their inclusion criteria and attempted to answer questions that would be covered by the NIH consensus panel regarding maternal and neonatal outcomes with VBAC. Using what they construed to be the best studies, they found maternal mortality to be significantly lower (relative risk [RR], 0.33; 95% confidence interval [CI], 0.13-0.99) with TOL than with elective repeat cesarean section (RCS). If they only looked at term

VOLUME 27 • NUMBER 5 • SEPTEMBER 2010 • PAGES 33-40

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

pregnancy, the RR was 0.27 (95% CI, 0.09-0.85). Fortunately, the actual risk of a patient dying from either route was low — 4/10,000 for TOL and 13/10,000 for elective RCS.

Regarding uterine rupture, the pooled data from the best studies showed an overall rate of uterine rupture to be 0.47% for TOL and 0.03% for elective RCS. The average stay in the hospital for TOL was 2.6 days vs 3.9 days for RCS. Perinatal mortality was higher with TOL than RCS (0.11% vs 0.06%; RR, 2.06; 95% CI, 1.35-3.13). Much of this increased risk was contributed by those needing emergency cesarean section during a TOL. There were no significant differences between TOL and RCS regarding the need for hysterectomy, transfusion, or the rate of perinatal infection. Even with pooled data, there was insufficient information for the authors to comment on neonatal sepsis or neurological outcomes.

In summary, the group found a higher rate of uterine rupture with TOL (< 1/200) and perinatal death (1.3/1000), but less chance of maternal death and fewer days in the hospital.

■ COMMENTARY

The Guise et al study served as a source of outcome data, along with many other studies, that the NIH panel used in their deliberations and the ultimate report. Here is the backdrop, and undoubtedly the motivation behind the NIH panel's creation. In 1990, the cesarean section rate in the United States was 22.7% and the VBAC rate was 19.9%. At about that time, there was a push to decrease the cesarean section rate to 15% and VBACs were encouraged as a way to avoid repeat cesarean sections. Following this stated goal, the VBAC rate rose to 28.3% during the next 6 years, while the cesarean section rate dropped to 20.7%. However, soon thereafter, VBAC fell victim to the circumstances described below, causing the rate to drop steadily to 8%. Now the cesarean section rate in the United States is 32.8% (2008 data), and, currently, about 1.5 million cesarean sections are done yearly at a cost of $7.8 billion.[1]

What were the circumstances behind the above trend? In 1999 the American College of Obstetricians and Gynecologists (ACOG) issued practice guidelines that suggested patients be "offered" VBAC, instead of their previous 1990 wording, "encouraged," and the guidelines indicated that centers offering TOL should have a physician capable of doing a cesarean section to be "immediately available" during a patient's labor. Anesthesia guidelines followed the same "immediately available" requisite. At the same time, another VBAC deterrent emerged, as demonstrated by a 2009 ACOG survey showing that 30% of obstetricians stopped doing VBACs because of fear of litigation. Not surprisingly, some hospitals decided to no longer offer this option and many practitioners followed suit.

So, for those women who want a TOL, and who have a provider that supports it and a center that permits it, here is what they can be told about the real risks and benefits of TOL. Based on all available data:

1. The chance of a successful vaginal delivery is, on average, 74%, with a 63% chance in patients with no previous vaginal delivery, an 83% chance with a vaginal delivery prior to the previous cesarean section, and a 95% chance in those with a prior VBAC.

2. The risk of uterine rupture is about 0.47% overall, but undoubtedly lower in ideal candidates. Rates of rupture are higher with more than one prior cesarean section and in those who are induced, but the data do not support there being a higher rate when oxytocin augmentation is used for spontaneous labor.

3. Maternal mortality is lower (RR, 0.37), but perinatal mortality is higher (RR, 2.6). Perinatal death occurs in 6% of uterine ruptures, and in 3% of ruptures at term (overall, representing 2 perinatal deaths per 10,000 TOL).

4. Regarding downstream maternal complication of TOL, specifically pelvic floor disorders, the NIH panel concluded that elective cesarean section "should not be considered protective against stress incontinence and prolapse."

5. Maternal benefits of TOL would include a 60%-80% chance to avoid a cesarean section and its postoperative complications, and a decrease in the chances of placenta previa and accreta in subsequent pregnancies.

The statement in the report that is most debatable is:

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
DIRECTOR OF MARKETING: Schandale Kornegay

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.

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.
(Student/Resident 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 7% 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 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.

"Unfortunately, there is no reliable way to predict who will have a uterine rupture." Uterine wall thickness has been repeatedly shown to correlate with uterine rupture during TOL,[2,3] and Bujold et al have correlated uterine scar thickness < 2.3 mm (OR, 4.5), a birth-to-birth interval of < 18 months (OR, 6.7), and single-layer closure (OR, 5.7) with the risk of rupture.[4]

Therefore, it is likely that patients who fulfill some, but not necessarily all, of the following criteria should expect a low risk of uterine rupture and its consequences.

1. A previous VBAC or any vaginal delivery
2. More than 18 months between births
3. Only one prior cesarean section
4. A uterine wall thickness > 2.3 mm
5. A double-layer closure
6. An estimated fetal weight < 4000 g
7. Spontaneous labor

The most difficult variables to deal with are the fears of providers about their legal vulnerability, the continued inability of hospitals to comply with TOL guidelines, and the common misconception among patients that cesarean section will prevent urinary complications and later sexual dysfunction. ■

References

1. Gotoh H, et al. Predicting incomplete uterine rupture with vaginal sonography during the late second trimester in women with prior Cesarean. *Obstet Gynecol* 2000;95:596-600.
2. Rozenberg P, et al. Ultrasonographic measurement of lower uterine segment to assess risk of defects of scarred uterus. *Lancet* 1996;347:281-284.
3. Grobman WA, et al. Prediction of uterine rupture associated with attempted vaginal birth after cesarean delivery. *Am J Obstet Gynecol* 2008;199:30.e1-5.
4. Bujold E, et al. Prediction of complete uterine rupture by sonographic evaluation of the lower uterine segment. *Am J Obstet Gynecol* 2009;201:320.e1-6.

Stress Incontinence After Midurethral Sling: Now What?

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: *In the approximately 20% of patients not cured of incontinence by a midurethral sling, a pubovaginal sling or a repeat procedure using a minimally invasive synthetic midurethral sling appears to be appropriate.*

Source: Walsh CA, Moore KH. Recurrent stress urinary incontinence after synthetic midurethral sling procedure. *Obstet Gynecol* 2010;115:1296-1301.

In this article, the authors address common questions related to management of those patients who have recurrent stress incontinence after already having a midurethral sling (MUS) using a synthetic mesh. They use the presentation of two cases as a starting point and the questions they pose are the common ones that we and our patients ask. Using the available data in the literature, useful answers are provided, thereby helping the reader move patient care in a positive direction.

■ COMMENTARY

I love this article. It's relevant to our daily practice, but, more importantly, it verbalizes the same issues that both physicians and patients want clarified. It uses the data that are available to us (there isn't as much as we would like) and makes recommendations for care. What the reader will take away from the article is that large databases are lacking, but there is a reasonable way to approach these patients that can maximize success rates.

We all know that MUS with synthetic mesh is becoming/has become the standard first-line surgical management for stress incontinence (SUI). We also know, and, hopefully inform our patients, that the procedure is far from perfect, having about a 20% failure rate. How to approach these patients based on the data in print doesn't take us very far from what we already do for those patients with primary stress incontinence before their MUS. In a shortened version, here is what the authors offer (note that the answers to questions after MUS are very similar to the answers before MUS):

• **Causes of incontinence after MUS:** urinary tract infections (UTI), overactive bladder (OAB), overflow incontinence, urethral diverticulum, fistulae, and recurrent/persistent SUI (most common cause).

• **Risk factors for MUS failure:** low urethral resistance, advanced patient age, OAB symptoms. Data regarding body mass index (BMI) are conflicting.

• **Assessment of patients with MUS failure:** history, physical (including cough stress test, assessment of urethral mobility, mesh erosion, hypoestrogenism, pelvic floor strength and POP-Q), and culture, uroflowmetry (with post-void residual), and cystometry/cystoscopy.

• **Non-surgical options:** weight loss, pelvic floor training, pessary, and possibly duloxetine (although not FDA-

approved for this indication).

• **Surgical options:** repeat MUS, pubovaginal sling with allograft or autograft, periurethral bulking, retropubic colposuspension, and artificial sphincter.

• **Cures and complications after repeat MUS:** complications are similar after the second procedure compared to the first. A repeat MUS appears to be comparable to pubovaginal sling, although data comparing the two procedures are lacking.

Since our patients deserve the best shot we can give them, be it the first or second procedure, this article provides us with a reminder that we should rely on the limited data available to us and make the best judgement we can for each patient. Relying on the basic principles that we all learned about stress incontinence and not taking shortcuts, we can offer the operation (or non-surgical treatment) that maximizes each patient's satisfaction with this challenging and sometimes frustrating situation. ■

Paclitaxel and Carboplatin: A Relevant Combination in Uterine Carcinosarcoma

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

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

Synopsis: *Paclitaxel + carboplatin is a safe and effective combination therapy in patients with advanced primary or recurrent carcinosarcoma of the uterus. Further clinical development is warranted.*

Source: Powel MA, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: A Gynecologic Oncology Group study. *J Clin Oncol* 2010;28:2727-2731.

Carcinosarcoma of the uterus is a rare condition accounting for less that 4% of all uterine neoplasms. Previous work has identified that the most active single agents are platinum, ifosfamide, paclitaxel, and doxorubicin. Ifosfamide combinations have proved to be more efficacious relative to ifosfamide alone, but substantially more toxic. Paclitaxel + carboplatin has been intimated from retrospective reviews to be active in this disease. In response, the Gynecologic Oncology Group (GOG) conducted a prospective, 2-stage, open label, multi-institutional study of combination paclitaxel (175 mg/m^2) and carboplatin (AUC 6) in women with stage III/IV or recurrent carcinosarcoma. All patients had to have measurable disease and were treated until toxicity, progression, or complete clinical remission. The study design allowed for early study termination for inactivity. Fifty-five patients were accrued with 9 being excluded (5 wrong histology, 2 wrong primary site, 2 never treated). Of the 46 evaluable patients, response was documented and confirmed by second imaging study in 25 (6 complete and 19 partial responses; overall response rate: 54%). The regimen was well tolerated with expected hematological toxicity and minimal non-hematological grade 4 toxicity (1 cardiovascular, 2 pain); 59% received 6 or more cycles of therapy. Paclitaxel + carboplatin is active in this setting and met prespecified criteria for further clinical development. As such, the current chemotherapy backbone is the focus of a large prospective phase III non-inferiority trial against ifosfamide and paclitaxel.

■ COMMENTARY

Carcinosarcoma, also known as malignant mixed müllerian tumor (MMMT) is a rare uterine neoplasm associated with an aggressive phenotype, being frequently metastatic at primary diagnosis or recurring in short order after primary adjuvant therapy. The rarity of the tumor challenges the ability to expeditiously evaluate modalities and agents of therapy, which has limited our options for these patients. The disease has a unique signature wherein the primary site (uterus) is composed of malignant stroma and glands, but metastatic sites are nearly always of the epithelial component. Despite this, the biology of this disease may be different than high-grade endometrioid or non-endometrioid (serous or clear cell) cancer. Retrospective comparisons of carcinosarcoma to epithelial cancers demonstrate that the former is associated with a poorer prognosis independent of stage or histology. Nevertheless, risk for systemic spread in apparently localized cases and extrapelvic post-treatment failure have largely dictated systemic adjuvant chemotherapy in the management of these neoplasms.

Through a dedicated phase II queue in the GOG, several agents have been systematically studied for activity in patients with known metastatic or recurrent carcinosarcoma. From this long list, just 4 agents have emerged with sufficient promise (response rates from 10% to 42%) to be evaluated in the phase III setting: doxorubicin, ifosfamide, paclitaxel, and cisplatin. Phase III trials, heretofore, have most recently compared ifosfamide combinations (cisplatin or paclitaxel) to single agent ifosfamide. Both trials demonstrated superior response and progression-free survival (also overall survival in the ifosfamide + paclitaxel combination) for the doublet over the control arm.

However, toxicity was substantial, frequently leading to dosing delays and use of marrow stimulants to maintain schedule.

The current trial evaluated a ubiquitous doublet in solid tumors with a well-known and comfortable toxicity profile in this rare tumor. The favorable activity and acceptable toxicity experience provided the rationale to examine the doublet in an ongoing phase III clinical trial in women with primary or recurrent carcinosarcoma against combination ifosfamide + paclitaxel. Results from this trial won't be available for some time; however, chemotherapy combinations with new biological agents (such as angiogenesis and PARP inhibitors) are continuing with the expectation of moving the therapeutic opportunities forward for these women.

In addition, microarray signatures suggest the histology of the tumor is more relevant than site of origin. As a result, at least one uterine carcinosarcoma trial (GOG 261) is being amended to accept ovarian carcinosarcomas, as well as those arising in the peritoneal cavity. ■

Additional Reading

1. Amant F, et al. Endometrial carcinosarcomas have a different prognosis and pattern of spread compared to high-risk epithelial endometrial cancer. *Gynecol Oncol* 2005;98:274-280.
2. Bansal N, et al. Uterine carcinosarcomas and grade 3 endometrioid cancers: Evidence for distinct tumor behavior. *Obstet Gynecol* 2008;112:64-70.
3. Sutton G, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. *Gynecol Oncol* 2000;79:147-153.

Special Feature

Tranexamic Acid: Non-hormonal Treatment for Heavy Menstrual Bleeding

WITHOUT FANFARE, THE FDA APPROVED ORAL TRANEXAMIC acid tablets (Lysteda™), the first non-hormonal product cleared to treat heavy menstrual bleeding in the United States. Tranexamic acid (TA) was initially approved by the FDA in 1986 as an injection (Cyklokapron®) to reduce or prevent bleeding during and following tooth extraction in patients with hemophilia.

Tranexamic acid [4-(aminomethyl)cyclohexane-1-carboxylic acid] is an antifibrinolytic that competitively inhibits activation of plasminogen, thereby reducing conversion of plasminogen to plasmin (fibrinolysin), an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the procoagulant factors V and VIII. Although tranexamic acid also directly inhibits plasmin activity, this requires higher doses than are needed to reduce plasmin formation. While clinicians in the United Kingdom, Europe, and many other countries have had oral forms of TA available for the indication of heavy menstrual bleeding for many years, gynecologists in the United States have no direct experience with this drug. Since this novel and interesting new treatment option is now available for your patients, I thought a short review could provide context for its use.

Do women with HMB require treatment?

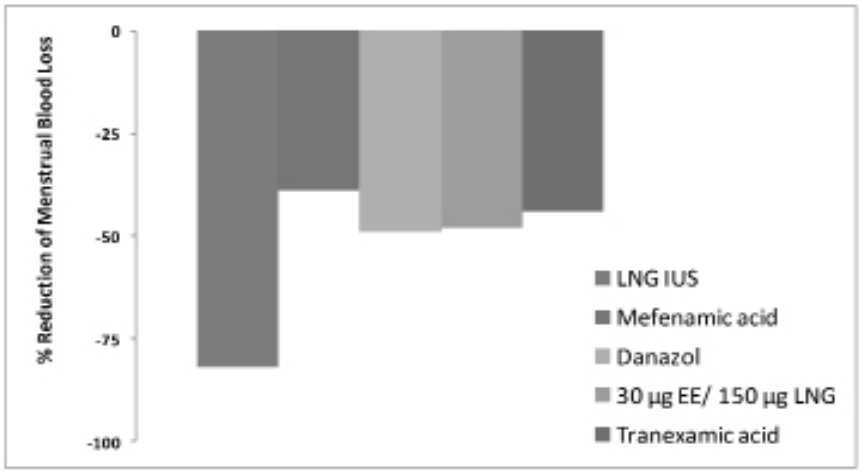
The terms used to describe abnormal uterine bleeding are poorly defined. To improve communication, research, and patient care, a consensus group of leading academic experts led by Ian Fraser of the University of Sydney has proposed eliminating the terms menorrhagia, metrorrhagia, and dysfunctional uterine bleeding, and replacing these with clear descriptive terminology easily translated into any language.[1] The term heavy menstrual bleeding (HMB) is now the preferred term for excessive bleeding. The normal volume of flow is defined as measured menstrual blood loss of 5-80 mL. The 80 mL threshold comes from detailed studies that determined that women become anemic when blood loss exceeds this amount.[2] While the 80 mL definition makes sense for research, it offers little guidance for clinicians. Not all women that complain of HMB will become anemic and a woman's perception of her own menstrual loss is the key determinant in her presentation to the clinic for evaluation and therapy, a position endorsed by the National Institute for Clinical Excellence (NICE) in the United Kingdom.[3]

That said, menstrual disorders account for more than 12% of total gynecologic emergency room visits[4] and estimates of the economic costs due to lost productivity as a result of HMB vary between $1692 and $3600 per patient per year.[5,6] Compared to women with normal or light bleeding, women with HMB are significantly less likely to be employed[6] and more likely to use health care services.[7] About 17% of the roughly 600,000 hysterectomies performed annually in the United States are done to manage menstrual disorders.[8,9] While surgical options such as hysterectomy and endometrial ablation are effective treatments for heavy menstrual bleeding, both approaches have significant risks and costs, and health authorities in New Zealand and the United Kingdom have recommended that medical therapies be considered before surgery.

How effective are hormonal therapies for HMB?

Hormonal therapies are useful in alleviating menstrual symptoms in women with excessively heavy or symp-

Figure. Typical reduction in bleeding after 2-3 cycles of treatment.[14,18]



tomatic menstrual periods. Progestogen-only methods can be used in women with contraindications to estrogen therapy. Until the October 2009 approval of the LNG IUS in the United States, the only approved therapies for "abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology" had been cyclic oral medroxy progesterone acetate (MPA) and norethindrone (NET), but neither of these is indicated for contraception. A Cochrane review found that no randomized placebo-controlled trials of oral progestogens for HMB have been performed.[10] The LNG IUS provides a high local level of levonorgestrel directly to the endometrium. While bleeding is unpredictable during the early months of use, it is typically light and improves such that by 6 months most users report either light regular cycles or amenorrhea. A number of observational[11,12] and randomized[13-15] studies have demonstrated the superiority of LNG IUS to all other medical options *(see Figure, above)*, with an effect comparable to that achieved with endometrial ablation.[5,16,17]

Combined oral contraceptives (COC) reduce the duration and intensity of menstrual bleeding, and are widely used to manage abnormal menstruation despite few objective data and no labeling indications to support this practice. Fraser and McCarron used a crossover design to study women with ovulatory HMB and found that the reduction in bleeding achieved with a COC (30 µg EE/150 µg LNG) was similar to that observed with danazol and the nonsteroidal agent mefenamic acid (approximately 30%-50%).[18] New data presented at the 2009 meetings of the International Federation of Obstetrics and Gynecology[19] and the American Society of Reproductive Medicine[20] provided evidence that a novel extended oral contraceptive regimen containing estradiol valerate and dienogest (E2V/DNG) may be more effective than other COC, with a reduction in measured blood loss of more than 60%. The E2V/DNG pill has been approved in Europe for over a year, and was recently approved for contraception in the United States (Natazia™, Bayer Healthcare). A second indication for the treatment of HMB is under review.

How effective are other medical therapies for HMB?

NSAIDs are widely available and easy to use, but not all will be equally effective. The randomized study by Fraser demonstrated that mefenamic acid reduced measured blood loss by up to 39%; this was not significantly different than the reduction seen with a COC (43%) and danazol (49%), but was better than naproxen (12%). Unfortunately, mefenamic acid is not available without a prescription, so cost is higher than with over-the-counter NSAIDs such as ibuprofen. Gastrointestinal tolerance also limits the acceptability of NSAIDs. Many women object to the androgenic side effects of danazol, and since this drug also carries a black box warning for DVTs, there is no real advantages to it over a COC.

What does tranexamic acid offer?

Tranexamic acid reduces menstrual blood loss by about one-third. The pivotal U.S. trials (one 3-cycle treatment and one 6-cycle treatment) that led to marketing approval are described in the package insert but are not published. HMB was defined as an average menstrual blood loss of ≥ 80 mL as assessed by the alkaline hematin method, so the results are comparable to existing literature including the recently completed LNG IUS and E2V/DNG OC studies. A dose of 3900 mg (two 650 mg tablets TID) resulted in a 39% reduction in mean menstrual blood loss from baseline. These results are similar to other published randomized studies with TA. While impressive, they fall short of the results observed in U.S. women treated with the LNG IUS (71%) and the E2V/DNG COC (62%).[20]

Who are good candidates for tranexamic acid?

Women with idiopathic heavy menstrual bleeding that would prefer not to use a hormonal therapy or NSAID will benefit from TA. One particular group will be women seeking pregnancy. I frequently see patients complaining of heavy bleeding after stopping hormonal contraceptive therapy in order to get pregnant. We have had little to offer these women except NSAIDs, iron, and good wishes for a speedy conception. Since TA is Category B for pregnancy and is used only during menstruation (well before ovulation and fertilization), even the most risk-averse preconception patients should find it acceptable.

Users of the copper IUD represent another group that

could benefit from TA. A randomized study demonstrated this reduced bleeding by about 50%, but side effects were greater than with a NSAID.[21]

What are the side effects and contraindications?

Among the side effects reported during clinical trials of TA, only sinus and nasal symptoms (25% vs 17% placebo), back pain (21% vs 15%), and musculoskeletal pain (11% vs 3%) appear to be related to use of the drug (data from package insert).

Women with risk factors for thrombosis should not use TA due to an increased chance of arterial and venous clots. Therefore, any women with a medical condition that would represent a contraindication to hormonal therapy should probably not use TA. While use of TA in a woman already using a combined hormonal method is not listed as contraindication in the labeling, there is a specific warning that co-administration with a combined method may increase the risk of clot formation. Therefore, risks should be considered along with potential benefits. Caution should also be observed in women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates, or oral tretinoin as the risk of clots may increase. Tretinoin (a treatment for acute promyelocytic leukemia) should not be confused with isotretinoin, the treatment for acne.

Many women with HMB also suffer from dysmenorrhea. TA will not improve these symptoms, but NSAIDs can be safely co-administered.

When will tranexamic acid be available to clinicians, and how should it be prescribed?

Tranexamic acid will be marketed under the brand name of Lysteda (Ferring Pharmaceuticals). While Ferring is well known as a leading supplier of gonadotropins for use in infertility, this will be its first product for use in general gynecology patients, so a large sales force is not currently in place. The product was introduced at the 2010 ACOG meeting in San Francisco, and should be available from pharmacies.

TA is supplied as a 650 mg tablet. The recommended dose of TA is two tablets (1300 mg) three times a day (3900 mg/day) for a maximum of 5 days during monthly menstruation. Dose adjustment is needed in women with renal failure.

Bottom line

Oral tranexamic acid provides an important new nonhormonal option to manage idiopathic heavy menstrual bleeding. Clinicians in the United States need to recognize that this therapy has been available around the world for a long time and is not a panacea. Similar to hormonal therapy, TA should not be used in women at high risk for thrombosis. The reduction in bleeding is similar to that observed with traditional oral contraceptives and NSAIDs, but less than that reported with the LNG IUS or the new E2V/DNG pill. Despite these limitations, TA presents an excellent new treatment choice for women with HMB preferring to manage symptoms episodically and in those seeking pregnancy or simply wishing to avoid hormonal therapy. I expect the drug will have a meaningful impact in the care of our patients. ■

References

1. Fraser IS, et al. A process designed to lead to international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. *Fertil Steril* 2007;87:466-476.
2. Hallberg L, et al. Menstrual blood loss and iron deficiency. *Acta Med Scand* 1966;180:639-650.
3. National Collaborating Centre for Women's and Children's Health. Heavy menstrual bleeding Commissioned by the National Institute for Health and Clinical Excellence. Available at: www.nice.org.uk/nicemedia/live/11002/30404/30404.pdf. Accessed July 23, 2010.
4. Curtis KM, et al. Visits to emergency departments for gynecologic disorders in the United States, 1992-1994. *Obstet Gynecol* 1998;91:1007-1012.
5. Hurskainen R, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: Randomized trial 5-year follow-up. *JAMA* 2004;291:1456-1463.
6. Cote I, et al. Work loss associated with increased menstrual loss in the United States. *Obstet Gynecol* 2002;100:683-687.
7. Cote I, et al. Use of health services associated with increased menstrual loss in the United States. *Am J Obstet Gynecol* 2003;188:343-348.
8. Wu JM, et al. Hysterectomy rates in the United States, 2003. *Obstet Gynecol* 2007;110:1091-1095.
9. Whiteman MK, et al. Inpatient hysterectomy surveillance in the United States, 2000-2004. *Am J Obstet Gynecol* 2008;198:34.e1-7.
10. Lethaby A, et al. Cyclical progestogens for heavy menstrual bleeding. *Cochrane Database Syst Rev* 2008;(1):CD001016.
11. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;97:690-694.
12. Xiao B, et al. Therapeutic effects of the levonorgestrel-releasing intrauterine system in the treatment of idiopathic menorrhagia. *Fertil Steril* 2003;79:963-969.
13. Reid PC, Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: A multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment

charts. *BJOG* 2005;112:1121-1125.
14. Milsom I, et al. A comparison of flurbiprofen, tranexamic acid, and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *Am J Obstet Gynecol* 1991;164:879-883.
15. Endrikat J, et al. A Canadian, multicentre study comparing the efficacy of a levonorgestrel-releasing intrauterine system to an oral contraceptive in women with idiopathic menorrhagia. *J Obstet Gynaecol Can* 2009;31:340-347.
16. Hurskainen R, et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: A randomised trial. *Lancet* 2001;357:273-277.
17. Kaunitz AM, et al. The levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: A systematic review and meta-analysis. *Obstet Gynecol* 2009;113:1104-1116.
18. Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. *Aust N Z J Obstet Gynaecol* 1991;31:66-70.
19. Fraser IS, et al. A novel oral contraceptive comprising estradiol valerate/dienogest for the treatment of heavy and/or prolonged menstrual bleeding without organic cause: A double-blind, randomised, placebo-controlled trial. *Int J Gynecol Obstet* 2009;107:S183.
20. Jensen J, et al. A multicenter, double-blind, randomized, placebo-controlled study of oral estradiol valerate/dienogest for the treatment of heavy and/or prolonged menstrual bleeding. *Fertil Steril* 2009;92:S32.
21. Ylikorkala O, Viinikka L. Comparison between antifibrinolytic and antiprostaglandin treatment in the reduction of increased menstrual blood loss in women with intrauterine contraceptive devices. *Br J Obstet Gynaecol* 1983;90:78-83.

CME Questions

15. Compared with repeat cesarean section, a trial of labor (TOL) is associated with:
a. a lower perinatal mortality.
b. a lower rate of maternal death.
c. the same rate of uterine rupture.
d. a higher rate of uterine prolapse.
e. None of the above

16. The rate of uterine rupture with TOL is higher when patients are induced or when oxytocin is used to augment labor.
a. True
b. False

17. Which of the following is *not* a category associated with a lower rate of rupture and higher rate of success with TOL?
a. A birth-to-birth interval > 1 year
b. A uterine scar thickness > 2.3 mm
c. An estimated fetal weight of < 4000 g
d. A double-layer uterine closure during the prior cesarean section
e. A prior successful VBAC

18. Which of the following agents has *not* been documented to have clinical efficacy in the uterine carcinosarcoma?
a. Paclitaxel
b. BSI-201 (a PARP inhibitor)
c. Ifosfamide
d. Cisplatin

19. Tranexamic acid is:
a. safe to use in women seeking pregnancy.
b. a good option to use in women with a history of thrombosis.
c. more effective in reducing heavy menstrual bleeding than oral contraceptives.
d. a good treatment for dysmenorrhea.

Answers: 15. b, 16. b, 17. a, 18. b, 19. a.

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.*

Weight-loss Drug Effective Without Cardiac Side Effects?

In this issue: Lorcaserin submitted for FDA review, FDA advisory panel votes against phentermine/topiramate, mixed vote on rosiglitazone, advisory panel votes to remove breast cancer indication from bevacizumab labeling, no increase in seizures found with DTaP vaccine, new REMS for quinine.

Weight loss without cardiac side effects

A new weight-loss medication may soon be available in the United States. Arena pharmaceuticals has filed a new drug application with the FDA for lorcaserin, a selective serotonin 2C-receptor agonist, and will likely get a formal review this fall. Unlike previous nonselective serotonergic agonists such as fenfluramine and dexfenfluramine, which were effective at causing weight loss, but also inhibited serotonin 2B receptors in the heart and were associated with valvulopathy, lorcaserin is specific for the serotonin 2C receptor in the brain.

Results from a company-sponsored study were published in the in *New England Journal of Medicine* and validate the effectiveness of the drug. The phase III trial was conducted at 98 academic and private trial sites, where 3180 patients were randomly assigned to receive lorcaserin 10 mg or placebo twice daily. After 1 year, patients receiving the active drug were randomly reassigned in a 2:1 ratio to continue to receive lorcaserin or change to placebo. All patients were age 18-65 years with a BMI of 30-45 or 27-45 kg/m^2 with one coexisting condition, including hypertension, dyslipidemia, cardiovascular disease, impaired glucose tolerance, or sleep apnea. Patients were also counseled on lifestyle modification. Echocardiography was done at baseline and every 6 months thereafter.

At the end of 1 year, 47.5% of patients receiving lorcaserin lost 5% or more of their baseline body weight as compared with 20.3% of patients receiving placebo ($P < 0.001$). The average patient in the lorcaserin group lost 5.8% of their body weight compared with 2.2% in the placebo group ($P < 0.001$), and more patients in the active treatment group lost 10% or more of their baseline body weight than in the placebo group (22.6% vs 7.7%; $P < 0.001$). In those who lost weight with the active drug, the loss was maintained in a greater proportion of patients who continued to receive lorcaserin in year 2 compared to those who were reassigned to placebo (67.9% vs 50.3%; $P < 0.001$). Markers of cardiovascular risk were improved in the active treatment group including C-reactive protein, fibrinogen levels, lipid levels, and insulin resistance. Systolic and diastolic blood pressures also decreased slightly in the lorcaserin group. Significantly, there was no evidence of cardiac valvulopathy found with use of lorcaserin and the rate of serious side effects was similar in the two groups.

The authors conclude that lorcaserin was associated with significant weight loss and improved maintenance of weight loss as compared to placebo (*N Engl J Med* 2010;363:245-256). Already being tagged the new, safe "diet drug," it is a sure bet that approval of lorcaserin will be associated with tremendous interest from our patients. ■

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.

Advisory panel votes against Qnexa

An FDA advisory panel recommended against approving (10-7 vote) the combination weight-loss drug Qnexa® (phentermine/topiramate) because of concerns about safety. The drug appears to be effective at inducing weight loss, but is associated with significant side effects including depression, anxiety, sleep disorders, attention, memory, and language and other cognitive disorders, as well as metabolic acidosis, increased heart rate, and teratogenicity. Qnexa is a combination of two available drugs and both remain on the market individually. Phentermine was approved in 1959 and is currently indicated as short-term treatment for weight reduction. It was part of the infamous Fen/Phen combination along with fenfluramine (later dexfenfluramine; both fenfluramine and dexfenfluramine were eventually removed from the market when they were found to cause pulmonary hypertension and cardiac valvulopathy). Topiramate is approved for the treatment of seizures and migraine prophylaxis. The FDA generally follows the recommendations of its expert panels. ■

Mixed vote on rosiglitazone

The same FDA committee also recently ruled on the embattled diabetes drug rosiglitazone (Avandia®), and the vote was decidedly mixed. GlaxoSmithKline's rosiglitazone has been under intense scrutiny since 2007 when a study from the Cleveland Clinic linked the drug to an increased rate of heart attacks (*N Engl J Med* 2007;356:2457-2471). Recently, the FDA has evaluated reports from the *New York Times* and others that the company suppressed crucial safety information about the drug for years. At the July meeting of the Endocrinologic and Metabolic Advisory Committee, 12 members voted to withdraw rosiglitazone from the market, 10 voted to keep the drug on the market with additional warnings and restrictions, 7 wanted additional warnings only, and 3 members voted for no label changes. The FDA is not required to follow the advice of its advisory panels, and it is unclear what course they will take when they finally make a decision later this year. ■

Breast cancer indication for bevacizumab

The Oncologic Drugs Advisory committee of the FDA has recommended removing the indication for breast cancer treatment for bevacizumab (Avastin®). The 12-1 vote was made after data were presented that the drug provided no survival benefit when used in combination with docetaxel, while contributing significant adverse effects. Bevacizumab, a humanized monoclonal antibody, which blocks new blood vessel formation (angiogenesis inhibitor), also carries indications for treatment of colon, lung, kidney, and brain cancers. ■

No increase in seizures with DTaP vaccine

The diphtheria-tetanus-acellular pertussis vaccine (DTaP) does not increase the risk of seizures in children, according to a recent article published on-line in *Pediatrics*. The previously used diphtheria-tetanus-whole-cell pertussis vaccine (DTP) is associated with seizures, but there were limited data on DTaP. Using data from the CDC's Vaccine Safety Data linked project, a retrospective study from 1997 through 2006 at 7 managed-care organizations was performed. Eligible children were age 6 weeks to 23 months and had not previously received DTP. Of the more than 433,000 children who were vaccinated, there were 7191 seizure events. The adjusted incident rate for seizures across all doses was 0.87 in the cohort analysis and 0.91 in the comparison group with the same patients during unexposed periods. The authors conclude that they did not observe an increased risk for seizures after DTaP among children age 6 weeks to 23 months. ■

New REMS for quinine

The FDA banned the OTC use of quinine sulfate for the treatment of nocturnal leg cramps in 1994 after receiving more than 150 reports of adverse reactions, including 23 deaths. Quinine sulfate (brand name Qualaquin®) remains the only quinine product on the market, but is approved only for the treatment of uncomplicated malaria caused by *Plasmodium falciparum*. Qualaquin, however, is much more commonly used off-label for nighttime leg cramps. The FDA continues to get reports of life-threatening hematologic reactions associated with quinine sulfate including thrombocytopenia, hemolytic-uremic syndrome/TTP, hearing loss, and cardiovascular problems. Between 2005 and 2008 there were 38 cases of serious side effects including 2 deaths. The FDA has announced a new Risk Evaluation and Medication Strategy (REMS) for Qualaquin that will include a Medication Guide explaining what the medication is and is not approved for, as well as the potential side effects of the drug. The medication guide specifically states that "Qualaquin should not be used for nighttime leg cramps," and those using it for this indication are at risk of serious side effects (FDA Drug Safety Communication, July 8, 2010). ■