RELIAS MEDIA

Vol. 36, Issue 3, July 2019
ReliasMedia.com

OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Changes in Cervical Cancer Staging

By Melissa Moffitt, MD

Gynecologic Oncologist, Assistant Professor, Department of OB/GYN, Oregon Health & Science University, Portland

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

SYNOPSIS: This paper is an epidemiologic validation of recent changes in cervical cancer staging.

SOURCE: Matsuo K, Machida H, Mandelbaum RS, et al. Validation of the 2018 FIGO cervical cancer staging system. *Gynecol Oncol* 2019;152:87-93.

The International Federation of Gynecology and Obstetrics (FIGO) recently revised the staging system for cervical cancer.[1] Matsuo et al validated the new staging system using the Surveillance, Epidemiology, and End Results (SEER) database.[2] Using Kaplan-Meier curves, they showed that cancer-specific survival for the new Stage IB subgroups were distinct from one another: Patients with Stage IB2 (tumor size 2-4 cm) were twice as likely to die of their disease as those with Stage IB1 (tumors < 2 cm with at least 5 mm depth of invasion). The new subgroups also had differences in clinical and histologic features. In addition, the authors showed that the cancer-specific survival outcomes for the new Stage IIIC1, which includes patients with pelvic lymph node metastasis, are more closely related to characteristics of the primary tumor than to the lymph node metastasis. For instance, Stage IIIC1 patients whose primary tumors were confined to the cervix had improved outcomes over the Stage IIIC1 patients whose tumors involved the parametria, vagina, or pelvic sidewall.

■ COMMENTARY

Until the recent update to the FIGO cervical cancer staging system, cervical cancer was staged based on clinical exam and a few allowable imaging studies that were easily accessible in low-resource settings. This was reasonable, as the vast majority of cervical cancer cases are located in developing countries. The staging did not account for pelvic or aortic lymph node metastasis since this was not identifiable clinically. Nonetheless, pelvic and aortic lymph node metastases have been known to be important prognostic factors.[3] Thus, in developed countries, where CT scans, PET CTs, and surgical or radiology-guided biopsies are common, it is standard practice to assign a cancer stage using the 2014 FIGO clinical stage but annotate it with findings from imaging or pathology.

Financial Disclosure: *OB/GYN Clinical Alert*'s Editor Jeffrey T. Jensen, MD, MPH, reports that he is a consultant for and receives grant/research support from ObstetRx, Bayer, Merck, and Sebela; he receives grant/research support from Abbvie, Mithra, and Daré Bioscience; and he is a consultant for CooperSurgical and the Population Council. Peer Reviewer Catherine Leclair, MD; Nurse Planner Andrea O'Donnell, FNP; Editorial Group Manager Leslie Coplin; Editor Jonathan Springston; and Accreditations Manager Amy M. Johnson, MSN, RN, CPN, report no financial relationships relevant to this field of study.

OB/GYN Clinical [ALERT]
Evidence-based commentaries on women's reproductive health

OB/GYN Clinical Alert (ISSN 0743-8354) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *OB/GYN Clinical Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

GST Registration Number: R128870672.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmedia.com
ReliasMedia.com

Questions & Comments:
Please contact Executive Editor **Leslie Coplin**, at lcoplin@relias.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $299

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.
Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias LLC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias LLC designates this enduring material for a maximum of 2 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Relias LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2] will be awarded to participants who meet the criteria for successful completion. California Board of Registered Nursing, Provider CEP#13791.

This CME activity is intended for the OB/GYN. It is in effect for 36 months from the date of the publication.

Thank You, Molly Brewer; Welcome Melissa Moffitt

Associate Editor Molly Brewer, DVM, MD, has decided to step down from her role on the editorial board of *OB/GYN Clinical Alert* to devote more attention to her busy workload as professor of gynecologic oncology and chair of the department of OB/GYN at the University of Connecticut. I appreciate her contributions and insights into advances in screening and treatment for gynecologic cancer over the past three years. We will miss her valuable commentaries.

Change always brings new opportunity and with this departure comes some good news. Dr. Melissa Moffitt, an assistant professor of OB/GYN at Oregon Health & Science University, will take over the responsibility of keeping us up to date on topics in gynecologic oncology. Dr. Moffitt finished medical school at the University of California-Davis in 2004, her OB/GYN residency at the University of Massachusetts Medical School in 2008, and her gynecologic oncology fellowship at Los Angeles County and University of Southern California in 2011. Dr. Moffitt has a special interest in medical education and is excited to share her enthusiasm for teaching through regular contributions. Dr. Moffitt's first contribution is included in this issue.

— Jeffrey T. Jensen, MD, MPH, Editor

The 2018 FIGO cervical cancer staging system keeps the backbone of staging clinical, while incorporating results from imaging and pathology. The new staging adds Stage IIIC1 for pelvic lymph node metastasis and IIIC2 for aortic lymph node metastasis, similar to the FIGO staging of lymph nodes in endometrial cancer. The use of imaging, such as a PET CT, or pathology from a biopsy are necessary to assign either Stage IIIC1 or IIIC2. When imaging is used to identify pelvic or aortic lymph node metastasis, the patients are assigned as Stage IIIC1r or IIIC2r, respectively, with the "r" referring to radiology. Similarly, when a CT-guided biopsy or pathology from a lymphadenectomy is used to identify patients with pelvic or aortic lymph node metastasis, those patients are assigned Stage IIIC1p or IIIC2p, respectively, with the "p" indicating a pathology result.

Using retrospective data, Matsuo et al used the SEER database to show expected outcomes for each new stage. They highlighted the importance of splitting Stage IB from two subgroups to three subgroups, reflecting the improved outcomes for patients with tumors localized to the cervix with smaller (< 2 cm) tumors over those patients with larger (> 2 cm) tumors. The new 2018 FIGO staging also differentiates tumors < 2 cm in other important ways. For instance, fertility-sparing radical trachelectomy is best suited for patients with cervical tumors < 2 cm, per the National Comprehensive Cancer Network guidelines. Also, there is interest in allowing less radical surgery for patients with tumors < 2 cm with other low-risk tumor characteristics such as stromal invasion < 10 mm, no lymphovascular space invasion, and squamous, adeno- or adenosquamous histology.[4] This idea of offering less radical surgery to select early-stage cervical cancer patients is part of the impetus driving the development of the Querleu-Morrow classification for radical hysterectomy.[5] This radical hysterectomy classification system describes a less-radical modified radical hysterectomy where the parametria are transected halfway between the cervix and the ureter.

In addition to the new FIGO staging system and its validation, surgical treatment of early-stage cervical cancer has changed substantially. Two recently published large studies showed poorer oncologic outcomes for patients with early-stage cervical cancer when treated with laparoscopy (with or without robotic assistance) compared with laparotomy.[6,7] Combining the randomized prospective data from Ramirez et al[6] with the Melamed et al[7] cohort study using the SEER database revealing essentially the same worsened outcomes for early-stage, potentially curable, cervical cancer patients, most gynecologic oncologists have moved back to a laparotomy. Even those with microscopic cervical malignancy now are counseled on the recent studies and are considered for a vaginal or laparotomy approach. Although it is unknown at this time exactly what aspects of laparoscopy and robotic surgery lead to increased recurrence and cervical cancer deaths in early-stage patients, some theories have evolved: use of the uterine manipulator disrupting the tumor and stimulating metastasis, and CO_2 insufflation causing dispersion of tumor cells or influencing inflammation in a way that encourages metastasis.

Given the recent changes in cervical cancer staging and treatment, it is more important than ever when discussing cervical cancer with patients to be specific and detailed regarding findings on exam, radiology, and pathology and recommendations for treatment. I suggest stating the actual tumor size or the staging system used when discussing early cervical cancers. In addition, when surgical treatment for the patient is appropriate, clarity regarding surgical approach and extent of radicality are crucial. In particular, for the general gynecologist who occasionally performs a simple hysterectomy for patients with Stage IA1 cervical cancer, knowing the new FIGO 2018 staging system and counseling the patient on a nonlaparoscopic approach are prudent. ■

REFERENCES

1. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol Obstet* 2018;143(Suppl 2):22-36.
2. Matsuo K, Machida H, Mandelbaum RS, et al. Validation of the 2018 FIGO cervical cancer staging system. *Gynecol Oncol* 2019;152:87-93.
3. Wagner AE, Pappas L, Ghia AJ, Gaffney DK. Impact of tumor size on survival in cancer of the cervix and validation of stage IIA1 and IIA2 subdivisions. *Gynecol Oncol* 2013;129:517-521.
4. Tseng JH, Aloisi A, Sonoda Y, et al. Less versus more radical surgery in stage IB1 cervical cancer: A population-based study of long-term survival. *Gynecol Oncol* 2018;150:44-49.
5. Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol* 2008;9:297-303.
6. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018;379:1895-1904.
7. Melamed A, Margul DJ, Chen L, et al. Survival after minimally invasive radical hysterectomy for early-stage cervical cancer. *N Engl J Med* 2018;379:1905-1914.

ABSTRACT & COMMENTARY

Behavioral Interventions for Menopausal-Related Insomnia Improve Depression

By Nicole Cirino, MD, CST, IF

Reproductive Psychiatrist, Associate Professor of Psychiatry and OB/GYN, Oregon Health & Science University, Portland

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

SYNOPSIS: In a randomized, controlled trial comparing the behavioral interventions cognitive behavioral therapy for insomnia (CBTI) and sleep reduction therapy (SRT) to a control intervention of sleep hygiene education, investigators found CBTI and SRT therapy improved insomnia and depressive symptoms in postmenopausal women with menopausal-related insomnia.

SOURCE: Kalmbach DA, Cheng P, Arnedt JT, et al. Treating insomnia improves depression, maladaptive thinking, and hyperarousal in postmenopausal women: Comparing cognitive-behavioral therapy for insomnia (CBTI), sleep restriction therapy, and sleep hygiene education. *Sleep Med* 2019;55:124-134.

Insomnia symptoms are common complaints during the menopausal transition, and up to 50% of women experience these symptoms.[1] Menopausal-related insomnia disorder describes insomnia that occurs or is exacerbated during perimenopause or menopause, and is believed to be related to fluctuations in estrogen, progesterone, and cortisol levels. Effective treatments include cognitive behavioral therapy for insomnia (CBTI), sleep reduction therapy (SRT), hormone replacement therapy (HRT), antidepressants, exercise, and yoga.[2] Insomnia also is strongly correlated with depressive symptoms in adults. In addition, depressive symptoms are increased during the menopausal transition. Kalmbach et al attempted to address the effect of CBTI or SRT on insomnia and depressive symptoms in women with menopausal-related insomnia.

Behavioral interventions often are considered first-line interventions for insomnia in the general adult population.[3] Common behavioral interventions for insomnia include CBTI and SRT. The theory behind the effectiveness of these treatments is that acute insomnia can progress into chronic insomnia because of cognitive arousal (rumination and worry) and dysfunctional beliefs about sleep (catastrophizing negative effects of a poor night's sleep). CBTI treatments aim to address this component of insomnia comprehensively, while SRT is a unique intervention that is part of the full CBTI protocol that specifically addresses time in bed (TIB).

Sleep restriction therapy (SRT) is a standard behavioral strategy used as part of CBTI and as a standalone intervention. It involves restricting a patient's TIB (sleep window) to match his or her average self-reported total sleep duration. The sleep window is titrated weekly, based on sleep efficiency (the proportion of TIB spent asleep), to identify the patient's core sleep requirement. Spielman et al proposed that decreasing a person's opportunity to sleep across successive nights would build homeostatic sleep pressure, stabilize circadian control of sleep and wakefulness, and dampen presleep cognitive and physiological hyperarousal, which would lead to less time to fall asleep and more consolidated, uninterrupted sleep.[4]

Kalmbach et al used a single-site, randomized, controlled trial format to randomize 117 postmenopausal women (56.34 ± 5.41 years of age) with peri- or postmenopausal

onset of insomnia to one of three treatments: sleep hygiene education, SRT, or CBTI. Exclusion criteria included sleep apnea, restless legs, bipolar disorder, and prior CBTI. Blinded assessments were performed at baseline, post-treatment (approximately six weeks), and six-month follow-up. The authors used the Beck depression inventory, second edition (BDI-II) to measure depression and a variety of scales to assess cognitive and behavioral properties associated with insomnia: dysfunctional beliefs and attitudes about sleep scale (DBAS), presleep arousal scale (PSAS), event-related rumination inventory (ERRI), and Penn State worry questionnaire (PSWQ). Of the study participants, 3.4% were on HRT and 23.1% underwent medical menopause. Vasomotor or other menopausal symptoms were not elicited and, thus, not used in randomization. In addition, 4.3% of participants endorsed moderately severe depression at intake (BDI-II > 20) while the average BDI-II was 8.26 ± 5.00 (subclinical depression range). All interventions were offered in a primary care or sleep medicine office-based setting over six weeks in either face-to-face, telephone, or email format. Improvements in insomnia were strongly correlated with

[Cognitive behavioral therapy for insomnia and sleep reduction therapy are easy, side effect free, and effective behavioral treatments for patients with these common menopausal symptoms.]

improvements in depression and dysfunctional beliefs about sleep in both post-treatment and six-month follow-up. Patients receiving SRT or CBTI both reported lower depressive symptoms six months after completing treatment. SRT patients reported a medium decrease in depressive symptoms, whereas CBTI patients reported a larger decrease in symptoms. Change from pre- to six-month follow-up BDI-II score was -2.91 ($P < 0.01$) in the SRT group and -5.14 ($P < 0.001$) in the CBTI group. Sleep hygiene education alone did not produce any durable treatment effects. In fact, depressive symptoms were higher at the six-month follow-up. SRT direct effects on depression were not captured until the six-month follow-up visit. Results showed that compared to sleep hygiene education, short-term specialized behavioral interventions (CBTI and SRT) helped alleviate subclinical depressive symptoms and improve insomnia by reducing maladaptive thinking and somatic hyperarousal.

■ COMMENTARY

A paucity of data exists regarding behavioral interventions specifically for insomnia related to menopause, despite its high prevalence in this population. Kalmbach et al described an effective model for a two- to six-session office-based behavioral intervention, which was delivered by a registered nurse under guidance of a licensed mental health professional. Access to evidence-based behavioral interventions for insomnia has been a barrier to treatment in many clinical settings. This intervention could be provided in ambulatory settings for the common complaints of menopausal-related insomnia and depressive symptoms. This reflects the trend of delivering behavioral insomnia interventions in an integrated medical care setting. The Veterans Administration (VA), which also sees a high prevalence of insomnia in its population, but struggles with access, has released an evidence-based online app, the CBT-i Coach. This free, publicly available, patient-facing smartphone app is intended to augment clinician-delivered CBTI by facilitating the delivery of major CBTI treatment components, including sleep educational materials, daily sleep diary completion, stimulus control guidelines, SRT, anxiety management, and cognitive therapy tools.[5] It is not specific to the VA population and can be used for general insomnia by anyone.

Studying specific behavioral interventions for insomnia in this population can help identify the most effective interventions for menopausal-related insomnia. Kalmbach et al found that CBTI was most effective, followed by SRT. Sleep hygiene education had no lasting clinical effect on insomnia or depressive symptoms. They did not address which perimenopausal and postmenopausal patients may respond best to this treatment. This population had a high incidence of medically induced menopause. Vasomotor symptomatology, which is correlated with both insomnia and depression, was not elicited. Furthermore, the women in this study had average BDI scores of 8.26 ± 5.00 and were in the subclinical depression range. It is unclear and not yet recommended for insomnia interventions alone to be used to treat those who meet criteria for clinical depression.

Obviously, one of the benefits of successful office-based behavioral interventions is the low side effect profile, particularly for women who may not be good candidates for hormone therapy or antidepressant treatment. CBTI and SRT are easy, side effect free, and effective behavioral treatments for many patients with these common menopausal symptoms. Hopefully, more innovative models of delivery will be available to the OB/GYN clinician in the future. ■

REFERENCES

1. Kravitz HM, Ganz PA, Bromberger J, et al. Sleep difficulty in women at midlife: A community survey of sleep and the menopausal transition. *Menopause* 2003;10:19-28.
2. Eichling PS, Sahni J. Menopause related sleep disorders. *J Clin Sleep Med* 2005;1:291-300.
3. Sateia MJ, Buysse DJ, Krystal AD, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017;13:307-349.
4. Spielman AJ, Saskin P, Thorpy MJ. Treatment of chronic insomnia by restriction of time in bed. *Sleep* 1987;10:45-56.
5. Kuhn E, Weiss BJ, Taylor KL, et al. CBT-I Coach: A description and clinician perceptions of a mobile app for cognitive behavioral therapy for insomnia. *J Clin Sleep Med* 2016;12:597-606.

ABSTRACT & COMMENTARY

Should Antibiotic Prophylaxis Be Used for Surgical Treatment of Early Pregnancy Loss?

By Rebecca H. Allen, MD, MPH

Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women and Infants Hospital, Providence, RI

Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: In this randomized, controlled trial of more than 3,000 women in developing countries with incomplete or missed abortion at less than 22 weeks' gestation, antibiotic prophylaxis prior to uterine evacuation reduced infection rates when a strict definition for pelvic infection was used, but not when a more expanded definition was used.

SOURCE: Lissauer D, Wilson A, Hewitt CA, et al. A randomized trial of prophylactic antibiotics for miscarriage surgery. *N Engl J Med* 2019;380:1012-1021.

This was a randomized, controlled trial conducted in Malawi (three hospitals), Pakistan (five hospitals), Tanzania (three hospitals), and Uganda (two hospitals) comparing doxycycline 400 mg plus metronidazole 400 mg to placebo two hours prior to surgical evacuation of the uterus for spontaneous abortion (incomplete or missed abortion) at less than 22 weeks' gestation. The surgery was conducted according to local practice and could include manual vacuum aspiration, suction curettage, or sharp curettage. Exclusion criteria included evidence of induced abortion, current pelvic infection, need for immediate surgery, current or recent (within seven days) antibiotic use, age younger than 16 years, or other contraindications to doxycycline and metronidazole. The primary outcome was pelvic infection within 14 days after surgery. The investigators studied two definitions for pelvic infection: 1) strict criteria requiring the presence of two or more of four clinical features — purulent vaginal discharge; fever > 38.0º C; uterine, parametrial, or adnexal tenderness on exam; and a white cell count of more than 12×10^9 per liter; and 2) expanded criteria that allowed the diagnosis of pelvic infection with only the presence of one criteria but with symptoms of sufficient severity that the clinician judged treatment was required.

A total of 3,412 women were randomized between June 2014 and April 2017. After withdrawals, 1,700 patients in the antibiotic prophylaxis group and 1,704 in the placebo group were included in the intention-to-treat analysis. Sharp curettage was used for 70% of the procedures, 23.2% manual vacuum aspiration, and 6.2% suction curettage. The majority of the cases (83%) were incomplete abortions. There was no difference between the two groups in terms of age, gestational age, HIV status, and socioeconomic indicators. The rate of pelvic infection with the strict criteria was 1.5% in the antibiotic group and 2.6% in the placebo group (relative risk [RR], 0.60; 95% confidence interval [CI], 0.37-0.96). The rate of pelvic infection with the expanded criteria was 4.1% in the antibiotic group and 5.3% in the placebo group (RR, 0.77; 95% CI, 0.56-1.04). There were no significant interactions according to maternal age, gestational age, HIV infection status, type of miscarriage, country of recruitment, timing of antibiotic prophylaxis, or residence in an urban or rural location. The only factor that affected the results was the type of surgery where the effect of the antibiotics appeared greater with manual vacuum aspiration (rate of infection, 1.3% antibiotic group vs. 4.1% placebo group; RR, 0.32; 95% CI, 0.12-0.86) than with sharp curettage (rate of infection, 5.3% antibiotic group vs. 6.0% placebo group; RR, 0.89; 95% CI, 0.64-1.23).

■ COMMENTARY

Antibiotic prophylaxis for surgically induced abortion has been the standard of care for many years based on strong evidence.[1,2] However, recommendations for antibiotic prophylaxis for uterine evacuation for the indication of incomplete or missed abortion are inconsistent, mainly because of the lack of adequate trials. Extrapolating from induced abortion data, most providers do administer antibiotics prior to surgery, which aligns with the American College of Obstetricians and Gynecologists' (ACOG) recommendations.[2-4] It is unclear why the same procedure would have different risks of infection depending on the indication. One might theorize that women with early pregnancy loss are more likely to have known partners and, thus, have a lower risk of sexually transmitted infections. However, this has not been studied. The antibiotic regimen recommended by ACOG is 200 mg of doxycycline at least one hour preoperatively; however, other agents, such as azithromycin and metronidazole, have been used.[2,4] Therefore, Lissauer et al intended to study, with sufficient sample size, the utility of antibiotic prophylaxis in low-resource countries, given that there is a higher incidence of infections after surgery in these countries compared to high-income countries and that women may not be able to access postoperative care if they develop complications.

The findings of this study are difficult to interpret because of the two definitions of pelvic infection used. The expanded criteria were instituted mid-trial because study clinicians were concerned that potential infections

were missed in women who had only one sign of clinical infection. Therefore, the investigators decided to broaden the definition of pelvic infection. Now, there is evidence showing reduced infections with antibiotics when the strict definition of pelvic infection was used and no difference when the wider criteria were used. Looking at the data further, antibiotics made more of a difference compared to sharp curettage among women undergoing manual vacuum aspiration. Given that manual vacuum aspiration and suction curettage are practiced in the United States for uterine evacuation, as opposed to sharp curettage, this result is more relevant to U.S. practice. ACOG does not recommend the practice of sharp curettage alone for uterine evacuation, but it still is used widely internationally.[3]

One other aspect of this study that differs from U.S. practice is the high proportion of incomplete abortions (roughly 80%) treated compared to missed abortions. Therefore, the results may not be generalizable to the United States since the proportion of incomplete to missed abortions likely is reversed. U.S. providers treat many more women with missed abortions compared to incomplete abortions. It is unknown if this would change the results, although the investigators did not find the type of miscarriage to affect the findings. These investigators used two antibiotics and a higher dose of doxycycline than normally is used in the United States. Interestingly, there was no difference in vomiting (1.1% vs. 1.3%) and diarrhea (1.2% vs. 1.3%) between the two groups. My takeaway from this trial is that antibiotic prophylaxis for uterine evacuation for early pregnancy loss still is beneficial in the United States. The intervention is not expensive, if 200 mg of doxycycline is used, and has few side effects. ■

REFERENCES

1. Low N, Mueller M, Van Vliet HA, Kapp N. Perioperative antibiotics to prevent infection after first-trimester abortion. *Cochrane Database Syst Rev* 2012;(3):CD005217.
2. Achilles SL, Reeves MF; Society of Family Planning. Prevention of infection after induced abortion: Release date October 2010: SFP guideline 20102. *Contraception* 2011;83:295-309.
3. ACOG Practice Bulletin No. 200. Early Pregnancy Loss. American College of Obstetricians and Gynecologists. 2018.
4. ACOG Practice Bulletin #195. Prevention of Infection After Gynecologic Procedures. American College of Obstetricians and Gynecologists. 2018.

ABSTRACT & COMMENTARY

Progesterone: Not a Treatment for Threatened Abortion

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: Investigators of this well-designed, randomized, controlled trial conclusively demonstrated that progesterone supplementation does not reduce the risk of early pregnancy loss in women who experience first trimester bleeding.

SOURCE: Coomarasamy A, Devall AJ, Cheed V, et al. A randomized trial of progesterone in women with bleeding in early pregnancy. *N Engl J Med* 2019;380:1815-1824.

First-trimester bleeding commonly precedes spontaneous abortion, but not all women who experience bleeding go on to miscarry. The "pro-gestational" steroid hormone progesterone, initially produced by the corpus luteum and later by the placenta, is essential for the maintenance of pregnancy. However, whether low progesterone levels contribute to pregnancy loss or if progesterone supplementation could reduce the risk of miscarriage is controversial. Coomarasamy and colleagues previously reported results from a randomized trial of progesterone in women with a history of unexplained recurrent pregnancy loss, finding no benefit.[1] Here, they evaluated whether progesterone treatment could reduce pregnancy loss in women experiencing the common scenario of "threatened abortion," first trimester bleeding.

Coomarasamy et al conducted a multicenter, randomized, double-blind, placebo-controlled trial. They recruited women 16 to 39 years of age presenting with vaginal bleeding in the setting of pregnancy under 12 weeks' gestational age with evidence of a viable intrauterine pregnancy on ultrasound. They considered the absence of fetal heart activity with a crown-rump length > 7 mm or lack of a fetal pole in the setting of a mean gestational sac diameter > 25 mm evidence of a non-viable pregnancy that would not benefit from treatment. For safety, they also excluded women with life-threatening bleeding.

The authors used a central randomization facility to assign participants to treatment: twice-daily self-administration of vaginal suppositories containing either 400 mg of micronized progesterone or a matching placebo. Eligible women initiated treatment at the time of randomization and continued use of the suppositories through up to 16 completed weeks of gestation (if the pregnancy continued). The central randomization system allowed the investigators to balance the trial-group assignments according to maternal age (< 35 years vs. ≥ 35 years), body mass index < 30 kg/m^2 vs. ≥ 30 kg/m^2), fetal heart activity (present vs. absent), estimated gestation at presentation (< 42 days vs. ≥ 42 days), and amount of vaginal bleeding (pictorial blood loss assessment chart score of ≤ 2 vs. ≥ 3) for evaluation of the outcome with respect to these important characteristics. The investigators defined birth of a live-born baby after at

least 34 weeks of gestation as the primary outcome. Key secondary outcomes included the time from conception to the end date of pregnancy, ongoing pregnancy at 12 weeks of gestation, pregnancy loss before 24 weeks of gestation, and live birth before 34 weeks. A power analysis determined that a sample size of 1,972 women in each treatment group would provide 90% power to detect a 5% difference in the incidence of live births after at least 34 weeks of gestation (65% vs. 60%), at a two-sided alpha level of 0.05. They picked 5% as a minimally important clinical difference based on a national survey of clinical practitioners in the United Kingdom. The final sample size of 4,150 women accounted for an expected 5% loss to follow-up.

The study team screened 23,775 patients with pregnancy bleeding. Of these, 12,862 met eligibility requirements and 4,153 consented to participation (progesterone: 2,079; placebo: 2,074). Follow-up was excellent, with data available for the primary outcome in 97%. They found no difference in the incidence of live births after at least 34 weeks of gestation (progesterone: 75% [1,513/2,025]; placebo: 72% [1,459/2,013]; relative risk [RR], 1.03; 95% confidence interval [CI], 1.00-1.07). The incidence of adverse events did not differ significantly between the groups. Similarly, there was no difference in the secondary outcome, including incidence of live birth before 34 weeks and pregnancy loss before 24 weeks.

Based on these results, the authors concluded that progesterone therapy for women experiencing first trimester bleeding does not reduce the risk of pregnancy loss or increase the incidence of live birth.

■ COMMENTARY

One of the biggest challenges in obstetrics is the management of expectation. As a reproductive biologist, I marvel at the complex sequence of events that must occur to establish pregnancy. How amazing that this works so frequently and successfully that we actually require contraception! Reproductive loss occurs in all organisms. In mammals, one of the opportunities for loss includes failure to establish or maintain pregnancy. For a variety of reasons, many conceptuses fail to survive. Wilcox used a highly sensitive assay for βhCG and estimated that 22% of all conceptions do not result in clinical pregnancy.[2] Women who go on to miss their expected menses have about a 15% chance of miscarriage. The available evidence suggests most early pregnancy loss occurs as a result of aneuploidy.[3] Given the considerable energy that women must invest in pregnancy, it makes sense that the body recognizes these nonviable pregnancies and withdraws support. However, our medical system has effectively sold the public on the idea that we work miracles. I don't know about you, but I don't believe in miracles. I find science far more compelling.

Women experiencing first trimester bleeding are in a vulnerable position. We all have been touched by the profound sadness that accompanies early pregnancy loss. In the setting of a highly desired pregnancy, first trimester bleeding puts women on an emotional roller coaster. The inevitable questions are "what did I do?" and "what can I do now?"

The history of active treatment of threatened miscarriage provides a cautionary tale. Interest in treatment of miscarriage led to the use of thalidomide and diethylstilbestrol with disastrous consequences. When I trained, these experiences greatly influenced our approach to "first, do no harm" and avoid any medical treatments for threatened abortion. Since most first trimester loss results from genetic abnormalities not likely to benefit from medical therapy, this approach makes sense. Still, many clinicians seem pressed to offer some sort of treatment. Given that high levels of the natural steroid progesterone occur in pregnancy, and that progesterone levels drop in women experiencing pregnancy loss, progesterone replacement has emerged as an active treatment.

The group led by Coomarasamy has made major contributions to the science of management of early pregnancy loss. These investigators have designed and conducted high-quality randomized, controlled trials to evaluate whether progesterone supplementation improves outcomes in women at risk for miscarriage. They first addressed the important question of recurrent pregnancy loss by randomizing women with a history of three or more unexplained first trimester losses to receive 400 mg of micronized progesterone or placebo capsules placed in the vagina twice daily as soon as a pregnancy test became positive. They randomized 836 women (404 progesterone, 432 placebo) and found no difference between groups in the primary outcome of live birth rate beyond 24 weeks estimated gestational age (65.8% progesterone, 63.3% placebo; RR, 1.04; 95% CI, 0.94-1.15) or any of the secondary outcomes. These data provide a convincing argument against the use of progesterone as a prophylactic treatment for recurrent miscarriage.

In this study, Coomarasamy et al evaluated the same approach for women experiencing a symptomatic threatened abortion. The authors used ultrasound to exclude pregnancies with predictable outcomes: an absent fetal pole or evidence of a fetal pole > 7 mm with no fetal heart activity. They also excluded women with serious hemorrhage. The resulting evaluation group reflects symptomatic women best managed expectantly in the setting of desired pregnancy. The demonstration that supplemental progesterone did not reduce the risk of pregnancy loss provides strong evidence against treatment. Although there was no evidence of harm, the treatment involves cost and inconvenience. I also worry that women with imperfect adherence to a twice-daily treatment schedule might blame themselves if the pregnancy ultimately fails. Nothing good comes from prescribing progesterone as a preventive measure or a treatment for threatened miscarriage. Since it feels good to do something, it is better to prescribe chicken soup.

A number of DNA sequencing approaches now are being pushed for better diagnosis of genetic causes of early

pregnancy loss. In my opinion, these represent an enormous waste of resources. At our institution, the lab charges patients about $300 to "hold" the specimen. If insurance will pay, the fee is refunded. If insurance does not pay, and the patient does not self-pay (about $1,500) to complete the test, the deposit is lost.

Diagnosis is not treatment and does not improve outcomes unless it informs future actions. I believe we need to go back to the basics. Women experiencing recurrent pregnancy loss deserve compassion and encouragement, not unnecessary interventions and tests. The $300 for genetic testing is better spent on a weekend at the coast and a romantic dinner. ■

REFERENCES

1. Coomarasamy A, Williams H, Rai R. Progesterone in women with recurrent miscarriages. *N Engl J Med* 2016;374:894.
2. Donaghay M, Lessey BA. Uterine receptivity: Alterations associated with benign gynecological disease. *Semin Reprod Med* 2007;25:461-475.
3. Hodes-Wertz B, Grifo J, Ghadir S, et al. Idiopathic recurrent miscarriage is caused mostly by aneuploid embryos. *Fertil Steril* 2012;98:675-680.

Help Us Help You

We'd love to hear from you how we can do better! Please take five minutes to complete our annual user survey (https://bit.ly/2Xe4NjV), and we'll enter you to win a year-long subscription to Relias Media.

CME/CE QUESTIONS

1. **A 28-year-old G2P1011 is found to have a 3 cm squamous cell carcinoma of the cervix. Her PET CT was negative. What stage is she per the new 2018 FIGO staging?**
   a. Stage IA2
   b. Stage IB1
   c. Stage IB2
   d. Stage IB3
2. **Which of the following best characterizes sleep reduction therapy (SRT) as a behavioral intervention?**
   a. SRT is an easily accessible and available intervention in most office-based settings.
   b. SRT has not shown an effect on rumination, worry, or catastrophizing a poor night's sleep.
   c. Sleep hygiene interventions include SRT.
   d. SRT involves restricting a patient's time in bed to increase consolidated sleep.
3. **In the study by Lissauer et al, sharp curettage alone was used for uterine evacuation in what percentage of cases?**
   a. 30%
   b. 50%
   c. 70%
   d. 90%
4. **Compared to placebo, women experiencing first trimester bleeding randomized to treatment with twice-daily vaginal micronized progesterone experienced which of the following?**
   a. No difference in the incidence of live birth after 34 weeks.
   b. A 20% decrease in the risk of pregnancy loss before 12 weeks.
   c. A cessation of vaginal bleeding within 48 hours.
   d. A two-fold increase in the risk of serious intrauterine infection.

CME/CE 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.

[IN FUTURE ISSUES]

Polycystic Ovary Syndrome: Etiology Likely Heterogeneous?

A Conservative Option for Fecal Incontinence