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.

Postplacental Insertion of Levonorgestrel-releasing IUS

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, Editor

Synopsis: *Immediate postplacental insertion of a levonorgestrel intrauterine system results in a significantly higher rate of expulsion and does not increase the number of women using an IUD at 6 months of follow-up.*

Source: Chen BA, et al. Postplacental or delayed insertion of the levonorgestrel intrauterine device after vaginal delivery: A randomized controlled trial. *Obstet Gynecol* 2010;116:1079-1087.

The authors enrolled women desiring postpartum use of a levonorgestrel-releasing intrauterine system in a randomized trial to determine whether use of the device would be higher when insertion occurred immediately postpartum rather than delaying placement to the standard postpartum visit. Subjects were randomly assigned to postplacental or delayed intrauterine device (IUD) insertion when admitted in labor. Post-enrollment exclusion events included intrapartum infection, hemorrhage, and cesarean delivery. Eligible subjects randomized to immediate insertion received the device within 10 minutes after delivery of the placenta, while those in the delayed group had the IUD insertion performed at the scheduled postpartum visit 6-8 weeks later. All of the women were asked to follow up in person at 6-8 weeks and at 6 months, and were contacted by telephone at 3 months. Expelled IUDs were replaced per patient preference.

IUD placement occurred in 98% (50/51) of subjects randomized to postplacental insertion and 90% (46/51) of those in the delayed groups ($P = 0.2$). Expulsion within 6 months occurred in 24% (12/50) of those in the immediate group, but in only 4.4% ($P = 0.008$) of those women receiving the device at the postpartum visit. There was no difference in overall usage of an IUD at 6 months (84% immediate, 77% delayed; $P = 0.32$). However, for ineligible patients, only 11 of 41 (26.8%) were using IUDs at 6 months and two (4.9%) had become pregnant.

VOLUME 27 • NUMBER 9 • JANUARY 2011 • PAGES 65-72

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

■ COMMENTARY

The best way to prevent unintended pregnancy is effective contraception. Highly effective long-acting reversible contraception (LARC) methods provide the best protection because they are free from user failure. LARC methods include both IUDs (LNG and copper) and contraceptive implants. After decades of misunderstanding, the IUD has returned to a position of prominence as a first-line method appropriate for most women. The link between IUDs and pelvic inflammatory disease and infertility has been debunked by solid evidence demonstrating that common infections like chlamydia, and not the IUD, cause tubal disease.[1] Use of IUDs has also increased due to the added health benefits of reduced menstrual bleeding seen with the levonorgestrel system. Compared to the typical use failure of almost 8% seen with combined oral contraceptives, the failure rate with the IUD is < 1%.

Postpartum women are at high risk for unintended pregnancy during the first year, and this is particularly true among high-risk women such as adolescents.[2] This occurs even with almost universal counseling regarding contraception prior to discharge from the hospital. Since women who do not breastfeed may ovulate within 4 weeks after delivery, contraception should be initiated within 3 weeks in non-breastfeeding women.[3] Given that the postpartum visit is often delayed beyond this time, Chen and colleagues hypothesized that immediate postplacental insertion would reduce the risk of pregnancy and provide long-lasting contraception.

To be an effective method of contraception, the IUD must move beyond its position as a theoretical concept and occupy a more effective position within the uterus. To address this, the authors of this study assessed how many subjects were using the IUD at the 6-month follow-up. Although there was a trend toward greater IUD use at 6 months in the group receiving the device immediately postpartum, this was not statistically significant. Moreover, the incidence of device expulsion was almost 6-fold higher in the immediate group. Therefore, the high continuation rate at 6 months in the immediate group was influenced in part by a policy of free replacement of the device upon request after expulsion. Whether a liberal replacement policy like this is possible outside the research setting is unknown. So for simple matters of economy, immediate postplacental insertion of a levonorgestrel IUS may not work out. For my money, I would rather reduce the potential barriers to obtaining the device at the postpartum or interval visit.

On the other hand, women in the delayed group received confirmation of the postpartum IUD appointment by research staff prior to hospital discharge and a reminder call prior to the appointment. These steps exceed the standard of care at many institutions (but are still less expensive than an IUS or an unintended pregnancy). Moreover, research populations may differ from the general population in terms of compliance. The investigators addressed this point by following women who consented to participate, but were found to be ineligible. These individuals were not provided with special instructions or with a free IUD. Not surprisingly, only 27% received an IUD by 6 months and there were two repeat pregnancies among 41 participants. This might reflect the extreme of the other end, but is also one view of the real world.

Taking all this together, it is important to look at how likely your obstetric patient is to return for a postpartum check, and to consider the timing of this visit. Although expulsion is higher with immediate postplacental insertion, it is otherwise safe and well-tolerated and might be worth it for some patients. However, since most women are compliment with a postpartum visit, routine insertion should be delayed. While the package insert states that the IUD should not be placed until full involution, this term is poorly defined and the risk of pregnancy is present after 4 weeks in nonbreastfeeding women. Drs. Dan Mishell and Leon Speroff wrote an excellent review in 2008, advocating moving the postpartum visit to 4 weeks and including IUD insertion at this time.[3]

Consider offering immediate postplacental insertion to women at high risk for loss to follow-up, but recognize that it is far more cost-efficient to insert the device at a postpartum visit for everyone else. Liberal use of post-insertion verification of IUD position with a vaginal ultrasound should help provide reassurance if insertion at 4 weeks makes you nervous. ■

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

EXECUTIVE EDITOR: Coles McKagen
SENIOR MANAGING EDITOR: Paula Cousins

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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

Back Issues: $42.

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

AHC Media LLC

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.

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

References

1. Hubacher D, et al. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *N Engl J Med* 2001;345:561-567.
2. Kershaw TS, et al. Short and long-term impact of adolescent pregnancy on postpartum contraceptive use: Implications for prevention of repeat pregnancy. *J Adolesc Health* 2003;33:359-368.
3. Speroff L, Mishell DR, Jr. The postpartum visit: It's time for a change in order to optimally initiate contraception. *Contraception* 2008;78:90-98.

Intrapartum Tests for Group B Streptococcus

ABSTRACT & COMMENTARY

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado Health Sciences Center, Denver

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

Synopsis: *Two rapid screening tests for group B streptococcus are reasonably sensitive, but the most predictive of the two, a polymerase chain reaction, may still not have a short enough turnaround time to be of value in the contemporary management of intrapartum patients, which, according to updated CDC guidelines described below, requires at least 4 hours of antibiotics before delivery.*

Source: Daniels JP, et al. Intrapartum tests for group B streptococcus: Accuracy and acceptability of screening. *BJOG* 2010 Oct 13; Epub ahead of print; doi:10.1111/j.1471-0528.2010.02725.

The rate of sepsis with group B streptococcus (GBS) in neonates of colonized mothers is now less than 1%. However, the devastating effects in affected babies are well worth preventing with a rational regimen of prophylaxis, and the strategy published by the Centers for Disease Control and Prevention (CDC) in 2002[1] seems to have decreased neonatal GBS sepsis by 50%-80%.[2] This protocol calls for screening everyone at 35-37 weeks and treating those with positive cultures with intrapartum antibiotic prophylaxis (IAP), along with those with some other risk factors described below.

Recently, rapid assays have emerged that have the potential to guide the practitioner in choosing who to treat with IAP, but some of the kinks need to be worked out. A paper published in the *British Journal of Obstetrics and Gynecology* may help put into proper perspective the benefits of two rapid tests for GBS in intrapartum patients. The two assays that were evaluated were a polymerase chain reaction (PCR) and an optical immunoassay (OIA). The authors were interested in their accuracy in predicting GBS, as well as their clinical efficacy based on how quickly the answers were available.

Over a 2-year period the authors reviewed intrapartum data on patients who were enrolled in the study early in pregnancy. Once these patients were in labor or being induced they had vaginal and rectal samples taken with two sets of three swabs fastened together during sampling, but separated later so that each of the three swabs would be tested for GBS via PCR, OIA, or, the ultimate answer, enriched culture methodology. Neonates were tested through swabbing of their ear canals. Clinicians were blind to the results and generally used a uniform protocol for IAP, based on risk factors for GBS.

The results were illuminating. In the end, the authors had useful data on 1394 patients, 22% of whom had one or more risk factors. Positive GBS cultures were found in 21% of all mothers, 29% in those with risk factors, and 19% in those without. Neonatal colonization occurred overall in 8.5%, in 36% of colonized women, and in 1% of culture-negative women. Three babies had active infection and all survived. Despite the recommended protocol, only 71% of those with a definite indication for IAP and 50% with any risk factor for GBS received antibiotics.

OIA was the quicker method, with a mean sampling-to-answer time of 38.8 minutes vs 80.8 minutes for PCR. However, the accuracy for predicting a positive GBS culture was more sensitive with the PCR (84% vs 72%) and more specific (87% vs 57%). Rectal PCR performed better than vaginal PCR, with a sensitivity of 71% vs 58%. A positive vaginal or rectal PCR gave a 65% probability for a positive GBS culture, and a negative test had a probability of 5%. There was a higher maternal GBS prevalence for those with risk factors (29% vs 19%), but those with risk factors had heavier growth in the culture. After adjusting for the effect of antibiotics, the odds of neonatal colonization were far lower (odds ratio = 0.22) when IAP was given > 4 hours, compared with a non-significant effect when antibiotics were given < 4 hours prior to delivery.

■ COMMENTARY

The authors found that, although PCR was a more accurate predictor of GBS colonization, a lag of 80 minutes may be too long in some cases, since there was a negligible effect of IAP when given less than 4 hours before delivery. The other findings provide useful information when used in combination with the conclusions of other studies.

So, where do we stand now on GBS screening? In Great Britain, uniform screening at 35-37 weeks is not the standard, and the clinicians in the study used risk factors alone for consideration of IAP. These were:

1. Patients with a previous child with GBS infection
2. Those with suspected chorioamnionitis
3. Those with preterm premature rupture of the membranes
4. Those with GBS bacteruria
5. Those with prolonged rupture of membranes in term pregnancies (> 18 hours)
6. Those mothers with a temperature > 100.4º F.

The CDC has come out this month with revamped recommendations that again involve screening all pregnant women at 35-37 weeks with vaginal/rectal cultures.[3] An exception would be a woman who had a positive urine culture (and who would automatically get IAP). Although screen-positive patients having C-sections with intact membranes would not need IAP, virtually all other screen-positive patients would. The new guidelines indicate that patients with a previous history of neonatal sepsis would automatically be offered IAP, and would not need to be screened. The new guidelines also suggest IAP for patients with the other risk factors listed above. Patients admitted with preterm labor should be cultured and treated, but the antibiotics could be stopped if the cultures return as negative.

The antibiotic regimen would include penicillin G, 5 million units IV followed by 2.5 million units IV q 4h. Another option would be ampicillin 2 g IV, followed by 1 g IV q 4h. In patients with penicillin allergy, cefazolin (if there was a low risk for anaphylaxis) and clindamycin or erythromycin (if there is a high risk for anaphylaxis) could be substituted. If antibiotic sensitivities are available, vancomycin can be used if the bacteria are resistant to clindamycin or erythromycin.

One would hope that rapid, cheap tests for GBS will become available soon that will allow better selection of truly vulnerable patients/neonates. This would allow us to avoid the creation of super-resistant strains of bacteria from shotgun administration of antibiotics to those who really do not need them. ■

References

1. Schrag S, et al. Prevention of perinatal group B streptococcal disease. *MMWR Recomm Rep* 2002;51(RR-11):1-22.
2. Van Dyke MK, et al. Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med* 2009;360:2626-2636.
3. Prevention of Perinatal Group B Streptococcal Disease: Revised Guidelines for CDC, 2010. *MMWR Recomm Rep* 2010;59(RR-10):1-36.

Tranexamic Acid Reduces Menstrual Blood Loss

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, MPH, Editor

Synopsis: *Oral tranexamic acid is well-tolerated and significantly reduces menstrual blood loss and improves health-related quality of life in women with heavy menstrual bleeding.*

Source: Lukes AS, et al. Tranexamic acid treatment for heavy menstrual bleeding: A randomized controlled trial. *Obstet Gynecol* 2010;116:865-875.

The authors randomized women with objectively validated heavy menstrual bleeding (mean menstrual blood loss [MBL] of 80 mL or more per cycle, confirmed using the alkaline hematin methodology during two pretreatment cycles) to treatment with oral tranexamic acid 3.9 g/d or placebo for up to 5 days per cycle for 6 menstrual cycles. The primary outcome was a 3-component efficacy endpoint that specified that treatment with tranexamic acid needed to result in a reduction in MBL that was: 1) significantly greater than placebo, 2) greater than 50 mL, and 3) greater than an amount established to be meaningful to women. Health-related quality of life was measured using the Menorrhagia Impact Questionnaire (MIQ), a validated patient reported outcome instrument.

Compared to those women that received placebo (n = 72), subjects randomized to tranexamic acid (n = 115) experienced a significantly greater reduction in MBL (-69.6 mL [40.4%] vs -12.6 mL [8.2%]; $P < 0.001$), and all women treated with tranexamic acid met the 3-component efficacy endpoint with a reduction of at last 50 mL, which surpassed the threshold (-36 mL) considered meaningful to women. Furthermore, women treated with tranexamic acid experienced significant improvements in quality of life with fewer limitations in social, leisure, and physical activities, work inside and outside the home, and self-perceived menstrual blood loss not experienced by women that received placebo ($P < 0.01$). The treatment was well-tolerated and the incidence and severity of adverse events was similar to placebo.

■ COMMENTARY

Although I reviewed oral tranexamic acid as a treatment for heavy menstrual bleeding (HMB) in the Special Feature section of the September 2010 issue of *OB/GYN Clinical Alert*, I wanted to draw your attention back to this drug now that the pivotal U.S. trial has been published. A rigorous placebo-controlled double-blind study was performed, and

the criterion for successful treatment was a three-component outcome. The first required that treatment with the drug should result in a significantly greater reduction in MBL than placebo. Since statistical significance is primarily a question of sample size, the other two criteria actually attempt to bridge the gap between statistical significance and clinical relevance. The study set a 50 mL reduction as the minimum threshold for a clinically important drop in MBL. In addition, successful treatment required that subjects experience a reduction in MBL blood loss that women considered meaningful. Another study was performed (but not published) to determine that the minimum reduction in blood loss that women considered meaningful was 36 mL; therefore, the requirement of a 50 mL minimum reduction effectively trumped this criterion. More simply put, this study demonstrated that tranexamic acid was effective in reducing MBL by 50 mL.

So how does this stack up with other therapies? First, a reduction in MBL occurred during the first treatment cycle, and there was no significant difference in the magnitude of the reduction from the first to the sixth treated cycle. Therefore, women taking tranexamic acid will have a pretty good idea of the ultimate benefit after the first treatment cycle. Reduction in MBL with tranexamic acid was about the same regardless of the presence of leiomyomas or heavier baseline MBL. This rapid and consistent effect will make counseling very easy. Women simply need to initiate therapy at the onset of bleeding, and take two 650 mg tablets three times each day as long as the bleeding remains heavy. Many of our patients use a similar approach with NSAIDs to manage menstrual symptoms. Compliance with therapy is better when you are actively treating a symptom like bleeding (or pain), as the severity of symptoms motivates behavior.

As I mentioned in the September Special Feature, the research definition of excessive MBL is > 80 mL as women become anemic with losses that exceed this level. Therefore, it is important to note that only 43% of subjects that received tranexamic acid (and 17% using placebo) had a reduction in MBL below this threshold. Although women will appreciate any reduction in blood loss, clinicians need to be aware of the limitations of this new treatment. Comparator studies have shown that the absolute reduction of MBL with tranexamic acid is slightly greater than that achieved with NSAIDs, but less than that achieved with hormonal treatments.[1]

Although there were no serious adverse events with treatment, the product carries labeling that it should not be used in women at risk for thrombosis. Women with idiopathic HMB without this contraindication who would prefer not to use a hormonal therapy or NSAID will benefit from tranexamic acid. Those women with modestly heavy bleeding who prefer to take treatment as needed rather than every day will find tranexamic acid particularly appealing. Women seeking pregnancy will appreciate the fact that tranexamic acid is category B.

Beyond this, I think that women and clinicians that wish to achieve a greater reduction in MBL will likely be disappointed with tranexamic acid. Fortunately, we have other good medical options including the LNG IUS.[2] The September issue of the *Green* journal published results of the US HMB study with the LNG IUS (please note that I am a coauthor on that publication and am a consultant for Bayer Healthcare). The LNG-IUS reduced measured MBL by an average of -128.8 mL (compared to only -17.8 mL for the active comparator, oral medroxyprogesterone acetate). The reduction of bleeding with the IUS was more than 70%. The proportion of women with successful treatment (MBL < 80 mL and a 50% reduction) was significantly higher for the levonorgestrel-releasing intrauterine system (84.8%) compared to MPA (22.2%; $P < 0.001$). The new oral contraceptive with estradiol valerate and dienogest also looks interesting. This is a hot topic and we will see more in the coming months. ■

References

1. 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.
2. Kaunitz AM, et al. Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding: A randomized controlled trial. *Obstet Gynecol* 2010;116:625-632.

Special Feature

Primary Ovarian Surgical Cytoreduction: When? How Much? Why?

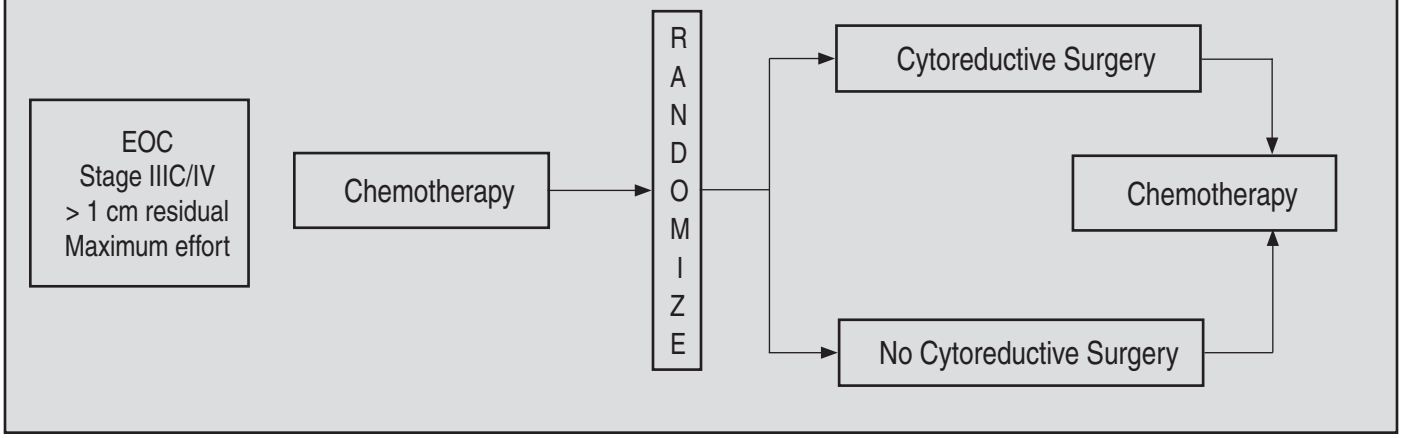
By Robert L. Coleman, MD

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

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

Nearly every reference source discussing the primary management of advanced ovarian cancer will highlight the role of surgical cytoreduction as an important first step in the care of this disease. Citing control of symptoms, improved chemotherapy exposure, reduction of potentially chemoresistant tumor cell volumes, and favorable immunological effects, advocates of the approach

Figure 1. Schema demonstrating the procedure for interval surgery.



further support their position by highlighting improvement in nearly every outcome parameter that has been addressed when primary surgery (PS) is performed and performed well. These include higher rates of tumor response, more frequent negative second look surgery, and longer progression-free (PFS) and overall survival (OS). They will further highlight that alternative approaches have not yielded better outcomes, and in many reports, have reported worse outcomes. These approaches include a secondary attempt at cytoreduction following an initial maximal attempt, "interval cytoreduction" (IC), and a pre-emptive approach where chemotherapy following biopsy to establish the diagnosis is administered ahead of a maximal surgical, "neoadjuvant chemotherapy" (NACT). Since ovarian cancer is a chemosensitive disease, post-chemotherapy disease volumes are likely to be significantly reduced providing both a better opportunity to achieve a more complete surgical resection of remaining disease and do so with reduced morbidity. Advocates of the neoadjuvant approach further highlight that induction chemotherapy helps identify those women unlikely to benefit from surgical exploration, as it is unlikely that a woman will gain any increase in her clinical situation with disease not responsive to chemotherapy. Since the single most important independent predictor of overall survival in chemo-naïve patients is the volume of postoperative residual disease, advocates of each approach bring the increased likelihood of complete surgical resection, that is, removal of all visible tumor, to the debate.

Globally, there is wide variation in the proportion of patients considered for each of these approaches, but the latter, NACT, has been more uniformly practiced in patients with poor performance status, or in those with extensive unresectable intra-abdominal or extra-abdominal parenchymal metastatic disease. As a result, comparative data between series of patients categorized by surgical approach are heavily biased and difficult, if not impossible, to interpret. Several meta-analyses have been done in this respect, reaching alternative conclusions. However, in no case has the NACT approach been found to be superior to the primary surgical approach. Nevertheless, in the absence of a randomized phase III trial comparing PS to NACT, the debate was largely framed by inferences from predominately retrospective and a few prospective non-randomized clinical trials, with no clear consensus as to the appropriateness of the approach.

Interval Cytoreduction

Before discussing PS and NACT and the study by Vergote and colleagues that addressed this question,[1] a review of the intermediate approach, IC, is warranted. In this approach, patients in whom a maximal attempt at initial surgery was performed and was unsuccessful in removing disease bulk to less than 1 cm are treated with chemotherapy for (usually) 3 cycles and then returned for a second surgery to remove any remaining disease. Following the second surgery, patients are usually returned to chemotherapy for 3-6 additional cycles *(see Figure 1, above)*. There have been two randomized phase III studies that have been reported addressing this approach. In the first, 425 women with suboptimally cytoreduced (> 1 cm tumor residuum) stage IIIC and IV disease were treated with cyclophosphamide and cisplatin for 3 cycles and, if not progressive (319; 75%), randomized to a second surgical attempt vs continued therapy. In the second, 550 women were registered and treated with paclitaxel and cisplatin followed by randomization (425; 77%) to a secondary surgery or continued chemotherapy. Figure 2 *(page 71)* highlights the features and outcomes of these two trials. Since the GOG trial enrolled a substantially higher proportion of patients who underwent a maximal initial cytoreductive effort, and in light of its use of contemporary chemotherapy, the GOG trial is considered by most as the definitive trial of the IC approach. As a result, it is widely thought that an unsuccessful maximal attempt at primary surgery by a qualified gynecologic oncologist is reflective of a disease biology that is also characteristic of poor chemosensitivity. As a result, this approach is rarely practiced in the United States.

Figure 2. Outcomes of two phase III trials of interval surgery

Parameter	EORTC/GCCC Cisplatin/CTX	GOG 152 Paclitaxel/Cisplatin
N (randomized)	425 (319; 75%)	550 (425; 77%)
Stage IV	Yes	No
Progressed before randomization	9%	5%
Ovaries remaining after first surgery	32%	Rare
SLL allowed	Yes	No
Consolidation allowed	Yes (36% vs 51%)	No
% CR at interval surgery	17%	?
PFI (months)		
Interval surgery	18	10.5
No surgery	13	10.8
	P = 0.013	RR: 1.017; *P* = NS
Survival (months)		
Interval surgery	26	32
No surgery	20	33
	P = 0.012	*P* = NS

Comparing PS and NACT

Recently, the first randomized phase III comparing the other two approaches, PS and NACT, was published. This highly anticipated clinical trial's results have been in the public domain and under publication consideration for approximately 2 years, which highlights the peer-reviewed scrutiny the manuscript received before its publication in the September 2010 issue of the *New England Journal of Medicine*. The study was a collaborative effort of two independently funded trial organizations, the EORTC-Gynaecological Cancer Group (EORTC-GCG) and National Cancer Institute of Canada (NCIC) Clinical Trials Group. Eligible patients were those with biopsy-proven stage IIIC and IV disease or those with a fine needle aspirate and additional evidence of metastatic disease including a biomarker profile (CA125:CEA > 25) favoring mullerian origin. The study design was 1:1 randomization of eligible patients to either primary surgical cytoreduction or neoadjuvant chemotherapy, which was defined as 3 cycles of paclitaxel and carboplatin at standard doses and infusion schedule. Planned adjuvant therapy in the PS arm was at least 6 cycles of paclitaxel and carboplatin; in the NACT arm, surgical cytoreduction was performed in the absence of disease progression after 3 cycle of paclitaxel and carboplatin, followed by surgical debulking and at least 3 additional cycles of chemotherapy *(see Figure 3)*. A provision was made early on in the trial that suboptimally cytoreduced PS patients could undergo an interval secondary surgery; however, upon the revelation of the data outlined above, this was subsequently removed. Of 670 randomized patients, 632 were ultimately randomized. The population had extensive disease burden with 62% of patients harboring metastatic lesions of 10 cm or greater. Optimal cytoreduction (defined as postoperative tumor residuum of 1 cm or less) was achieved in 42% of PS patients and 81% of NACT patients. Postoperative adverse events rates (hemorrhage, infection, venous thrombosis) and mortality were significantly higher after PS compared to NACT. The statistical endpoint was non-inferiority; in other words, the trial was powered to address that the NACT approach was not more than 25% inferior to standard PS in overall survival. The hazard ratio for death between the arms was 0.98 (90% confidence interval [CI], 0.84-1.13; $P = 0.01$ for non-inferiority), rejecting the null hypothesis that NACT was inferior to PS. The same was true for progression (hazard ratio, 1.01; 90% CI, 0.89-1.15). As has been documented previously, resection of all macroscopic disease was the strongest independent predictive factor for overall survival. The authors concluded that while NACT is a viable alternative to PS in patients with bulky stage IIIC-IV disease, complete tumor resection should be the goal of surgery, whether performed initially or after NACT.

The Controversy

The study is a tribute to the cooperative group charter and their ability to address questions that would be otherwise impossible to formally answer. Further, since the trial includes centers in multiple geographic locations and consists of surgeons of various skill sets, the results are ultimately generalizable to those who would fit the eligibility criteria. So why the controversy? The root of the current debate lies not in the conduct of the trial or the comparative nature as designed. There fundamentally is even little controversy in the conclusions; the focus of the debate lies in the observed median outcomes in both arms. That is, a median PFS of 12 months and OS around 30 months are far lower than what would be expected in this population (Stage IIIC-IV) and suggests the surgical effort in the control group is substandard. In fact, GOG protocol 111, a randomized clinical trial of cyclophosphamide and cisplatin vs paclitaxel and cisplatin in exclusively suboptimally cytoreduced ovarian cancer patients (> 1 cm residual disease) had a median PFS of 18 months and an OS of 38 months. Even the mixed population of GOG protocol 182 provided a median PFS of 16 months and OS of 44 months in more than 4300 patients from U.S. and European centers. As a result, the optimal debulking rates by country were evaluated and, indeed, there was variation in optimal rates ranging from around 40% to more than 80%. However, there was strong correlation between the optimal debulking rates within centers for both PS and NACT, which may explain the consistency of the results. In all, no differences could be discerned between participating sites, patients, and outcomes that could explain the absolute values.

An exhaustive subgroup analysis was provided by the study organization as a supplement to the article to ad-

dress questions about the trial's results that have been raised since initial presentation. However, this has done little to quench the thirst for re-evaluation in centers or organizations with higher rates of optimal resection rates, and potentially among patients with more favorable risk profiles. Recent documentation of the frequency and impact of complete tumor resection may lend credence to this effort. While there is variance among institutions in the rate of PS optimal debulking defined by the 1 cm yardstick, the impact on overall survival is far lower than the impact of zero tumor residual, which varies by an even greater degree globally. In addition, this effect on survival could have been diluted in the current study as zero tumor residual was accomplished more frequently after NACT in centers with low rates of zero tumor residual after PS. In this fashion, the impact of the strongest predictive variable may not have been realized in the PS cohort.

Conclusion

The take home message from this trial and discussion is that the NACT approach, which heretofore had been relegated predominately to our poorest prognosis and sickest patients, indeed has a viable role in the management of ovarian cancer. This is not dissimilar to other solid tumors, such as colorectal and breast cancer, where the approach has also been associated with organ preservation and a prime opportunity to obtain tissue for post-therapeutic biomarker assessment of effect. This valuable asset will ultimately lead to a more "personalized" or directed therapy following surgery, which could greatly enhance treatment effect. However, until data from a NACT approach the expected norms in the United States following PS, the controversy surrounding a potential underappreciated adverse effect on PFS and OS will loom. Unfortunately, it is not clear that any trial of this sort will ever be accomplished in the United States, though a trial is currently being conducted in Europe. Until then, a bias will continue to drive primary treatment approaches in ovarian cancer. ■

Reference

1. Vergote I, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010;363:943-953.

CME Questions

32. Compared to those women that have an IUD placed at the 6-week visit, postpartum women who receive an IUD within 10 minutes of delivery of the placenta are more likely to:
a. experience a pelvic infection.
b. express regret over the decision to obtain an IUD.
c. not become pregnant at 1 year.
d. undergo spontaneous expulsion of the device.
e. experience difficulty with device removal at 5 years.

33. Regarding the new CDC guidelines, which of the following is most appropriate?
a. Patients with unknown GDS status would be treated if having PROM > 18 hours.
b. Patients with strongly positive urine cultures for GBS would not need to the screened at 35-37 weeks.
c. Patients with preterm labor and unknown GBS status would receive antibiotic treatment and be cultured on admission.
d. Penicillin would be the first choice of treatment in those patients not allergic to it.
e. All of the above

34. Women taking oral tranexamic acid will achieve a reduction in measured menstrual blood loss that is:
a. the same as that achieved by women using the LNG IUS.
b. greater than that achieved by women using combined oral contraceptives.
c. a meaningful reduction of about 50 mL.
d. below an absolute level of 80 mL in most users.

Answers: 32. d, 33. e, 34. c.

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.*

Rivaroxaban: Another Warfarin Replacement

In this issue: Rivaroxaban may be dabigatran's first competitor; a new way to measure non-adherence to medication therapy; FDA Actions.

Another Warfarin Replacement on Horizon

Just as Boehringer Ingelheim begins marketing dabigatran (Pradaxa®) as a replacement for warfarin, a competitor drug may be on the horizon. As reported at the American Heart Association (AHA) meetings in November, rivaroxaban, an oral drug factor Xa inhibitor, is as effective as warfarin at preventing stroke and blood clots in patients with nonvalvular atrial fibrillation.

The ROCKET AF study (Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients with Nonvalvular Atrial Fibrillation) looked at more than 14,000 patients with atrial fibrillation. Patients were randomized to warfarin or rivaroxaban (20 mg/day). The time in therapeutic range for warfarin was 57.8%. With a primary endpoint of stroke and non-CNS systemic embolism, rivaroxaban was associated with a rate of 1.71 events per 100 patient-years vs 2.16 for warfarin (P = 0.015 for superiority and P < 0.001 for non-inferiority). On an intention to treat (ITT) basis, event rates were 2.12 for rivaroxaban vs 2.42 for warfarin (P = 0.117). There were 55 intracranial bleeds with rivaroxaban compared with 84 with warfarin (P = 0.019). Rivaroxiban also showed numerically fewer MIs (0.91 vs 1.12 per 100 person-years; P = 0.12). All-cause mortality was 1.87 in the rivaroxaban group vs 2.21 in the warfarin group (P = 0.073). In the ITT analysis, mortality was 4.52 vs 4.91 (P = 0.152), respectively.

This study (presented at the American Heart Association Scientific Sessions; Chicago, IL; Nov. 15, 2010) was the seventh Phase III trial in the development of rivaroxaban, with other studies evaluating the drug for prevention and treatment of venous thromboembolism, indications that Bayer and Johnson & Johnson have already filed with the FDA. It is also expected that a new drug application will be filed soon for the prevention of stroke in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban requires no monitoring and has few drug interactions. Rivaroxaban has the advantage of being dosed once a day compared to twice-daily dosing for dabigatran. ■

Non-adherence: A New Way to Measure

A new study examines drug adherence in an interesting way — by looking at the rate of prescriptions abandoned at the pharmacy. Traditional non-adherence studies have looked at refill rates, pill counting, and patient reports of medication use. But prescriptions abandoned at the pharmacy represent a potential opportunity to intervene and improve adherence at the very onset of the prescribing process.

Researchers used the CVS pharmacy database to evaluate more than 10 million prescriptions

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.

filled by more than 5 million patients. The overall abandonment rate was 3.27%, although nearly half of those were eventually filled by the same drug or a similar drug within 30 days. Not surprisingly, patients were least likely to abandon opiate prescriptions, and were most likely to abandon expensive prescriptions. Prescriptions with a copayment of $40-$50 and those with a copayment of more than $50 were 3.4 times and 4.68 times more likely to be abandoned, respectively, than prescriptions with no copayment ($P <$ 0.001 for both comparisons). New users of medications were more likely to abandon prescriptions than prevalent users, and prescriptions that were delivered to the pharmacy electronically were 1.64 times more likely to be abandoned than those that were not electronic ($P < 0.001$); however, they were unable to determine whether written prescriptions were never delivered to the pharmacy by patients.

The authors concluded that prescription abandonment represents an important opportunity to intervene and improve adherence (*Ann Intern Med* 2010;153:633-640). An accompanying editorial points out that the rate of abandonment in this study was actually quite low. Others studies have suggested that 17%-20% of patients do not pick up new prescriptions, and 8% of patients' prescriptions are denied by health plans. Physicians and pharmacists are urged to remain mindful that costs are an important barrier to adherence and that lower cost alternatives should be prescribed "whenever feasible" (*Ann Intern Med* 2010;153:680-681). ■

FDA Actions

The FDA has asked the manufacturers of propoxyphene-containing pain medications (Darvon®, Darvocet®, and generics) to withdraw them from the market. The withdrawal is based on new data showing the drugs are associated with serious and fatal heart arrhythmias. Health care professionals are advised to stop prescribing propoxyphene and patients are asked to contact their health care providers to discuss switching to other pain medications. Propoxyphene has been the target of consumer groups for more than 30 years because of evidence of poor efficacy in treating pain and a high level of side effects including falls. ■

The FDA has approved duloxetine (Cymbalta®) for the treatment of chronic musculoskeletal pain. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was previously approved for treating depression, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. The new indication for musculoskeletal pain includes low back pain and osteoarthritis. The expanded indication was based on the results of four double-blind, placebo-controlled trials, which showed that patients treated with duloxetine had significantly greater pain reduction than those patients treated with placebo. Duloxetine is marketed by Eli Lilly and Company. ■

The FDA has approved lurasidone for the treatment of schizophrenia in adults. The drug is classified as an atypical antipsychotic, and like other drugs in this class, carries a boxed warning regarding an increased risk of death associated with off-label use to treat behavioral problems in older adults with dementia. Common adverse reactions include drowsiness, feelings of restlessness, nausea, agitation, and Parkinsonian symptoms such as bradykinesia, tremor, and muscle stiffness. Lurasidone will be marketed by Sunovion Pharmaceuticals as Latuda™. ■

The FDA has approved a new injectable cephalosporin, ceftaroline, to treat community-acquired bacterial pneumonia (CABP) and bacterial skin infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Ceftaroline was approved based on data from four studies that showed the drug to be as effective as ceftriaxone for the treatment of CABP and as effective as vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections. The recommended dose for patients with normal renal function is 600 mg given as a one-hour IV infusion every 12 hours. Ceftaroline is marketed by Forest Laboratories as Telflaro™. ■

The FDA's Vaccines and Related Biological Products Advisory Committee has recommended an expanded indication for Gardasil®, Merck's quadravalent human papillomavirus vaccine to prevent anal intraepithelial neoplasia and anal cancer in males and females ages 9-26. The approval was based on a phase III double-blind, placebo-controlled trial in which more than 4000 males were randomized to receive the three-dose vaccine or placebo. There was a significant reduction in the rate of anal intraepithelial neoplasia or anal cancer, especially in men who have sex with men. The vaccine is already approved for prevention of genital warts and cervical, vulvar, and vaginal cancer in females ages 9-26 and prevention of genital warts in males ages 9-26. ■