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INSIDE

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LNG IUS vs Medical Therapy for Heavy Menstrual Bleeding

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH

Synopsis: *In a randomized study of women who presented to primary care providers with a complaint of excessive menstrual bleeding, the levonorgestrel intrauterine system was more effective than other medical treatments (tranexamic acid, NSAID, combined oral contraceptives, progestin-only pill, Depo-Provera) in reducing the effect of heavy menstrual bleeding on quality of life.*

Source: Gupta J, et al. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *N Engl J Med* 2013;368:128-137.

Although the levonorgestrel intrauterine system (LNG IUS) has been shown to be an effective treatment for heavy menstrual bleeding (HMB), previous clinical trials included rigorous criteria focused primarily on measuring the severity of bleeding. These evaluations (that involve the collection of menstrual hygiene products) generally are not used in day-to-day assessment of HMB so the applicability of these studies to clinical practice is in question. Alternatively, the ECLIPSE (Effectiveness and Cost-Effectiveness of Levonorgestrel-Containing Intrauterine System in Primary Care against Standard Treatment for Menorrhagia) study was designed as a pragmatic, multicenter, randomized trial to compare the LNG IUS with other medical treatments for the management of menorrhagia. In primary care clinics in the United Kingdom, women 25-50 years old who presented with self-reported excessive menstrual bleeding involving at least three consecutive menstrual cycles were eligible to participate. Exclusions included intention for pregnancy in the next 5 years, current use of hormonal therapy, irregular bleeding (unless an endometrial biopsy was normal), intermenstrual or postcoital bleeding, findings suggestive of large fibroids (e.g., an abdominally palpable 10-12 week size uterus), contraindications to (or a strong preference for) the LNG IUS, or one of the other usual medical treatments. No further workup or imaging studies were mandated by the protocol.

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A total of 571 women with HMB at 67 clinical sites were randomized to treatment with either the LNG IUS or one of several usual medical treatments (tranexamic acid, mefenamic acid, combined oral contraceptives, progestin-only pills, or injectable medroxyprogesterone acetate), according to the preference of each attending physician. Outcomes were assessed over a 2-year period. The primary outcome was the patient-reported score on the Menorrhagia Multi-Attribute Scale (MMAS, ranging from 0 to 100, with lower scores indicating greater severity). The MMAS captures menstrual cycle distress according to several domains (practical difficulties, social life, family life, work and daily routine, psychological well-being, and physical health). Secondary outcomes included general quality-of-life measures, sexual-activity scores, and whether surgical intervention occurred during the follow-up interval.

Although MMAS scores improved from baseline to 6 months in both the LNG IUS and usual-treatment groups and were maintained over the 2-year period, the improvements were significantly greater in the LNG IUS group than in the usual-treatment group (mean between-group difference, 13.4 points; 95% confidence interval, 9.9-16.9). Moreover, the improvements were significantly greater in the LNG IUS group for all MMAS domains and for seven of the eight general quality-of-life domains. At 2 years, more women continued use of the LNG IUS than the usual medical treatment (64% vs 38%, $P < 0.001$). However, there were no significant between-group differences in the rates of surgical intervention, sexual-activity scores, or serious adverse events between groups.

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Questions & Comments
Contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

■ COMMENTARY

HMB is the preferred term for excessive bleeding.[1] 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] Although the 80 mL definition makes sense for research, it offers little guidance for clinicians. Not all women who 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 clinical women-focused diagnosis of HMB is the position endorsed by the National Institute for Clinical Excellence (NICE) in the UK.

The LNG IUS is an approved treatment for heavy menstrual bleeding in many countries, including the United States and throughout Europe. Well-designed randomized, controlled trials have established that the LNG IUS effectively reduces measured menstrual blood loss in women rigorously screened to establish baseline bleeding in excess of 80 mL/cycle.[3] Other recently approved therapies in the United States include the estradiol valerate/dienogest (E2V/DNG) oral contraceptive[4] and tranexamic acid.[5] Although a direct comparison is not available, the published studies show that the proportion of women with a reduction in MBL ≤ 80 mL or at least ≥ 50% reduction from baseline to treatment cycle 7 with E2V/DNG (68.2% and 70%, respectively)[6] appears to be much higher than that achieved with tranexamic acid (43% and 35%, respectively).[5] Although other combined oral contraceptives (COC) reduce the duration and intensity of menstrual bleeding and are widely used to manage abnormal menstruation, little objective data and no labeling indications exist to support this practice. The effectiveness of oral or injectable progestogens also has not been established with rigorous methodology.[7] Nonsteroidal anti-inflammatory drugs are widely available, easy to use, and appropriate for the treatment of menstrual pain. A 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 better than naproxen (12%). In other words, the comparators used in the ECLIPSE study — while generally accepted as usual care — have not been shown to be particularly effective. It's not a surprise that the LNG IUS is the clear winner.

Still, this study adds to the growing literature that the LNG IUS is a first-line treatment for women with HMB, and is applicable to primary care practice. It is great to see this published in a high-profile journal like the *New England Journal of Medicine*, as it should encourage your primary care colleagues to send more women with HMB to your office for IUS insertion! ■

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Laparoscopy vs Laparotomy in Early Uterine Cancer: We Still Don't Know

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: *LAP2 was a randomized, Phase 3 trial to evaluate and compare the modality of surgical staging (laparoscopy vs laparotomy) in endometrial cancer. The primary endpoint was assessing non-inferiority of laparoscopy relative to laparotomy on recurrence-free survival. Although the estimated recurrence rates and 5-year overall survival were nearly identical between the arms, the noninferiority objective (i.e., the statistical proof that the laparoscopic approach is not inferior to laparotomy in terms of overall survival) was not met.*

Source: Walker JL, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 study. *J Clin Oncol* 2012;30:695-700.

LAP2 WAS A PHASE 3 CLINICAL TRIAL TO ASSESS THE NONinferiority of laparoscopy compared with laparotomy for recurrence of uterine cancer after surgical staging. Eligible patients had clinical stage I-IIA disease, were histologically either adenocarcinoma or sarcoma, and were randomly allocated (2 to 1) to laparoscopy (n = 1696) or laparotomy (n = 920). Patients in both arms were to have a standard surgical staging: hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and paraortic lymphadenectomy. The primary endpoint was noninferiority of recurrence-free interval defined as no more than a 40% increase in the risk of recurrence with laparoscopy compared with laparotomy (upper limit hazard ratio: 1.4). Over a median follow-up of 59 months, there were 309 recurrences (210 laparoscopy, 99 laparotomy) and 350 deaths (229 laparoscopy, 121 laparotomy). The estimated 3-year recurrence rates were 11.4% and 10.2% for laparoscopy and laparotomy, respectively (90% lower bound, -1.28; 95% upper bound, 4.0). The estimated hazard ratio for laparoscopy relative to laparotomy was 1.14 (90% lower bound, 0.92; 95% upper bound, 1.46), falling short of the protocol-specified definition of noninferiority. The estimated 5-year overall survival was almost identical in both arms at 89.8%. Multivariate analysis identified age, surgical stage, cell type, myometrial invasion, and lympho-vascular invasion as independent factors influencing recurrence; however, there was no difference by surgical approach among these factors. The authors concluded that the study, which previously had reported the superiority of laparoscopic surgical management on short-term safety and length-of-stay endpoints, did not meet its noninferiority endpoint. However, the quantified risks were small, providing accurate information for decision making for women with uterine cancer.

■ COMMENTARY

The standard operative procedure for patients with primary endometrial cancer is hysterectomy, bilateral salpingoophorectomy, and surgical staging including assessment of the pelvic and paraortic lymph nodes. Traditionally, this has been done via exploratory laparotomy (ceiliotomy), where access to pelvic and abdominal areas is generally assured. However, more than 20 years ago, each of the critical steps in surgical staging for this disease was found to be feasible via minimally invasive surgical (MIS) techniques.[1,2] Over these past 2 decades, the standard approach has increasingly been replaced by laparoscopy and robotic endoscopy.[3] Critics argued that compromised procedures due to patient (e.g., body habi-

tus limiting exposure), surgeon (e.g., loss of tactile feedback and limited capability to assess the high paraortic nodes), and technical (e.g., potential for aerosolization of tumor cells by CO_2) factors would increase the likelihood of recurrence and lower survival in patients undergoing the MIS approach.[4-7] LAP2 initially was launched to assess morbidity and mortality of MIS in endometrial cancer staging, but was amended in 2001 to also address the noninferiority of MIS relative to laparotomy. The trial was designed with a 2:1 randomization and established confidence limits for noninferiority based on an anticipated recurrence rate in the laparotomy arm of 15%. The statistics are important in understanding the "accurate" interpretation of the study. As strictly demonstrated, the lower limit of the confidence interval assessing inferiority crosses 1.0. This would, under normal circumstances, reject the null hypothesis of inferiority for MIS, concluding that there was not a substantial increase in recurrence for the MIS approach. However, because the observed recurrence rate was substantially lower than anticipated, the upper limit of this same confidence interval crosses 1.4, which under the initial assumptions would have rejected the alternate hypothesis (that is, MIS is noninferior to laparotomy). So in an argument, both conclusions could be supported, and strictly speaking, the study's conclusions are ambiguous. Fortunately, the actual differences in recurrence rate, site of recurrence, 3-year recurrence risk, 5-year overall survival, and just about every other metric are nominal and "practically" identical. This colossal effort on behalf of the Gynecologic Oncology Group is to be commended as the history of completing this trial with all of the excitement for MIS at the time was a challenge. Currently, the MIS approach is preferred particularly in patients who have very high body mass index, as the operative and postoperative morbidity can be substantially ameliorated. However, when the surgical output is compromised by the approach, it cannot be justified. ■

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Clinical Briefs

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

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

Synopsis: *Three recent studies have shown that subcuticular closure with sutures, while adding more cesarean operative time, results in fewer wound disruptions than using staples; that discharge on post-op day 1 for planned cesarean section results in no greater morbidity and patient satisfaction than day 2 discharge; and that 17 alpha-hydroxyprogesterone caproate does not seem to decrease the rate of preterm birth in those with short cervices and no previous preterm deliveries.*

During the past few months, there has been a plethora of articles published with important clinical implications, and I have found it difficult to pick just one to review. Therefore, in an effort to pack in as many important nuggets as possible, I have resorted this month to a method I used a few years ago — "quick hits." The first two studies involve an operative technique[1] and length of stay[2] for patients having cesarean sections, and the third study involves the use of 17 alpha-hydroxyprogesterone for the prevention of preterm birth.[3]

Study 1: Staples vs Suture Closure for Cesarean Section

Figueroa et al compared outcomes in 390 patients randomized to either staples (n = 190) or subcutical sutures (n = 200) for skin closure at the time of cesarean section.[1] Outcomes were evaluated at the time of discharge (3-4 days post-op) and again at the postpartum visit (4-6 weeks post-surgery).

The staples group had a 7.1% incidence of wound disruption and/or infection at time of discharge vs 0.5% for the absorbable sutures, and 14.5% vs 4.9% at 4-6 weeks post-op, respectively. Average operative time was increased by 10 minutes for suture closure (58 minutes vs 48 minutes) but there were no differences in patient satisfaction, pain perception, or "cosmesis score."

■ **COMMENTARY**

Quite simply, using staples cuts operative time by 10 minutes, but comes with some costs. There was a 14-fold increase in wound morbidity at the time of discharge and a 3-fold increase at 4 to 6 weeks postoperatively in the staple group. All other factors were essentially the same, including the cosmesis score, but I don't understand how an infected or disrupted scar can be as pretty as an unaffected one.

Study 2: Hospital Stays After Planned Cesarean Sections

A group from Malaya addressed the emerging practice of early discharge after planned cesarean.[2] These investigators compared outcomes after randomizing women to discharge on postoperative day 1 (n = 142) or postoperative day 2 (n = 148). The authors were interested in a variety of outcome variables but focused primarily on patient satisfaction and the desire/ability to breastfeed exclusively through 6 weeks postpartum.

The results showed that both groups had a high satisfaction rate (85%) and identical rates of continued breastfeeding (44%). In addition, there were no differences in maternal morbidities.

■ **COMMENTARY**

When most of us were born, our mothers generally spent at least 1 week in the hospital following delivery. However, over the last 3 decades, post-op hospital stays have decreased appreciably. For example, in 1975 in England, 68% of patients who had cesarean sections stayed in the hospital for 3 days or more. This decreased to a point where less than 10% of those having a cesarean section in 2011 stayed in the hospital for 3 or more days.[4] Similar trends have occurred in the United States, where cost is a motive for early discharge. However, there also is another benefit of shorter hospitalizations. One recent study[5] shows that during an average hospital stay for medical patients (not even those having surgery), there is a 5.5% risk of adverse drug reactions and 17.6% chance of being infected by hospital-borne pathogens.[6] For every extra hospital day, the rates of the above problems rise by 0.5% and 1.6%, respectively.

To be fair, the Malaysian population may not represent a typical U.S. sampling, since the Malaysian mothers tended to go directly from the hospital to their parents' homes, where there was family help available for the post-op patients. Nevertheless, this study did not show that outcomes and patient acceptability suffered from discharge only 1 day after cesarean section.

Study 3: 17 Alpha-hydroxyprogesterone Caproate and Preterm Birth in Patients with Short Cervices

In 2003, a sentinel study emerged suggesting that weekly intramuscular injections of 17 alpha-hydroxyprogesterone caproate (17P) significantly decreased the rate of early delivery in patients with a history of preterm birth (PTB).[7] Later, some studies surfaced showing a possible benefit of vaginal progesterone in those patients with a short cervix, with and without a history of PTB.[8,9] These last studies highlighted the potential of universal screening with ultrasound for cervical length (CL). Based on these studies, there is debate as to the inferiority or superiority of vaginal vs intramuscular administration.

To address this question, Grobman et al conducted a multicenter (NICHD network) randomized trial in which 327 nulliparous patients with CLs of < 3 cm were given 17P and another 320 patients with short CLs were randomized to placebo.[3] The risk of PTB at less than 37 weeks was 25.1% vs 24.2%, respectively, and no significant differences were noted in adverse composite neonatal outcome (7% vs 9.1%) — thus showing no clear benefit of 17P in this group of patients.

■ **COMMENTARY**

It is still unclear whether the dissimilar results in previous studies were due to differences in the chemical makeup of the compounds or the route of delivery. This study does not support using 17P to treat patients without a history of PTB but with short cervices. Interestingly, some have assumed that 17P is a similar compound to, if not an identical twin of, vaginal progesterone preparations. However, it is not — 17P is less like a twin and more like a distant cousin of natural progesterone. Although controversial, the Hassan study[9] has galvanized a movement toward universal screening for PTB with transvaginal sonography. However, based on Grobman's data,[3] this recommendation would never gain clinical traction if 17P was the only option for PTB prevention since 17P did not show benefit. Time and time again, one study does not tell the whole story. Grobman's study[3] and the recent vaginal progesterone study[9] in singletons with short cervices will need to be repeated before expensive and ambitious diagnostic and therapeutic methods are universally applied to all pregnant patients. ■

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Special Feature

Postpartum Tubal Sterilization

By Rebecca H. Allen, MD, MPH

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

Synopsis: *Large variations in postpartum tubal sterilization rates exist among states and hospitals that are not explained by insurance status, mode of delivery, citizenship, or demographics. This implies that barriers to postpartum tubal sterilization are preventing access to this desired method of contraception.*

Source: Potter JE, et al. Hospital variation in postpartum tubal sterilization rates in California and Texas. *Obstet Gynecol* 2013;121:152-158.

Tubal sterilization is a highly effective, permanent, and safe method of contraception. Tubal sterilization is the second most common method of contraception used by women in the United States and the most common among women over 30 years of age.[1] Approximately half of all tubal sterilizations are performed in the immediate postpartum period, following nearly 10% of all births in the United States.[2] The procedure is convenient for the mother as she is already in the hospital for the delivery. Postpartum tubal sterilization can be performed during cesarean section or immediately after vaginal delivery through a small infraumblical incision up to 2 days postpartum.[3] The advantages of doing the procedure immediately postpartum are that existing epidural anesthesia can potentially be used and the woman does not have to restrict food and drink in preparation for the procedure another day.[4] Additionally, women do not have to prepare for an interval surgery when often the demands of caring for a newborn and/or young family can be overwhelming. Not surprisingly, postpartum sterilizations are performed more frequently in women undergoing cesarean delivery compared to vaginal delivery. Of note, sterilizations funded by Medicaid require that the woman be at least 21 years old and wait at least 30 days between signing the Medicaid consent form and having the procedure.[3] The consent form remains valid for 180 days. Exceptions can be made for emergency abdominal surgery or preterm deliveries. If the sterilization is not performed postpartum and the woman still desires the procedure, it can be done at least 6 weeks after delivery either through a laparoscopic or hysteroscopic approach. This delay in surgery imposes a number of inconveniences for the patient including using a reliable gap contraceptive, arranging for additional pre-and post-operative visits, and preparing for the day of surgery when the sterilization can be performed.

Unfortunately, women often face barriers to obtaining desired postpartum tubal sterilizations.[5] The study by Potter et al examined the variation in postpartum sterilization rates among hospitals in California and Texas. Both states have high unintended pregnancy rates (56% and 53%, respectively) and both have the largest number of Medicaid-covered births in the United States. The investigators were able to obtain data on virtually all deliveries and sterilizations in the two states in 2009. Information on private and Medicaid insurance status was also available. The total postpartum tubal ligation rate (proportion of births followed by a postpartum tubal ligation) was 6.7 in California and 10.2 in Texas. In California, the rates after cesarean section and vaginal delivery were 14.7 and 2.8, respectively. The corresponding rates in Texas were 19.5 and 4.9. The differences between the two states were similar among women with private insurance and Medicaid. The cesarean delivery rate was 36.6% in Texas and 33% in California but did not account for the differences. The investigators found that within each state there were large variations in the postpartum sterilization rate among

hospitals, even accounting for Catholic hospitals where sterilizations are not performed. The authors could not determine exactly why the sterilization rates were so different across hospitals. For cesarean deliveries, it may be issues with obtaining Medicaid consents in a timely fashion. For vaginal deliveries, there may be barriers involving Medicaid consents, availability of staff and operating rooms, and the priority that postpartum tubal ligations receive. In addition, there may be variation in physician counseling regarding sterilization and the accessibility of equally effective alternative options such as intrauterine devices and the contraceptive implant.

Indeed, many local studies have examined such barriers to postpartum sterilization. A study of 712 women at one hospital in Chicago showed that 46% of women requesting postpartum sterilization did not obtain the procedure. The investigators found that lack of valid Medicaid sterilization consent forms, a medical condition precluding the procedure, and lack of availability of an operating room were the most common reasons the procedures were not performed.[6] The same investigators also found that young age (21-25 years), African American race, request for sterilization in the second trimester, and vaginal delivery rather than cesarean section were risk factors for not obtaining a desired postpartum tubal sterilization.[7] The requirement for Medicaid consent at least 30 days prior to the procedure was developed to provide a window for women to think about their decision and prevent coerced sterilizations that had occurred in the past among disadvantaged populations. Nevertheless, this requirement often becomes a barrier for women who desire the procedure.[6,8-10] In addition, because Medicaid coverage can end shortly after birth for some women, lack of signed Medicaid consents prevents women from obtaining another method of contraception postpartum.[5]

Another study from San Antonio, Texas, of 429 women found completion of desired postpartum sterilizations to be 69%, and sterilization was more likely among women who were documented U.S. residents, married, of lower parity, had received prenatal care, and had private health insurance.[8] In this study, completion of postpartum sterilization at the time of cesarean section was no different between documented and undocumented U.S. residents; however, after vaginal delivery, significantly more documented U.S. residents obtained the procedure. This is because undocumented U.S. residents in Texas on emergency Medicaid must pay out of pocket for sterilization after vaginal delivery but not at the time of cesarean delivery. Their follow-up study reported that of the women who did not receive the requested sterilization, 46.7% became pregnant in the year after delivery.[11]

Similarly, we examined the barriers to postpartum sterilization in our own institution.[9] We performed a retrospective study from January 2007 to June 2007 among patients in the resident (often Medicaid) practice. During the study period, 626 women delivered. Of these subjects, 87 (14%) desired postpartum sterilization. Of these 87 subjects, 45 (51.7%) underwent sterilization as planned. Of the 42 women who did not receive the procedure, 22 (52.4%) changed their mind, eight (19%) did not have the required Medicaid consent form signed, four (9.5%) had prior abdominal surgery that caused the provider to cancel the procedure due to anticipated difficulty, two (4.8%) had significant anemia causing the elective procedure to be cancelled, two (4.8%) were considered too obese to be able to technically perform the procedure, two (4.8%) had chorioamnionitis, one (2.4%) had an intrauterine fetal demise at term, and one (2.4%) had no documentation. We found in multivariable analysis that cesarean delivery and older age were predictive of completion of postpartum sterilization while obesity was a risk factor for incompletion.

So what can we do to improve access to postpartum sterilization for those women who desire it? As a result of our study, we are trying to improve our antenatal contraceptive counseling and make sure that women who desire postpartum sterilization have a backup plan in case the sterilization does not happen. We also counsel obese women or those with many prior abdominal surgeries up front that they may not receive the sterilization postpartum depending on the attending physician's assessment. The American College of Obstetricians and Gynecologists (ACOG) also recommends signing Medicaid consent forms in a timely fashion during prenatal care and ensuring that copies of the consent are transferred to the delivery unit.[5] We have found that scanning consent forms into the electronic medical record has significantly helped in this regard. In addition, ACOG suggests working with hospital delivery units and obstetric anesthesia personnel to make the procedure a priority. Finally, offering immediate postpartum IUD or contraceptive implant insertion can provide an equally effective alternative if the desired sterilization is not completed. ■

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CME Objectives

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. **Compared with usual medical therapies, treatment of heavy menstrual bleeding with the LNG IUS in a primary care setting in the UK was found to result in a significant:**
   a. reduction in all domains of the Menorrhagia Multi-Attribute Scale.
   b. improvement in sexual function.
   c. improvement in all domains of general quality-of-life scales.
   d. reduction in serious adverse events.

2. **Which of the following factors is responsible for the ambiguous noninferiority conclusion of the study by Walker et al?**
   a. The sample size
   b. The inclusion of sarcoma
   c. The inaccurate clinical staging procedure
   d. The lower observed recurrence rate
   e. The rate of unexpected pre-progression deaths

3. **Which of the following is *not* a result of the wound closure study?**
   a. Patient satisfaction was essentially the same with suture vs staples.
   b. The was a 14-fold increase in risk of wound infection/disruption at the time of discharge in the suture group.
   c. There was no difference in the cosmesis score between groups.
   d. There was a higher risk of infection/disruption in the staples group at 4-6 weeks post op.

4. **In the Malaysian study, day 1 discharge patients had similar satisfaction rates but greater overall morbidity.**
   a. True
   b. False

5. **Which of the following does not fit the results of the studies regarding 17 alpha-hydroxyprogesterone caproate (17P)?**
   a. 17P has been shown to reduce preterm birth (PTB) in patients with a history of PTB.
   b. 17P has been shown to reduce PTB in patients with short cervices.
   c. Vaginal progesterone has not been tested in nulliparous patients with short cervices.
   d. What should work for 17P should also work for vaginal progesterone.

6. **In the study by Potter et al, variations in postpartum sterilization rates were due to:**
   a. differences in cesarean delivery rates.
   b. differences in the proportion of births funded by Medicaid compared to private insurance.
   c. differences in the number of Catholic hospitals in each state.
   d. unexplained reasons.

In Future Issues:

Gastric Bypass Surgery and Reproductive Function

Thyroid Disease in Pregnancy

PHARMACOLOGY WATCH

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Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■

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