

OB/GYN Clinical [ALERT]

Evidence-based commentaries
on women's reproductive health

ABSTRACT & COMMENTARY

The Levonorgestrel IUD Is Similarly Effective as the Copper IUD for Emergency Contraception

By Katherine Rivlin, MD, MSc

Assistant Professor, Obstetrics and Gynecology, The Ohio State University Medical Center, Columbus, OH

SYNOPSIS: In this randomized, noninferiority trial among patients seeking emergency contraception after at least one episode of unprotected intercourse within five days of presentation, the levonorgestrel 52-mg intrauterine device (IUD) was noninferior to the copper T30A IUD at preventing pregnancy one month after IUD insertion. Adverse events between the two groups were similar.

SOURCE: Turok DK, Gero A, Simmons RG, et al. Levonorgestrel vs. copper intrauterine devices for emergency contraception. *N Engl J Med* 2021;384:335-344.

Although not approved by the Food and Drug Administration (FDA) for use as emergency contraception (EC), clinical evidence supports that the copper intrauterine device (Cu IUD) is a highly effective EC method, with postinsertion pregnancy rates lower than 0.1%.¹ This EC failure rate is markedly lower than the rate for the two currently FDA-approved methods of EC available in the United States — oral ulipristal acetate (UA) and oral levonorgestrel (LNG). UA had a 1.8% failure rate and LNG had a 2.6% failure rate in one randomized, non-inferiority trial.²

When choosing birth control methods, patients tend to choose the levonorgestrel intrauterine device (LNG IUD)

more frequently than they choose the Cu IUD because of the favorable bleeding profile.³ Because the intrauterine device (IUD) has the added benefit of providing continued birth control when used as EC, the lack of evidence around the LNG IUD for EC has limited patient options.

From 2016 to 2019, six family planning sites in Utah enrolled English- or Spanish-speaking patients between the ages of 18 and 35 years presenting for EC after unprotected sexual intercourse within the last five days. To enroll, patients had to desire IUD initiation and pregnancy prevention for at least one year, have a negative urine pregnancy test (UPT), have a history of regular menses, and know the date of their last menstrual

Financial Disclosure: Dr. Rebecca H. Allen (editor) reports that she receives grant/research support from Bayer, and is a consultant for Bayer, Mylan, and Merck. Dr. Sarah J. Betstadt (peer reviewer) reports that she is on the speakers bureau for Merck. All of the relevant financial relationships listed for these individuals have been mitigated. None of the remaining planners or authors for this educational activity have relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

[INSIDE]

Are Modern Intrauterine Devices Associated with Infertility?
page 3

The Cost-Effectiveness of HPV Vaccination for Adults Aged 30 to 45 Years
page 4

HIV Management During Pregnancy
page 6

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.

© 2021 Relias LLC. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

This is an educational publication designed to present scientific information and opinion to health professionals to stimulate thought and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@reliasmmedia.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.
Canada: Add 7% GST and \$30 shipping.
Elsewhere: Add \$30 shipping.

ACCREDITATION



JOINTLY ACCREDITED PROVIDER™
INTERPROFESSIONAL CONTINUING EDUCATION
In support of improving patient care, Relias LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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

2 ANCC contact hours will be awarded to participants who meet the criteria for successful completion.

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

period. The study excluded patients who were breastfeeding, had vaginal bleeding of unknown cause, currently were using a highly effective method of birth control (such as sterilization, an IUD, or a contraceptive implant), had an intrauterine infection in the last three months, had untreated *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in the last 30 days, had a copper allergy, had used oral EC in the last five days, or had a known uterine cavity anomaly. Notably, the study team did not exclude patients who reported unprotected intercourse more than five days prior to enrollment, or between six and 14 days before IUD placement.

After a negative UPT, participants were randomized to placement of either the 52-mg LNG IUD or the Cu T380A IUD in a 1:1 ratio. Although participants were unaware of the IUD device they received, providers were aware of the randomization group, given the different appearance and insertion methods of the two IUDs. All inserting providers were nurse practitioners and certified nurse midwives with prior IUD insertion experience.

All participants then were scheduled for one-month follow-up and provided with a home UPT to take the morning prior to their follow-up visit. Participants could report the results of their UPT via text message, through an online survey, or at their follow-up visit. At in-person follow-up, another UPT was performed and the participant was informed of the inserted IUD type. For participants with missing one-month pregnancy data, the study staff called and sent text messages, and if UPT results still were missing, the investigators reviewed the medical records for reports of pregnancy. All participants were contacted again at three months and six months after insertion to assess IUD discontinuation, satisfaction, pain and bleeding outcomes, and adverse events.

Of the 711 participants who underwent randomization, 355 received the LNG IUD and 356 received the Cu IUD. Participants reported an average of 2.1 acts of unprotected intercourse in the five days prior to IUD insertion. At one month following IUD insertion, there was only one pregnancy in the LNG IUD group (0.3%; confidence interval [CI], 0.01-1.7) and no pregnancies in the Cu IUD group (0%; CI, 0.9-1.8). The one pregnancy in the LNG IUD group occurred following an act of unprotected intercourse 48 hours prior to IUD insertion. Pregnancy dating was consistent with conception at that time, confirming an EC failure. The pregnancy

ended in a spontaneous abortion at 10 weeks. One Cu IUD expelled, and one participant in the LNG IUD group switched to the Cu IUD at her follow-up visit. Adverse events, such as self-reported bleeding, cramping, and other IUD-associated side effects, were similar between the two groups.

■ COMMENTARY

This randomized controlled trial supports that the LNG IUD can provide EC safely and effectively following unprotected intercourse up to five days before insertion. Because the LNG IUD met the noninferiority threshold compared to the Cu IUD, the hormonal IUD joins the Cu IUD as one of our most effective methods of EC, far exceeding the efficacy of the orally available options. These findings are all the more remarkable given that the study team included patients with acts of unprotected intercourse prior to the five-day window, or six to 14 days before IUD placement. Such patients particularly are at high risk of pregnancy, and, therefore, often are excluded from EC studies. Such exclusions are frustrating to clinicians, given how commonly patients presenting either for EC or for a scheduled IUD insertion report acts of unprotected intercourse both in and beyond the preceding five-day window.

The low pregnancy rates in this study pave the way to quick-starting IUDs for such patients, assuming a negative UPT. Providers should remember in such situations to counsel patients on the risks of IUD insertions in the setting of an undiagnosed luteal phase pregnancy. Although such pregnancies are rare, pregnancies that occur in IUD users are more likely to result in miscarriage, ectopic pregnancy, or preterm delivery, or to be complicated by infection.⁴

Currently, when counseling patients on EC options, providers must keep in mind that both oral LNG and UA may be less effective in patients who are overweight or obese, and that concurrent UA administration and hormonal contraception initiation may reduce the ability of the UA to delay ovulation.^{5,6} In this study, body mass index did not appear to affect EC efficacy, and with the ongoing contraception provided by the IUD, providers need not worry about when to initiate a new contraceptive method. In their Access to Emergency Contraceptive Committee Opinion, the American College of Obstetricians and Gynecologists (ACOG) reviews barriers to EC access. Although oral LNG is available over the counter, financial, education, and healthcare practice barriers make accessing all

EC methods challenging for patients. ACOG recommends counseling that the Cu IUD is the most effective method of EC, and that healthcare providers consider integrating Cu IUD provision into their clinical practices and allow same-day IUD insertion.⁷ This study supports adding the LNG IUD to the EC toolbox and similarly integrating its use into clinical practice.

In their limitations section, the authors described the selection bias that may have resulted from excluding those patients who declined to be randomized to an IUD type. We do not randomize patients to IUD types in clinical practice, but until now, the absence of the LNG IUD from our EC methods has, in effect, created a similar exclusion. Many of us have counseled patients on EC options, and although some might be interested in an IUD and compelled by its higher EC efficacy, many are turned off by the associated Cu IUD side effects. Therefore, as with all clinical trials, we must pay tribute to those research participants who agreed to randomization, because in doing so they have expanded EC options, allowing our offerings to be both more effective and more patient-centered. ■

REFERENCES

1. Cleland K, Zhu H, Goldstuck N, et al. The efficacy of intrauterine devices for emergency contraception: A systematic review of 35 years of experience. *Hum Reprod* 2012;27:1994-2000.
2. Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: A randomised non-inferiority trial and meta-analysis. *Lancet* 2010;375:555-562.
3. Peipert JF, Zhao Q, Allsworth JE, et al. Continuation and satisfaction of reversible contraception. *Obstet Gynecol* 2011;117:1105-1113.
4. Castano PM, Westhoff CL. Experience with same-day placement of the 52 mg levonorgestrel-releasing intrauterine system. *Am J Obstet Gynecol* 2020;222:S883.e1-S883.e6.
5. Glasier A, Cameron ST, Blithe D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception* 2011;84:363-367.
6. Brache V, Cochon L, Duijkers IJM, et al. A prospective, randomized, pharmacodynamic study of quick-starting a desogestrel progestin-only pill following ulipristal acetate for emergency contraception. *Hum Reprod* 2015;30:2785-2793.
7. [No authors listed]. Committee Opinion No. 707 summary: Access to emergency contraception. *Obstet Gynecol* 2017;130:251-252.

ABSTRACT & COMMENTARY

Are Modern Intrauterine Devices Associated with Infertility?

By Rebecca H. Allen, MD, MPH, Editor

SYNOPSIS: In this prospective cohort study of 461 women, there was no association between intrauterine device use and time to conception (hazard ratio, 1.25; 95% confidence interval, 0.99-1.58). However, past *Mycoplasma genitalium* infection was found to be associated with longer times to conception and lower conception rates by 12 months (68% vs. 80%, $P = 0.02$).

SOURCE: Peipert JF, Zhao Q, Schreiber C, et al. Intrauterine device use, sexually transmitted infections, and fertility: A prospective cohort study. *Am J Obstet Gynecol* 2021; Mar 10. doi: 10.1016/j.ajog.2021.03.011. [Online ahead of print].

In the past, intrauterine devices (IUDs) were falsely associated with pelvic inflammatory disease and infertility. The authors of this study sought to determine if there was an association between the types of IUDs used currently and time to conception, after controlling for sexually transmitted infections (STIs). This was a multicenter, prospective cohort study in the United States that enrolled patients discontinuing the IUD (either copper T380A or levonorgestrel 52 mg), subdermal etonogestrel implant, oral contraceptive pills, contraceptive patch or vaginal ring, depot medroxyprogesterone acetate (DMPA), or barrier method of contraception. Inclusion criteria were women who were age 18 to 35 years, English- or Spanish-speaking, desiring conception, sexually active with a male partner, and who had stopped contraception in the past 120 days. Patients were excluded if they were pregnant, sterile, had a history of infertility, or if they used DMPA in the past five months, since DMPA can be associated with a longer return to fertility. Data included reproductive and medical history, whether they had ever used an IUD in the past, and socioeconomic status. Vaginal swabs were collected for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*,

Mycoplasma genitalium, and *Trichomonas vaginalis*. Serum was collected for evidence of past infection of *C. trachomatis*, *M. genitalium*, and *T. vaginalis*. Participants were followed up by phone at six, 12, 18, and 24 months after enrollment to inquire about pregnancy, menstrual cycle regularity, and frequency and timing of intercourse.

The investigators enrolled 498 women and 461 had available follow-up data for at least six months. A total of 275 women (60%) had ever used an IUD before and most of those (> 85%) stopped using their IUD recently to attempt conception. Women who had used an IUD before were more likely to be slightly older (age 28.6 years vs. 27.5 years) and had a previous pregnancy (72% vs. 46%), but there were no other significant differences between the two groups in terms of body mass index (BMI), race, marital status, socioeconomic status, and history of *Chlamydia*, *Mycoplasma*, or *Trichomonas* infection.

The rates of current infection were *N. gonorrhoeae*, 0.2%; *C. trachomatis*, 4.3%; *T. vaginalis*, 7.6%; and *M. genitalium*, 9.1%. The rate of women with a past infection

with either *C. trachomatis*, *T. vaginalis*, or *M. genitalium* was 42.8%. The most frequent past infection was with *M. genitalium* (33%). The median time from stopping contraceptive use to conception was 6.1 months (95% confidence interval [CI], 4.9-7.3) and 76.5% of women conceived by 12 months. In a multivariable model, older age, lower socioeconomic status, nulligravidity, Black race, and positive serology for *M. genitalium* infection all were significantly associated with a longer time to conceive. Past *M. genitalium* infection was associated with lower conception rates by 12 months (68% vs. 80%, $P = 0.02$). Being married or having a cohabitating partner was associated with a shorter time to conceive (hazard ratio [HR], 1.59; 95% CI, 1.13-2.24). Previous use of an IUD did not meet the cutoff for significance (HR, 1.25; 95% CI, 0.99-1.58).

■ COMMENTARY

Since the episode of the Dalkon Shield IUD in the 1970s, providers and patients have had concerns that IUDs could be related to infertility.¹ The current IUDs on the market in the United States are safe and effective. A study by Hubacher et al in 2001 showed that the copper T380A was not associated with an increased risk of tubal factor infertility; rather, past infection with *C. trachomatis* was the culprit.² A recent analysis of the levonorgestrel 52-mg IUD (Liletta) showed normal conception rates after discontinuation. In this study, among 165 women who attempted to conceive, 142 (86.1%) were able to become pregnant within 12 months, with a median time to conception of 92 days. However, there have been no large, prospective cohort studies evaluating this issue. The current study adds more evidence that IUD use is not associated with longer times to conception compared to other contraceptive methods. The authors wisely evaluated the influence of STIs on time to conception and found that *M. genitalium* particularly was influential. Infertility rates (failure to conceive in one year) were higher than normal in this study, but the authors attributed that to the study population they enrolled, which had higher proportions of women of lower socioeconomic status and with higher rates of STIs. STIs are known to be a risk factor for tubal infertility.

The strengths of the study include a multicenter cohort followed prospectively, with 95% of conceptions dated accurately. The limitations are subject recall as to exactly when contraceptives were stopped and attempts to conceive started, and the inability to analyze duration of IUD use.

The role of *M. genitalium* in infertility is unclear and more research is needed. First discovered in the 1980s, *M. genitalium* is sexually transmitted, is known to cause non-gonococcal urethritis in men, and is associated with cervicitis and pelvic inflammatory disease (PID) in women.³ Screening for *M. genitalium* among asymptomatic individuals currently is not recommended in the United States. Nucleic acid amplification tests are available for testing. Nevertheless, at least in our practice, it is not a routine test that is performed in the evaluation of women with cervicitis and PID, and it is not available in our laboratory. The Centers for Disease Control and Prevention's Sexually Transmitted Disease Treatment Guidelines from 2015 added a discussion of *M. genitalium* to its "Emerging Issues" section.⁴ Currently, testing and treatment of *M. genitalium* is suggested for cases in which patients fail the standard treatments for cervicitis and PID and have persistent symptoms. The best antibiotic to target *M. genitalium* appears to be moxifloxacin 400 mg orally for seven to 14 days. It remains to be seen whether *M. genitalium* will be part of routine STI testing in the future. However, at the very least, we can say that IUDs do not cause infertility. ■

REFERENCES

1. Boonstra H, Duran V, Northington Gamble V, et al. The "boom and bust phenomenon": The hopes, dreams, and broken promises of the contraceptive revolution. *Contraception* 2000;61:9-25.
2. Hubacher D, Lara-Ricalde R, Taylor DJ, et al. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *N Engl J Med* 2001;345:561-567.
3. Carr BR, Thomas MA, Gangestad A, et al. Conception rates in women desiring pregnancy after levonorgestrel 52 mg intrauterine system (Liletta®) discontinuation. *Contraception* 2021;103:26-31.
4. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2015. *MMWR Recomm Rep* 2015;64:1-137.

ABSTRACT & COMMENTARY

The Cost-Effectiveness of HPV Vaccination for Adults Aged 30 to 45 Years

By Rebecca B. Perkins, MD, MSc

Associate Professor, Department of Obstetrics and Gynecology, Boston University School of Medicine/Boston Medical Center, Boston

SYNOPSIS: This study evaluated the cost-effectiveness of extending the upper age limit of human papillomavirus (HPV) vaccination to age 30 to 45 years using two independent HPV microsimulation models and found that vaccinating in this age group was not cost-effective.

SOURCE: Kim JJ, Simms KT, Killen J, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. *PLoS Med* 2021; Mar 11. doi.org/10.1371/journal.pmed.1003534

Human papillomavirus (HPV) vaccination is considered a powerful tool for cancer prevention. Clinical trials and long-term population-level follow-up studies have demonstrated decreases in precancers and cancers.¹⁻³ However, these findings are based largely on HPV vaccination in adolescence, prior to exposure to oncogenic HPV types. Recently, HPV vaccination was given Food and Drug Administration approval for use in adults aged 26 to 45 years, and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices recommended shared decision-making in this age group.⁴ The recommendation is based on study findings of a reduced composite endpoint for genital HPV disease among previously uninfected women, and notes that vaccination is not routinely recommended for this age group because of a lack of anticipated population-level benefit.⁴ The study by Kim et al describes the findings of two microsimulation models of HPV infection. In these models, which have been validated previously against several population-level datasets, individuals can move between states of no infection, infection, precancer, and cancer. HPV-related diseases in the models included cervical, anal, oropharyngeal, vulvar, vaginal, and penile cancers, as well as genital warts. The models compared the cost effectiveness of HPV vaccination in women through age 26 years and in men through age 21 years with vaccination through ages 30, 35, 40, and 45 years. Over a wide range of model assumptions and sensitivity analysis, HPV vaccination at older ages was not cost-effective. Incremental cost-effectiveness ratios (ICERs) ranged from \$315,700 to \$440,600 per quality-adjusted life year (QALY) gained, which exceeds the commonly accepted upper threshold of \$200,000 per QALY. This supports current CDC recommendations not to routinely recommend HPV vaccination for this age group.

■ COMMENTARY

This study adds important evidence to help providers, patients, and policymakers decide when to discuss, accept, and reimburse HPV vaccination among patients aged 27 to 45 years. The effectiveness of HPV vaccination at preventing precancer and cancers declines in older adolescence, with several studies demonstrating significant drops in effectiveness after age 18.^{5,6} The people to most likely to benefit from HPV vaccination are those who have not been exposed to oncogenic HPV before, and are likely to be exposed in the future. This applies broadly to adolescents who have not yet begun sexual activity. However, since most people acquire HPV within a few years of beginning intercourse, relatively few adults are in this category.⁷⁻⁹ Primary care clinicians have many health maintenance topics that have clear benefits and are cost-effective, including cancer screenings, flu vaccination, smoking cessation, and cardiovascular disease prevention, to discuss with patients.¹⁰ This study supports current guidelines not to discuss HPV vaccination routinely with adult patients.⁴ Guidance is limited regarding which patients may benefit from HPV vaccination as adults. The American College of Obstetricians and Gynecologists (ACOG) supports CDC recommendations against routine

vaccination. ACOG notes that the women most likely to benefit from vaccination include younger women, those not in committed monogamous relationships, and those recently diagnosed with sexually transmitted infections.¹¹ One specific population that may benefit from HPV vaccination is patients who have been treated for cervical intraepithelial neoplasia, since data indicate that post-treatment vaccination may be beneficial to prevent recurrence.^{12,13} One meta-analysis found a 64% reduction in recurrence of cervical intraepithelial neoplasia grade 2 or higher.¹⁴ A randomized controlled trial in the Netherlands currently is exploring this question, which should provide more definitive data on whether vaccination should be routinely recommended after precancer treatment.¹⁵ ■

REFERENCES

1. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-1927.
2. Guo F, Cofie LE, Berenson AB. Cervical cancer incidence in young U.S. females after human papillomavirus vaccine introduction. *Am J Prev Med* 2018;55:197-204.
3. Lei J, Ploner A, Elfström KM, et al. HPV vaccination and the risk of invasive cervical cancer. *N Engl J Med* 2020;383:1340-1348.
4. Meites E, Szilagyi PG, Chesson HW, et al. Human papillomavirus vaccination for adults: Updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 2019;68:698-702.
5. Castle PE, Xie X, Xue X, et al. Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. *Prev Med* 2019;118:44-50.
6. Gertig DM, Brotherton JM, Budd AC, et al. Impact of a population-based HPV vaccination program on cervical abnormalities: A data linkage study. *BMC Med* 2013;11:227.
7. Winer RL, Lee SK, Hughes JP, et al. Genital human papillomavirus infection: Incidence and risk factors in a cohort of female university students. *Am J Epidemiol* 2003;157:218-226.
8. Partridge JM, Hughes JP, Feng Q, et al. Genital human papillomavirus infection in men: Incidence and risk factors in a cohort of university students. *J Infect Dis* 2007;196:1128-1136.
9. Burchell AN, Winer RL, de Sanjose S, Franco EL. Chapter 6: Epidemiology and transmission dynamics of genital HPV infection. *Vaccine* 2006;24 Suppl 3:S3/S2-61.
10. U.S. Department of Health and Human Services. Healthy People 2030. <https://health.gov/healthypeople>
11. [No authors listed]. Human papillomavirus vaccination: ACOG Committee Opinion, Number 809. *Obstet Gynecol* 2020;136:e15-e21.
12. Petrillo M, Dessole M, Tinacci E, et al. Efficacy of HPV vaccination in women receiving LEEP for cervical dysplasia: A single institution's experience. *Vaccines (Basel)* 2020;8:45.
13. Bogani G, Raspagliesi F, Sopracordevole F, et al. Assessing the long-term role of vaccination against HPV after loop electrosurgical excision procedure (LEEP): A propensity-score matched comparison. *Vaccines (Basel)* 2020;8:717.
14. Lichter K, Krause D, Xu J, et al. Adjuvant human papillomavirus vaccine to reduce recurrent cervical dysplasia in unvaccinated women: A systematic review and meta-analysis. *Obstet Gynecol* 2020;135:1070-1083.
15. van de Laar RLO, Hofhuis W, Duijnhoven RG, et al. Adjuvant Vaccination against HPV in surgical treatment of Cervical Intra-epithelial Neoplasia (VACCIN study) a study protocol for a randomised controlled trial. *BMC Cancer* 2020;20:539.

HIV Management During Pregnancy

By *Ahizechukwu C. Eke, MD, PhD, MPH*

Assistant Professor in Maternal Fetal Medicine, Division of Maternal Fetal Medicine, Department of Gynecology & Obstetrics, Johns Hopkins University School of Medicine, Baltimore

Human immunodeficiency virus (HIV) infection during pregnancy carries a significant burden to healthcare systems, and continues to be of significant public health concern.¹ In 2019, approximately 1.3 million of the 16.7 million women living with HIV became pregnant, with about 6,000 to 7,000 of these women living in the United States.² It is pertinent to note that approximately 85% of these 1.3 million women who become pregnant yearly around the world receive antiretroviral therapy (ART).² HIV in pregnancy is important because more than 90% of pediatric HIV is acquired during pregnancy or at the time of birth (perinatal transmission).²

Prior to the advent and wide use of ART, perinatal transmission of HIV to fetuses was approximately 25% to 40%. However, with therapy, the rate of perinatal transmission of HIV decreases to approximately 2%.³ The Pediatric AIDS Clinical Trials Group (PACTG 076), conducted a randomized, placebo-controlled clinical trial and the first prospective study of any ART in pregnant women, which was published in the *New England Journal of Medicine* in 1994. The study demonstrated that zidovudine therapy decreased perinatal HIV transmission from 25.5% in the control group (without therapy) to 8.3% in the single-dose zidovudine arm — a reduction of approximately 66%.⁴ Since the PACTG 076 trial was published, several randomized clinical trials have demonstrated the efficacy and safety of ART for the management of HIV during pregnancy.⁵

In most countries around the world, and especially in the United States, universal screening for HIV is recommended. Pregnant women are screened for HIV antibodies during the initial prenatal visit and this is repeated once or twice in the third trimester, depending on risk factors and local protocols. A rapid HIV testing during labor in women of unknown status also can be performed.⁶ Prior to screening, pregnant women usually are informed about the importance of an HIV screening test, the benefits to the mother and fetus, and that the HIV test is part of the standard prenatal testing algorithm. Pregnant women then have a right to refuse HIV testing after appropriate counseling (the “opt-out approach” to HIV testing).

In women who test positive for HIV antibodies for the first time during pregnancy or in women who were living with HIV before becoming pregnant, additional prenatal laboratory work at the initial prenatal visit includes HIV viral-load and CD4 count to assess HIV disease progression; a comprehensive panel to assess hepatic and renal function; complete blood count for hemoglobin concentration, and

platelet and white blood cell counts to assess marrow suppression by combination ART; hepatitis A and C antibodies, and hepatitis B surface antigen; and tuberculosis testing. After initiation of ART, it is recommended to serially monitor the HIV viral load every two to four weeks until it becomes undetectable, then every trimester (if viral load remains undetectable), and at 34 to 37 weeks of gestation to determine the best mode of delivery and management of the neonate.⁶ An HIV genotype becomes pertinent if there is evidence of viral resistance (usually when the HIV viral load is > 500 copies/mL to 1,000 copies/mL despite optimal medication adherence and use of potent ART). In women who are taking abacavir, pharmacogenomic testing for the HLA-B*5701 gene is recommended, since women who test positive to the HLA-B*5701 gene are at a high risk for developing life-threatening reactions to abacavir. In pregnant women living with HIV who opt for diagnostic testing, such as chorionic villous sampling and amniocentesis for fetal aneuploidy testing and umbilical cord blood sampling for fetal anemia diagnosis and treatment, it is reasonable to perform these procedures if the viral load is undetectable. In women on therapy with protease inhibitors, it is reasonable to perform the oral glucose tolerance testing with the 50 mg glucose load earlier (24 weeks of gestation) because of the known association between protease inhibitors and impaired glucose tolerance.⁷

ART in the form of highly active antiretroviral therapy (HAART) is the cornerstone for prevention of perinatal transmission of HIV, as well as for the continued health of the pregnant mother living with HIV. The current recommended treatment is comprised of the use of two non-nucleotide reverse transcriptase inhibitors (NRTIs) in combination with HIV medications from another class.³ In the NRTI class, commonly used ART during pregnancy includes tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), lamivudine, and abacavir, in combination with non-nucleotide reverse transcriptase inhibitors (NNRTI), such as efavirenz and rilpivirine; integrase strand inhibitors (Isi), such as dolutegravir and raltegravir; and protease inhibitors, such as darunavir and atazanavir. Recently, the Department of Health and Human Services (DHHS) guidelines classified these ART regimens for use in pregnant women living with HIV as either “preferred” (tenofovir disoproxil fumarate/emtricitabine; abacavir/lamivudine; dolutegravir; darunavir; ritonavir-boosted darunavir; ritonavir-boosted atazanavir) or “alternative” regimens (ritonavir-boosted lopinavir; rilpivirine; efavirenz; zidovudine).⁸ The ideal ART to use during pregnancy would depend on several factors, including prior effective regimens, the potential for adverse maternal effects and teratogenicity with ART,

hepatitis B or C co-infection, and compliance issues. Data from the Botswana Tsepamo study initially raised concerns for the association between dolutegravir and neural tube defects, but recent data demonstrated low risk for neural tube defects with dolutegravir-based regimens.⁹ Because of potential drug-drug interactions between darunavir and raltegravir/dolutegravir and between darunavir and tenofovir/atazanavir, therapeutic drug monitoring for women taking these medications should be considered. In women with HIV/hepatitis B co-infection, fixed-dose combinations that include TDF/lamivudine/emtricitabine are preferred. These should be taken into consideration before starting ART in naïve (not having used ART previously) or experienced (having used ART previously) women living with HIV.¹⁰

Delivery considerations are critical in pregnant women living with HIV.⁶ Laboratory evaluation of viral load between 34 and 36 weeks of gestation is the single most important factor that determines the optimal mode of delivery.⁶ Vaginal delivery is recommended at term (37w0d to 39w6d) if the HIV RNA viral load at the time of delivery is < 1,000 copies/mL and cesarean delivery at 38w0d if HIV RNA viral load is > 1,000 copies/mL.⁶ Intrapartum, women with a viral load > 1,000 copies/mL should receive intravenous zidovudine (2 mg/kg loading dose over one hour, then 1 mg/kg/hr continuous infusion) over two hours prior to vaginal or cesarean delivery.⁶ For women with a viral load < 1,000 copies/mL, although cohort studies in pregnant women living with HIV with viral loads of 50 copies/mL to 999 copies/mL have demonstrated a 1% to 2% risk of perinatal transmission, it is a reasonable practice to consider intravenous zidovudine for three hours in all women (irrespective of viral load) at the time of delivery.⁶ In women diagnosed with HIV for the first time during pregnancy, it is recommended that they receive 200 mg of intravenous zidovudine over three hours, a 200 mg stat dose of nevirapine, 400 mg twice daily of raltegravir, and 150 mg twice daily of lamivudine prior to delivery. Intrauterine pressure catheters, fetal scalp electrodes, and fetal scalp blood sampling should be avoided if possible because of the potential risk for perinatal HIV transmission.⁶ Amniotomy has been shown to be safe, since prospective cohort studies in pregnant women living with HIV with a viral load < 50 copies/mL have demonstrated no significant differences in perinatal transmission rates in women with rupture of membranes less than four hours compared to those greater than four hours (0.12% vs. 0.14%).¹¹

After delivery, discussions about the use of safe and effective contraception in women living with HIV is important, since there are potential drug-drug interactions between some HIV medications and hormonal methods of contraception. Such drug-drug interactions can raise concerns for decreased contraceptive efficacy of hormonal contraception in women living with HIV and can increase the risk of unwanted pregnancies. The U.S. Medical Eligibility Criteria for Contraceptive Use provides guidelines for these drug-drug interactions for reference. There are no interactions between ART and intrauterine devices or depot

medroxyprogesterone acetate, so these options are safe and effective for women living with HIV.¹²

Breastfeeding also is an issue of critical importance for women living with HIV because approximately 15% of newborns born to women living with HIV will become infected if they breastfeed for approximately 18 months to two years.⁵ Because of the potential for HIV transmission to the neonate, breastfeeding currently is not recommended in neonates and infants of women living with HIV (even if the viral load remains undetectable) in developed countries. ■

Dr. Eke is a K23 Mentored Patient-Oriented Research Career Development Recipient from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH); and a recipient of the Johns Hopkins Center for AIDS Research (CFAR) faculty grant. The content is solely the responsibility of Dr. Eke and does not necessarily represent the official views of the NIH or CFAR.

REFERENCES

1. Eke AC, Olagunju A, Momper J, et al. Optimizing pharmacology studies in pregnant and lactating women using lessons from HIV: A consensus statement. *Clin Pharmacol Ther* 2020; Sep 15. doi: 10.1002/cpt.2048. [Online ahead of print].
2. World Health Organization. HIV/AIDS. Published Nov. 30, 2020. <https://www.who.int/news-room/fact-sheets/detail/hiv-aids>
3. Eke AC, Brooks KM, Gebreyohannes RD, et al. Tenofovir alafenamide use in pregnant and lactating women living with HIV. *Expert Opin Drug Metab Toxicol* 2020; 16:333-342.
4. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med* 1994;331:1173-1180.
5. Eke AC, Olagunju A, Best BM, et al. Innovative approaches for pharmacology studies in pregnant and lactating women: A viewpoint and lessons from HIV. *Clin Pharmacokinet* 2020;59:1185-1194.
6. [No authors listed]. ACOG Committee Opinion No. 751: Labor and Delivery Management of Women With Human Immunodeficiency Virus Infection. *Obstet Gynecol* 2018;132:e131-e137.
7. Soepnel LM, Norris SA, Schrier VJ, et al. The association between HIV, antiretroviral therapy, and gestational diabetes mellitus. *AIDS* 2017;31:113-125.
8. Salama E, Eke AC, Best BM, et al. Pharmacokinetic enhancement of HIV antiretroviral therapy during pregnancy. *J Clin Pharmacol* 2020;60:1537-1550.
9. Zash R, Holmes L, Diseko M, et al. Neural-tube defects and antiretroviral treatment regimens in Botswana. *N Engl J Med* 2019;381:827-840.
10. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Updated Feb. 10, 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL_2020.pdf
11. Lathrop E, Jamieson DJ, Danel I. HIV and maternal mortality. *Int J Gynaecol Obstet* 2014;127:213-215.
12. Curtis KM, Tepper NK, Jatlaoui TC, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-103.

EDITOR
Jason Schneider

EXECUTIVE EDITOR
Shelly Mark

EDITORIAL GROUP
MANAGER
Leslie G. Coplin

EDITOR
Rebecca H. Allen, MD, MPH
Associate Professor, Department of Obstetrics and Gynecology, Warren Alpert Medical School of Brown University, Women & Infants Hospital, Providence, RI

ASSOCIATE EDITORS
Nicole H. Cirino, MD, CST, IF
Reproductive Psychiatrist, Associate Professor, Department of OB/GYN and Department of Psychiatry, Oregon Health & Science University, Portland

Ahizechukwu Eke, MD, MPH
Associate Professor in Maternal Fetal Medicine, Division of Maternal Fetal Medicine, Department of Gynecology & Obstetrics, Johns Hopkins University School of Medicine, Baltimore

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

Mitchell Linder, MD
Assistant Professor, Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital, Rochester, NY

Rebecca B. Perkins, MD, MSc
Associate Professor of Obstetrics and Gynecology, Boston University School of Medicine/Boston Medical Center, Boston

Katherine Rivlin, MD, MSc
Assistant Professor, Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, Columbus, OH

PEER REVIEWER
Sarah J. Betsch, MD, MPH
Associate Professor, Department of Obstetrics and Gynecology, URM Family Planning; Director, Ryan Residency Training Program, University of Rochester Medical Center, Rochester, NY

NURSE PLANNER
Jeanine Mikek, MSN, RN, CEN
Maternal Child Health Educator, Labor & Delivery, Mother Baby, Neonatal Intensive Care Unit & Pediatrics, IU Arnett Hospital, Lafayette, IN

CME/CE INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to ReliasMedia.com and click on My Account. First-time users must register on the site using the eight-digit subscriber number printed on your mailing label, invoice, or renewal notice.
3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%. Tests are taken with each issue.
4. After completing the test, a credit letter will be emailed to you instantly.
5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

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.

CME/CE QUESTIONS

1. In the study by Turok et al, the levonorgestrel intrauterine device was found to be:
 - a. less effective as emergency contraception than oral levonorgestrel.
 - b. noninferior to the copper intrauterine device for emergency contraception use.
 - c. less effective for emergency contraception in obese patients compared to normal weight patients.
 - d. at a higher risk of expulsion than the copper intrauterine device when used as emergency contraception.
2. In the study by Peipert et al, which of the following was associated with a shorter time to conception?
 - a. Past *Mycoplasma genitalium* infection
 - b. Low socioeconomic status
 - c. Married or living with a partner
 - d. Older age
3. Which of the following statements about the study by Kim et al is true?
 - a. Human papillomavirus (HPV) vaccination of mid-adults is not cost-effective.
 - b. Only cervical cancer was considered in the modeling.
 - c. The two models found different results.
 - d. HPV vaccination of adults is routinely recommended.
4. Which of the following is *not* a “preferred” antiretroviral for use in pregnant women living with human immunodeficiency virus?
 - a. Tenofovir disoproxil fumarate
 - b. Tenofovir alafenamide
 - c. Atazanavir
 - d. Emtricitabine

[IN FUTURE ISSUES]

Evaluation of an Inpatient Postpartum Human Papillomavirus Immunization Program

Interested in reprints or posting an article to your company's site? There are numerous opportunities for you to leverage editorial recognition for the benefit of your brand. Call us at (800) 688-2421 or email reliasmedia1@gmail.com to learn more.

For pricing on group discounts, multiple copies, site licenses, or electronic distribution, please contact our Group Account Managers at: Phone: (866) 213-0844 Email: groups@reliasmedia.com

To reproduce any part of Relias Media newsletters for educational purposes, please contact:

The Copyright Clearance Center for permission
Email: info@copyright.com
Phone: (978) 750-8400