RELIAS MEDIA

Vol. 36, Issue 5, September 2019
ReliasMedia.com

OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Should Obesity Be a Contraindication to Postpartum Tubal Sterilization?

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 retrospective cohort study of 279 women undergoing postpartum partial salpingectomy after vaginal delivery, the mean operative time for women with a BMI ≥ 30 kg/m^2 was only 5.5 minutes longer than the time for women with a BMI < 30 kg/m^2.

SOURCE: Deshpande NA, et al. Relationship between body mass index and operative time in women receiving immediate postpartum tubal ligation. *Contraception* 2019;100:106-110.

This was a retrospective cohort study conducted at the University of Pennsylvania between April 2013 and March 2017 of all women who underwent postpartum tubal ligation following a vaginal delivery. All procedures utilized the Pomeroy or Parkland method; no bilateral salpingectomies were performed. Women were excluded if their body mass index (BMI) was not documented at hospital admission for the delivery or if there was no operative or anesthesia record in the chart. The authors used the electronic medical record to abstract data on demographics, clinical characteristics, and the surgical procedure. The primary outcome was operative time, defined as incision time to closure time. The relationship between BMI and operative time was evaluated with multivariable linear regression adjusting for parity, prior abdominal surgery, age, time from vaginal delivery to postpartum tubal ligation (hours), quarter of the academic year, and patient race. The authors performed a secondary analysis evaluating a non-inferiority margin of 10 minutes operative time between women with a BMI ≥ 30 kg/m^2 and a BMI < 30 kg/m^2 and women with a BMI ≥ 40 kg/m^2 and a BMI < 40 kg/m^2.

A total of 279 women were included in the study with the following distribution: BMI < 25 kg/m^2 (n = 29, 10%), BMI 25-29.9 kg/m^2 (n = 79, 28%), BMI 30-34.9 kg/m^2 (n = 103, 37%), BMI 35-39.9 kg/m^2 (n = 44, 16%), and BMI ≥ 40 kg/m^2 (n = 24, 9%). The majority of procedures were performed on postpartum day 0 (71.3%), and all attempted procedures were completed. The mean

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; Editor Jason Schneider; Editorial Group Manager Leslie Coplin; 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 Editor **Jason Schneider** at jschneider@relias.com

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.

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.

total operative time was 46.1 minutes (95% confidence interval [CI], 43.7-48.6) for women with a BMI ≥ 30 kg/m^2 and 40.6 minutes (95% CI, 37.9-43.4) for women with a BMI < 30 kg/m^2. This difference was within the pre-specified 10-minute noninferiority margin (P < 0.01). There was a 35-second increase in procedure time per unit of BMI. Women with a BMI ≥ 40 kg/m^2 had a mean operative time of 48.2 minutes (95% CI, 42.3-54.0). Complication rates did not differ across BMI categories. The first and second academic quarters were associated with increased operative time and when controlled for, the difference in operative time between women with BMI ≥ 30 kg/m^2 and BMI < 30 kg/m^2 was reduced to 4.1 minutes (P > 0.01).

■ COMMENTARY

In the United States, postpartum partial salpingectomy is performed after 8-9% of all deliveries, representing half of all permanent contraceptive procedures.[1] A recent U.S. study from 2008 to 2013 estimated postpartum permanent contraception rates to be 683-711 per 10,000 deliveries.[2] The procedure was more common in women 35 years of age and older and during cesarean compared to vaginal delivery. Overall, postpartum tubal sterilization is convenient for the mother since she is already in the hospital for the delivery. The advantages of doing the procedure immediately postpartum are that existing epidural anesthesia potentially can be used and the woman does not have to restrict food and drink in preparation for the procedure another day.[3]

Despite the fact that the American College of Obstetricians and Gynecologists (ACOG) considers postpartum permanent contraception to be an "urgent" not "elective" procedure given the risks of unintended pregnancy in the future,[4] many hospitals do not prioritize postpartum requests.[5] It is estimated that approximately half of women who desire postpartum permanent contraception do not obtain the procedure for logistical issues, obstetric complications, medical reasons, or lack of a correctly signed federal sterilization consent form dated between 30 days and 180 days prior to the procedure if they have Medicaid insurance.[5-8]

One reason women may not undergo their desired procedure is obesity.[7] This may be due to the surgeon's reluctance to take on what he or she perceives to be a more difficult case for fear of not being able to complete the procedure or an increased risk of complications. Therefore, the authors of this study wanted to assess the relationship between BMI and operative time, using operative time as a proxy for the difficulty of the procedure. They found a difference in mean operative time of 5.5 minutes between the two groups (BMI < 30 kg/m^2 and BMI ≥ 30 kg/m^2), which was not clinically significant in their opinion. The authors reported that the procedures were performed by a diverse group of residents, fellows, and attendings at the hospital, which increases generalizability.

The limitations of the study included the fact that, as a retrospective study, there was no way to know how patients were selected for postpartum tubal ligation. It could be that only the most favorable patients were taken to surgery based on fundal height and abdominal examination. It is also unknown how many obese patients were denied procedures. Additionally, there is no information from the surgeon regarding their perception of the difficulty of the procedure. The use of operative time as a proxy measure of surgical complexity has certain flaws. Nevertheless, the findings are reassuring, and, anecdotally, we could do more to expand access to these procedures for obese women. We also should make sure that women who desire postpartum sterilization have a backup plan in case the sterilization does not happen. Offering immediate postpartum IUD or contraceptive implant insertion can provide an equally effective alternative if the desired sterilization is not completed. In addition, ACOG suggests working with hospital delivery units and obstetric anesthesia personnel to make the procedure a priority.[4] ■

REFERENCES

1. Chan LM, Westhoff CL. Tubal sterilization trends in the United States. *Fertil Steril* 2010;94:1-6.
2. Moniz MH, et al. Inpatient postpartum long-acting reversible contraception and sterilization in the United States, 2008-2013. *Obstet Gynecol* 2017;129:1078-1085.
3. Goodman EJ, Dumas SD. The rate of successful reactivation of labor epidural catheters for postpartum tubal ligation surgery. *Reg Anesth Pain Med* 1998;23:258-261.
4. American College of Obstetricians and Gynecologists. Committee opinion no. 530: Access to postpartum sterilization. *Obstet Gynecol* 2012;120:212-215.
5. Zite N, et al. Barriers to obtaining a desired postpartum tubal sterilization. *Contraception* 2006;73:404-407.
6. Thurman AR, et al. Unfulfilled postpartum sterilization requests. *J Reprod Med* 2009;54:467-472.
7. Boardman LA, et al. Barriers to completion of desired postpartum sterilization. *R I Med J* 2013;96:32-34.
8. Wolfe KK, et al. An updated assessment of postpartum sterilization fulfillment after vaginal delivery. *Contraception* 2017;96:41-46.

ABSTRACT & COMMENTARY

Patients' Views on Adverse Events Following Pelvic Reconstructive Surgery

By Chiara Ghetti, MD

Associate Professor, Obstetrics and Gynecology, Division of Female Pelvic Medicine and Reconstructive Surgery, Washington University School of Medicine, St. Louis, MO

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

SYNOPSIS: Patients see poor functional outcomes as severe adverse events following pelvic floor surgery.

SOURCE: Dunivan GC, et al. A longitudinal qualitative evaluation of patient perspectives of adverse events after pelvic reconstructive surgery. *Int Urogynecol J* 2019 Jun 11. doi: 10.1007/s00192-019-03998-7. [Epub ahead of print].

The objective of this study was to describe how patients view adverse events related to pelvic floor surgery and how these perspectives change over the perioperative period. This was a mixed method study that utilized semi-structured patient interviews and patient surveys. All English-speaking women planning to have pelvic floor surgery (urinary incontinence and/or prolapse surgery) were eligible to participate. Each subject completed three separate semi-structured interviews (one preoperatively up to 12 weeks prior to surgery, one six to eight weeks postoperatively, and the third at three months postoperatively). All participants received standard preoperative counseling prior to surgery. At each interview, participants were asked to list anticipated or experienced adverse events. In addition, participants were given a list of events providers categorize as adverse events, and at follow-up interviews were provided their personal initial adverse event list and asked to reflect on any changes. Interviews were audiotaped, transcribed, coded, and analyzed using qualitative iterative process.

Twenty subjects participated in the study. Each subject underwent surgery and completed three interviews. Participants had a mean age of 44 years, half were non-Hispanic white, one-quarter were Hispanic, and 25% were American Indian. Seventy-five percent had a college degree or higher. Subjects underwent a range of major to minor pelvic floor-related procedures including mid-urethral slings, neuromodulation, hysterectomy, and vaginal native tissue repairs.

Subjects' perceptions of AEs evolved over time. In pre-operative interviews, women listed surgery-related concerns, such as surgical or anesthetic complications, pain, and immediate post-op bladder drainage, as adverse events. At the initial post-operative interview, subjects' concerns related primarily to functional outcomes, in particular activities of daily living, sexuality, and symptoms relief. At the six-month interview, subjects identified failure to achieve functional goals of surgery, persistent incontinence, and sexual dysfunction as severe adverse events. Women voiced the need to receive additional information regarding what to expect during the perioperative period as well as long-term success and impact of surgery.

■ COMMENTARY

The main finding of this study is that women's concept of adverse events changes over time and that the failure to achieve their expected functional goals after surgery represents severe adverse events. This study builds on prior work by authors.[1] Dunivan et al completed focus groups of women preoperatively, within three months postoperatively, and one to five years postoperatively and reported on women's perspective of adverse events. However, the current study followed subjects longitudinally over preoperative and postoperative time points and therefore explores the evolution of women's perspectives over time.

Although this study included a small sample, each subject underwent three individual interviews and thematic saturation was achieved. The authors reported that women desired additional information regarding the perioperative expectations and long-term success and effect of surgery. Presenting data separately for subjects undergoing minor vs. major procedures or by indication for surgery could have strengthened the study. In addition, detailed information on standard perioperative counseling, the consent process, and postoperative information provided to subjects would allow readers to better understand findings and consider implementation into clinical practice.

This study confirms findings of prior studies and the importance of functional outcomes for women undergoing pelvic floor surgery in a diverse population. Researchers and clinicians are fortunate to have several validated condition-specific quality of life measures pertinent to the field of female pelvic medicine and reconstructive surgery.[2,3,4] Qualitative studies such as this can provide significant insight into the patient perspective that cannot be gleaned by quantitative measures alone. This study highlights the importance of patient-surgeon communication, thorough patient counseling with clarifying, and setting of clear expectations for patients undergoing reconstructive pelvic surgery. ■

REFERENCES

1. Dunivan GC, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Pelvic Floor Disorders Network.

Gaining the patient perspective on pelvic floor disorders' surgical adverse events. *Am J Obstet Gynecol* 2019;220:185.e1-185.e10.
2. Barber MD, et al. Psychometric evaluation of 2 comprehensive condition-specific quality of life instruments for women with pelvic floor disorders. *Am J Obstet Gynecol* 2001;185:1388-1395.
3. Rogers RG, et al. A new measure of sexual function in women with pelvic floor disorders (PFD): The Pelvic Organ Prolapse/Incontinence Sexual Questionnaire, IUGA-Revised (PISQ-IR). *Int Urogynecol J* 2013;24:1091-103.
4. Lowder JL, et al. Body image in the Pelvic Organ Prolapse Questionnaire: development and validation. *Am J Obstet Gynecol* 2014;211:174.e1-9.

ABSTRACT & COMMENTARY

Identify and Treat Urologic Injuries at Hysterectomy to Reduce Fistulas

By Robert W. Rebar, MD

Professor, Department of Obstetrics and Gynecology, Western Michigan University Homer Stryker M.D. School of Medicine, Kalamazoo

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

SYNOPSIS: In a large population-based cohort study, genitourinary fistulas were increased significantly if ureteral and/or bladder injuries were not identified and treated at the time of hysterectomy.

SOURCE: Dallas KB, et al. Urologic injury and fistula after hysterectomy for benign indications. *Obstet Gynecol* 2019;134:241-249.

Despite the fact that more than 600,000 hysterectomies are performed in the United States each year, information about genitourinary injury after hysterectomy has been limited. We can now add knowledge gleaned from a population-based cohort study of urologic injuries suffered by all women (except for those seen in Veterans' Administration hospitals) undergoing hysterectomy for benign indications. Using statewide data from California between the years of 2005 to 2011, information from this population aids in our understanding of the incidence and risk factors for the effect of urinary injuries on subsequent fistula formation.

The authors included 296,130 women (mean age 47.4 years) undergoing hysterectomy in the study. Open abdominal hysterectomy was performed in 36.9% of the women, laparoscopic hysterectomy performed in 26.1%, vaginal hysterectomy performed in 21.2%, and a laparoscopic-assisted vaginal approach was used in 12.3%. Fully 54.0% of the hysterectomies were performed for leiomyomas, 18.8% for endometriosis, and 29.3% for uterine bleeding, with 24% having multiple reasons for surgery. In addition to hysterectomy, 16.7% also underwent pelvic organ prolapse repair and 2.9% underwent a concomitant incontinence procedure.

Approximately 1.8% (5,455) had at least one genitourinary injury, with 2,817 (1.0%) ureteral injuries, 2,058 (0.7%) bladder injuries, and 834 (0.3%) genitourinary fistulas being identified. Overall, 86.2% of these injuries were identified (with 76.4% identified and repaired at time of surgery) and 13.8% were unidentified until they presented subsequently with a fistula. Fistula formation was markedly reduced if the injury was identified immediately for both ureteral (0.7% vs. 3.4%; odds ratio [OR], 0.28; 95% confidence interval [CI], 0.14-0.57) and bladder (2.5% vs. 6.5%; OR, 0.37; 95% CI, 0.16-0.83) injuries. The rate of fistula formation for those suffering concomitant ureteral and bladder injuries was twice as high when they were identified immediately and more than nine times higher for those identified later (2.7% vs. 25.0%), but the numbers were quite small in this latter group. Indwelling stent placement as the only means of treating a ureteral injury identified at hysterectomy was successful in preventing any future operative repair in 99% of cases; if identified after surgery, stent placement was successful less than 40% of the time.

Several factors altered the risk of injury. Genitourinary injuries at the time of hysterectomy were slightly but significantly more common in those undergoing open abdominal hysterectomy (2.0%) compared with a vaginal (1.5%) or a laparoscopic (1.7%) approach. Injuries were also significantly more common in cases undergoing concomitant pelvic organ prolapse repair (2.1% vs. 1.8%), an incontinence procedure (2.7% vs. 1.8%), or mesh use for prolapse repair (3.1% vs. 1.8%). There was a higher rate of injury in women converted from another approach to laparotomy (5.2% vs. 1.8%). Genitourinary injuries were also more common in women with a diagnosis of endometriosis (2.3%) compared with leiomyomas (1.8%) or abnormal uterine bleeding (1.7%). Injuries were more common in facilities in the bottom quartile of overall hysterectomy surgical volume (2.6%) compared to the rest of the cohort (1.8%).

■ COMMENTARY

It has been estimated that as many as one-third of women in the United States undergo hysterectomy by the age of 60 years.[1] Thus, as the authors noted in the introduction, the potential burden of genitourinary complications following hysterectomy is not trivial. It is for just this reason that I elected to review this study.

Most (76.4%), but not all, of the urinary injuries were identified and repaired at the time of surgery. However, 18.6% of the ureteral injuries and 5.5% of the bladder injuries were not identified until later. Immediate identification and repair significantly reduced the odds of developing a genitourinary fistula — and that is one of the major findings of this study. Thus, it is critical to identify such injuries, regardless of the surgical approach to the hysterectomy. The authors suggested that cystoscopy, although not 100% sensitive, should be considered as a part of every hysterectomy and seem to accept a study indicating that cystoscopy can reduce the incidence of urinary tract injuries.[2] In contrast, the AAGL in its 2012 practice guideline concluded that the low level of evidence and the limited data existing precluded recommending that cystoscopy should be performed with every laparoscopic hysterectomy.[3] The present cohort study reinforces the need for a large multicenter randomized trial to address the possible value of cystoscopy.

Dallas et al also found that simply placing ureteral stents at the time of hysterectomy significantly reduced the need for later ureteral repair surgery. This observation leads to the conclusion that stents should be used liberally whenever ureteral damage or even "kinking" is suspected. In contrast, later placement of stents is much less effective.

Not surprisingly, they also indicated the need to be particularly mindful of careful repair in women suffering both ureteral and bladder injuries at hysterectomy, as these women particularly are prone to develop later fistulas. The risk of fistula formation appeared increased if these injuries were not identified at the time of surgery, but here the numbers were quite small.

The authors also provided additional information about specific risk factors predisposing to fistula formation. Laparotomy was associated with increased risk compared to vaginal, laparoscopic, or laparoscopically assisted vaginal hysterectomy. Addition of an incontinence procedure or the use of mesh also increased the risk. With regard to the indication for hysterectomy, a diagnosis of endometriosis significantly increased the risk compared to hysterectomies performed for either leiomyomas or uterine bleeding. The authors also reported that urinary tract injuries were significantly increased in Asian women compared to white, black, Hispanic, and other women; they hypothesized that this may be because Asian women have the highest rate of hysterectomy performed for endometriosis.[4] Perhaps not surprisingly, the risk of injury was increased in facilities where hysterectomies are performed only rarely.

Despite the significance of these risk factors, the authors offered a note of caution: Most of the effect sizes of the statistically significant associations reported in this large cohort study fall within the range of potential bias (i.e., an odds ratio of > 1.0 or < 2.0 or < 1.0 and > 0.3. We frequently forget that associations do not prove causality. Our liberal reliance on "big data" today can lead to incorrect conclusions and to the promulgation of false beliefs. Thus, these findings should be viewed cautiously until such time as they are confirmed by prospective studies.

Although the cautions raised by the authors themselves are legitimate, all surgeons need to consider the findings of this study as they perform hysterectomies. They constitute the best data we have to date. The authors believed their findings support the liberal use of cystoscopy at the time of hysterectomy, with a low threshold for ureteral stent placement in individuals with suspected ureteral injury to reduce the risk of subsequent fistula development. It is difficult to argue with those conclusions. Cystoscopy is no more difficult to perform than is hysteroscopy and arguably should be mastered by everyone completing a residency in obstetrics and gynecology. Whether cystoscopy is always necessary with hysterectomy can be debated, but the need for surgeons to be careful not to damage the urinary tract during hysterectomy cannot be. Erring on the side of caution is seldom wrong. ■

REFERENCES

1. Wright JD, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. *Obstet Gynecol* 2013;122:233-241.
2. Chi AM, et al. Universal cystoscopy after benign hysterectomy: examining the effects of an institutional policy. *Obstet Gynecol* 2016;127:369-375.
3. AAGL Practice Report: Practice guidelines for intraoperative cystoscopy in laparoscopic hysterectomy. *J Minim Invasive Gynecol* 2012;19:407-411.
4. Jacoby VL, et al. Racial and ethnic disparities in benign gynecologic conditions and associated surgeries. *Am J Obstet Gynecol* 2010;202:514-521.

SPECIAL FEATURE

Hormonal Contraception and HIV: Does DMPA Increase Risk of Transmission?

By Jeffrey T. Jensen, MD, MPH, Editor

SOURCE: Ahmed K, et al. HIV incidence among women using intramuscular depot medroxyprogesterone acetate, a copper intrauterine device, or a levonorgestrel implant for contraception: A randomised, multicentre, open-label trial. *Lancet* 2019;394:303-313.

All people deserve satisfying and safe sexual lives free from coercion, bias, unwanted pregnancy, and the risks of sexually transmitted infection (STI). In our modern era, human immunodeficiency virus (HIV) represents the STI of greatest consequence if acquired. Therefore, clinicians, scientists, public health officials, and governments

have exerted considerable effort to stem the HIV epidemic. Since most heterosexual acts occur in a setting where pregnancy is not desired, the question of whether contraceptive methods modify the risk of HIV transmission has become a major area of interest in the fields of infectious diseases and family planning. In this special feature, I will review the evidence for the effect of hormonal and nonhormonal methods on HIV risk.

What current contraceptive methods offer protection from HIV? Only male and female condoms are FDA-approved for the indication of prevention of STIs including HIV. The term "universal condom" has been advocated to replace female condom, as many couples use female condoms for anal sex. Both the FDA (https://www.fda.gov/patients/hiv-prevention/condoms-and-sexually-transmitted-diseases) and CDC (https://www.cdc.gov/condomeffectiveness/) present information of their web pages that include instructions for the use of both male and female condoms. Although condoms are not 100% effective, strong evidence supports their use for risk reduction.[1] Vaginal diaphragms and cervical caps have not been shown to reduce the risk of HIV transmission.

What are MPTs? The term multipurpose prevention technology (MPT) refers to a class of products with dual activity to prevent both pregnancy and STIs (including HIV). While several approaches are in clinical trials, none have received regulatory approval. The most promising methods in clinical trials use vaginal MPT rings that deliver an antiretroviral (ARV) and a progestin [tenofovir/levonorgestrel (CONRAD: ClinicalTrials.gov Identifier: NCT03762382); dapivirine/levonorgestrel (International Partnership for Microbicides, NCT02855346)].

Vaginal gels that rely on non-hormonal approaches are also in development, but seem less promising due to higher failure rates likely for both pregnancy and HIV prevention. The NICHD Contraceptive Clinical Trials Network evaluated the contraceptive activity of C31G gel, a surfactant comprised of myristamine oxide and cetyl betaine with potent antiretroviral properties in vitro, in a randomized blinded study using a standard 4% nonoxyl-9 (N-9) based gel as a comparator.[2] Although this study demonstrated non-inferiority of C31G to N-9 (12-month pregnancy probabilities of 20% and 14% respectively), this was not an improvement over the expected high pregnancy rate. Not surprising, a concurrent study evaluating use of C31G for HIV prevention in Africa found no benefit.[3] Vaginal gels do not seem an effective answer for either pregnancy or HIV prevention.

Other concepts for MPTs that have not yet moved to clinical trials include oral pills, implants, and IUDs. Of these, the LARC methods hold promise, yet have many challenges. Implants have limited real estate to accommodate loading of sufficient drug to allow effective release levels of both contraceptive hormones and antiretroviral agents. While pairing a copper IUD with an ARV is an attractive idea, the amount of drug delivery space available on an IUD frame to permit multiyear use is even more limited. We recognize that failure rates for oral contraceptives in typical use (~8%) are much higher than in clinical trials (1-2%). However, combined pills actually work fairly well despite poor compliance, as a follicle must both develop and ovulate. How noncompliance would affect HIV risk would depend on the pharmacokinetics of the various ARVs.

Do spermicides increase the risk of HIV or other STI acquisition? Wilkinson and colleagues completed a systematic review of randomized trials that evaluated the effectiveness of vaginally administered nonoxynol-9 (N-9) for the prevention of HIV and other sexually transmitted infections (STIs) in women.[4] They found no statistically significant reduction in risk of HIV (relative risk [RR], 1.1; 95% confidence interval [CI], 0.88-1.42), gonorrhea (RR, 0.91; CI, 0.67-1.24), chlamydia (RR, 0.88; CI, 0.77-1.01), cervical infection (RR, 1·01; CI, 0.84-1.22), trichomoniasis (RR, 0.84; CI, 0.69-1.02), bacterial vaginosis (RR, 0.88; CI, 0.74-1.04), or candidiasis (RR, 0.97; CI, 0.84-1.12) comparing N-9 to placebo or no treatment groups. While N-9 use resulted in a significantly higher risk of genital lesions (RR, 1.18; CI, 1.02-1.36), the magnitude of this difference is very small. Nonetheless, the significance of genital lesions in increasing HIV acquisition has been documented in other studies, with herpes lesions and the presence of bacterial vaginosis large contributors to risk.[5,6] In 2007, the U.S. FDA issued a statement requiring labeling for all N-9 products warning consumers that they do not protect against HIV or STDs, and that N-9 can irritate the vagina and rectum and may increase the risk of HIV acquisition (https://www.federalregister.gov/d/07-6111/p-3).

In anticipation of future regulatory action that might lead to the withdrawal of N-9 from the market, other spermicides are in development. N-9 is a detergent-based surfactant, so the epithelial damage is not surprising. In contrast, products such as Acidform (Amphora, Evofem, San Diego), an acid-buffering gel that acts by creating an acidic vaginal environment hostile to viruses, bacteria, and to sperm, has been shown to have less vaginal irritation compared to N-9.[7] A phase III RCT comparing N-9 and Acidform has been completed, but results have not been published (NCT01306331). In a separate RCT, Evofem is evaluating Amphora™ to reduce risk of chlamydia acquisition (NCT03107377). This product has not been evaluated for HIV risk reduction.

Does hormonal contraception increase the risk of HIV acquisition? For several years, the question of whether hormonal contraception increases the risk of HIV acquisition has been a hot topic in the family planning and public health communities. Most of the concern has focused on the use of injectable depot intramuscular medroxyprogesterone acetate (DMPA-IM), one of the most popular modern methods in Africa, a region with a high burden of HIV and unintended pregnancy. Observational studies support an increased risk with DMPA use compared to other hormonal methods including other injectables.[8] However, a number of methodologic limitations and

confounders, principally decreased condom use among women not using hormonal contraception,[9] limit interpretation of these observational studies.

What is the latest data on DMPA-IM and HIV risk? The overall importance of this topic ultimately pushed leading international investigators and funders to organize the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial Consortium to conduct a multicenter randomized, open label trial at freestanding research centers, university-affiliated research centers, and clinical sites providing reproductive health services in Eswatini (Swaziland), Kenya, South Africa, and Zambia. The investigators recruited sexually active, non-pregnant, HIV-seronegative women aged 16 to 35 years (with no medical contraindications to study medications) who desired effective contraception, reported not having used injectable, intrauterine, or implantable contraception for the previous six months, agreed to randomization to a study medication, and to use the assigned method for 18 months. At enrollment, women were randomized to receive either an intramuscular injection of DMPA 150 mg (DMPA-IM group), or placement of a CuT380Ag (copper IUD group) or the levonorgestrel 2 rod implant (LNG implant). Women returned for scheduled follow-up visits at one month (to assess initial contraceptive side-effects) and then every three months for a planned duration of 18 months. At each visit, participants underwent testing for HIV and other STIs, and pregnancy was assessed at the final visit. Enrollment began on Dec. 14, 2015 and follow-up concluded on Oct. 31, 2018.

The primary endpoint was incident HIV infection. To ensure accuracy, they assessed plasma samples from the enrollment visit for detectable HIV RNA, and excluded those with a baseline positive result from the analysis (modified intention-to-treat (ITT) population). Secondary outcomes included pregnancy, serious adverse events, adverse events resulting in method discontinuation, and method continuation. The sample size of 7,800 was selected to provide 80% power to detect a 50% increase in the hazard of HIV for each contraceptive method compared with each of the others (i.e., DMPA-IM vs. copper IUD, DMPA-IM vs. LNG implant, and copper IUD vs. LNG implant). They selected a 50% increase in HIV risk as a meaningful difference that would inform policy change. They assumed an underlying HIV incidence of 3.5/100 woman-years, and a minimum of 250 HIV acquisition events per pairwise comparison. For the primary outcome, they used a significance level of 0.04 (96% confidence intervals).

A total of 7,830 women enrolled, with 2,609 randomly assigned to the DMPA-IM group, 2,607 to the copper IUD group, and 2,613 to the LNG implant group with over 98% in all groups contributing to the primary analysis. More than 94% completed the full 18 months of follow-up, or were terminated early due to HIV acquisition. Most of the participants continued with use of the assigned method (DMPA-IM 93%, copper IUD 89%, LNG implant 94%).

Incident HIV infection occurred in 397 women (overall IR 3.81/100 woman-years met the pre-specified criteria), with no difference in the incidence rate between treatments: DMPA-IM 4.19/100 woman-years (3.54-4.94); Copper IUD 3.94 (3.31-4.66); LNG implant 3.31 (2.74-3.98). In the modified ITT population, the hazard ratios (HRs) for HIV acquisition were 1.04 (96% CI 0·82–1·33) comparing DMPA-IM with copper IUD, 1.23 (0.95-1.59) comparing DMPA-IM with LNG implant, and 1.18 (0.91-1.53) comparing copper IUD with LNG implant. As expected, the incidence of pregnancy was low; 0.61/100 woman-years in the DMPA-IM group, 1.11 in the copper IUD group, and 0.63 in the LNG implant group; the two hormonal methods had significantly lower pregnancy incidence than the copper IUD. Most (71%) of the pregnancies occurred after discontinuation of the randomly assigned method.

Evaluating ECHO and the risks of hormonal contraception. The ECHO study results were highly anticipated and attracted considerable attention when released on June 13, 2019. The study met the specified objective of ruling out a 50% increase risk of HIV acquisition in women using DMPA-IM, and the sample size provided sufficient power to exclude a 30% difference. Overall, these results provide reassuring news for clinicians, funders, governments, and most of all women using DMPA-IM in countries with a high prevalence of HIV.

The study does have important limitations. It did not evaluate the risk of using DMPA-IM to no contraception, to oral methods, or to other injectables. As pre-exposure prophylaxis regimens become more common, the results may have less relevance. Despite these limitations, the results provide good news of absence of an important impact of DMPA-IM on HIV acquisition risk. Research makes a difference in clinical practice, and in women's lives! ■

REFERENCES

1. Holmes KK, et al. Effectiveness of condoms in preventing sexually transmitted infections. *Bull World Health Organ* 2004;82:454-461.
2. Burke AE, et al. Contraceptive efficacy, acceptability, and safety of C31G and nonoxynol-9 spermicidal gels: a randomized controlled trial. *Obstet Gynecol* 2010;116:1265-1273.
3. Feldblum PJ, et al. SAVVY vaginal gel (C31G) for prevention of HIV infection: A randomized controlled trial in Nigeria. *PloS One* 2008;3:e1474-e.
4. Wilkinson D, et al. Nonoxynol-9 spermicide for prevention of vaginally acquired HIV and other sexually transmitted infections: Systematic review and meta-analysis of randomised controlled trials including more than 5000 women. *Lancet Infect Dis* 2002;2:613-617.
5. Wall KM, et al. Risk of heterosexual HIV transmission attributable to sexually transmitted infections and non-specific genital inflammation in Zambian discordant couples, 1994-2012. *Int J Epidemiol* 2017;46:1593-1606.
6. Masese L, et al. Changes in the contribution of genital tract infections to HIV acquisition among Kenyan high-risk women from 1993 to 2012. *AIDS* 2015;29:1077-1085.

7. Bayer LL, Jensen JT. ACIDFORM: A review of the evidence. *Contraception* 2014;90:11-18.
8. Polis CB, et al. An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *AIDS* 2016;30:2665-2683.
9. Heffron R, et al. Objective measurement of inaccurate condom use reporting among women using depot medroxyprogesterone acetate for contraception. *AIDS Behav* 2017;21:2173-2179.

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 yearlong subscription to Relias Media.

CME/CE QUESTIONS

1. **In the study by Deshpande et al, what was the difference in operative time between women with a BMI < 30 kg/m^2 and women with a BMI ≥ 30 kg/m^2 after controlling for academic quarter?**
   a. 3.5 minutes
   b. 4.1 minutes
   c. 5.5 minutes
   d. 6.2 minutes
2. **Based on the study by Dunivan et al, women undergoing pelvic floor reconstructive surgery:**
   a. have similar concepts of adverse events in the preoperative and postoperative periods.
   b. see failure to achieve desired functional outcomes as severe adverse events.
   c. always feel they have all the information they need to have surgery.
   d. only list long-term concerns as adverse events.
3. **Genitourinary fistulas are more likely to develop following:**
   a. laparoscopic hysterectomy.
   b. immediate repair when identified at the time of hysterectomy.
   c. hysterectomies for benign conditions at institutions where there are large volumes of such procedures.
   d. failure to identify urinary tract injuries at hysterectomy.
4. **Use of ureteral stents at hysterectomy:**
   a. may increase the incidence of genitourinary fistulas.
   b. is never indicated.
   c. frequently obviates the need for later surgery in women with urinary tract injuries at hysterectomy.
   d. is warranted in all hysterectomies.
5. **The ECHO study evaluated the risk of HIV acquisition in sexually active women randomized to use of either DMPA, LNG implants, or a copper IUD. The study demonstrated that:**
   a. DMPA increased the risk of HIV by 50% relative to the LNG implant.
   b. DMPA increased the risk of HIV by 50% relative to the copper IUD.
   c. the copper IUD increased the risk of HIV by 50% relative to both the implant and DMPA.
   d. no significant difference in the risk of HIV with DMPA compared to copper IUD or implant.

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]

Molecular Analysis of Endometrial Cancer Corresponds With Outcomes in Young Women