RELIAS
Formerly AHC Media

Vol. 34, Issue 10, February 2018
AHCMedia.com

OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Breast Cancer and Hormonal Contraception: New Information or Sensationalism?

By Jeffrey T. Jensen, MD, MPH, and Leon Speroff, MD

Dr. Jensen is Leon Speroff Professor and Vice Chair for Research, Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland.
Dr. Speroff is Professor Emeritus of Obstetrics and Gynecology, Oregon Health & Science University, Portland.

Dr. Jensen reports he is a consultant for and receives grant/research support from Bayer, Merck, ContraMed, and FHI360; receives grant/research support from Abbvie, HRA Pharma, Medicines 360, and CONRAD; and is a consultant for the Population Council. Dr. Speroff reports no financial relationships relevant to this field of study.

SYNOPSIS: Highly publicized results from the Danish database demonstrate an increase in the risk of breast cancer associated with current use of hormonal contraception. Consistent with prior research, the risk is small, confined to current users, and disappears following discontinuation.

SOURCE: Mørch LS, Skovlund CW, Hannaford PC, et al. Contemporary hormonal contraception and the risk of breast cancer. *N Engl J Med* 2017;377:2228-2239.

Prior research supports that hormonal contraception results in a small increase in the risk of breast cancer in current users, with no residual effect on risk following discontinuation. Since the doses of estrogen used in oral contraceptives have decreased, and a variety of new progestins have been introduced since the publication of the results of the Collaborative Group on Hormonal Factors in Breast Cancer in 1996,[1] the group headed by Øjvind Lidegaard used the Danish Sex Hormone Register (DSHR) study, a nationwide cohort study that includes all women living in Denmark, to evaluate breast cancer risk with current lower-dose methods. They used the Danish Cancer Registry to identify primary invasive breast cancers and used other registries to obtain data on exposures and confounders.

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 Bayer, Merck, ContraMed, and FHI360; he receives grant/research support from Abbvie, HRA Pharma, Medicines 360, and Conrad; and he is a consultant for the Population Council. Peer Reviewer Catherine Leclair, MD; Nurse Planners Marci Messerle Forbes, RN, FNP, and Andrea O'Donnell, FNP; Editorial Group Manager Terrey L. Hatcher; Executive Editor Leslie Coplin; and Editor Journey Roberts report no financial relationships relevant to this field of study.

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

OB/GYN Clinical Alert (ISSN 0743-8354) is published 12 times annually by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518-9238
AHCMedia.com

GST Registration Number: R128870672. Periodicals Postage Paid at Cary, NC, and additional mailing offices.

POSTMASTER: Send address changes to *OB/GYN Clinical Alert*, Relias Learning 111 Corning Road, Suite 250 Cary, NC 27518-9238

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

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

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

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

Relias Learning designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Relias Learning LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Contact hours [2.25] 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.

The DSHR follows a cohort of Danish women between 15 and 79 years of age to assess the influence of hormone use on the risks of cardiovascular disease and cancer. The cohort includes all Danish women ≤ 49 years of age on Jan. 1, 1995, and ≥ 15 years of age as of Dec. 31, 2012 (a total of 1,837,297 women). Exclusions for prior cancer diagnosis, venous thrombosis, or treatment for infertility resulted in 1,797,932 women included in this study.

The National Prescription Register provided data on exposure. The authors categorized contraceptive use as current use or recent use (discontinuation within the previous six months) or previous use (discontinuation more than six months previously). Start of use was the date that the prescription was purchased, and end of use was 28 days after the last purchase. They assumed women used the levonorgestrel-releasing intrauterine system (LNG IUS) for four years unless the woman became pregnant or received a prescription for another hormonal contraceptive before the end of that time period. Both the etonogestrel and levonorgestrel contraceptive implants are available in Denmark. The authors did not differentiate between the two progestins, and lumped all implant use in a single category. The two implants have different duration of approved use, and the authors did not describe how duration of exposure was classified for users of this method. Women changing methods contributed to multiple categories according to their pattern of use as current, recent, or past users. Women who became pregnant beyond 22 weeks did not contribute data for months during the pregnancy and until six months after delivery. The authors did not evaluate breast cancer diagnosis during pregnancy.

To obtain information on potential confounders, the authors relied on other national registries. Notably, the National Health Register provided medical treatment codes, surgical codes, and discharge diagnoses. However, this database does not include baseline information on body mass, alcohol use, family history, smoking, or lifestyle. Similar problems exist with the other databases used to assess confounders. For example, information on family history was available only for women from the cancer registry (an undisclosed number), and data on body mass index (BMI) were available on fewer than half of the sample collected as part of the pregnancy registry.

The authors reported results based on a total of 11,517 cases of invasive breast cancer that occurred over 19.6 million women-years of follow-up during the interval of study. Compared to never users of hormonal contraception, current and recent users of hormonal contraception showed a small increase in risk (relative risk [RR], 1.20; 95% confidence interval [CI], 1.14-1.26). This risk was not increased with less than one year of use 1.09 (95% CI, 0.96-1.23), but became significant after one year, peaking at 1.38 (95% CI, 1.26-1.51) after 10 years of use. Overall, the increased risk stopped rapidly after discontinuation of a hormonal method, although one analysis suggested that women using hormonal contraception for five to 10 years maintained a small increased risk up to 10 years following discontinuation (RR, 1.3; 95% CI, 1.06-1.58).

Comparing the risk estimates of the various hormonal contraceptive methods and progestins yields interesting and confusing results. For example, while levonorgestrel combined pills were associated with a significant increase in risk, low androgen desogestrel pills showed a lower point estimate, and the risk associated with drospirenone pills was lower yet and not significant. Although this suggests an androgen effect could modify risk, one of the highest point estimates was seen with the antiandrogenic cyproterone pill. What about an estrogen effect? No risk discrimination was observed between 50 mcg and 20 to 40 mcg ethinyl estradiol pills, and the highest risk estimate of all combined pills was associated with the recently introduced estradiol valerate/dienogest pill. What about a progestin dose effect? Low-dose LNG progestin-only pills (30 mcg) showed a higher risk (RR, 1.93; 95% CI, 1.18-3.16) than combined (100 to 150 mcg) LNG pills (RR, 1.33; 95% CI, 1.20-1.48), with the LNG IUS (20 mcg/d release) only slightly lower (RR, 1.21; 955 CI, 1.11-1.33). Adding to the confusion, the authors reported no increased risk associated with use of contraceptive implants and depo medroxyprogesterone acetate. Keep in mind the point estimates for all methods are low (below 2.0), with overlapping confidence intervals.

The authors concluded that their results support that current low-dose hormonal contraceptives increase the risk of breast cancer, and they recommended that women consider nonhormonal methods to reduce this risk. To put this risk in perspective, they noted the overall absolute increase in breast cancers diagnosed among current and recent users of any hormonal contraceptive in the study was 13 (10 to 16) per 100,000 person-years. This

translates to approximately one additional breast cancer for every 7,690 women using hormonal contraception for one year.

■ COMMENTARY

I first learned of this paper from a *New York Times* headline delivered to my smartphone. Who could blame the *Times* for taking the bait? A prestigious medical journal reports a link between hormonal contraception use and breast cancer, topics of interest to virtually all women and many men. This drives readers, revenue, citations, and impact factor. Unfortunately, this sensational coverage highlights risk and lacks critical review, frequently resulting in concern from patients leading to discontinuation of hormonal contraception.[2]

I am delighted that Leon Speroff, the former editor and founder of *OB/GYN Clinical Alert* agreed to share his thoughts and long experience with hormonal contraception and contribute to this commentary. Leon noted that the greatest strength of this study is the large number of participants. This yields high statistical precision. At the same time, the larger the number of women in a study, the greater the effect of confounding variables. Table 1 provides a summary of common risk factors for breast cancer from the American Cancer Society. As I have mentioned repeatedly in my criticism of results from the Danish Registry studies, the absence of complete information on important baseline confounders limits the conclusions possible from database studies. While the authors claim to adjust for baseline confounders, a careful review of the supplemental material (available online) demonstrates that the various Danish registries have incomplete information on family history, BMI, and smoking for most of the women, and completely lack information on lifestyle choices, such as alcohol use, making adequate adjustment impossible. Since the study design does not effectively control for baseline confounding, the weak associations reported should be interpreted with extreme caution.[3]

Table 1: Risks Factors for Breast Cancer

Relative risk > 4.0 • Inherited mutations • Two or more first-degree relatives with early disease
Relative risk 2.1-4.0 • One first-degree relative
Relative risk 1.1-2.0 • First full-term pregnancy after age 30 years • Early menarche • Nulliparity • Never breast fed • Alcohol consumption

Source: American Cancer Society Breast Cancer Facts & Figures, Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2017-2018.pdf. Accessed Dec. 20, 2017.

Overall, Mørch et al reported a small increased risk of breast cancer confined to current/recent but not past users of hormonal contraception. This supports the hypothesis that hormonal therapy may promote the growth of pre-existing breast cancers, leading to early detection. This result first was described in the Collaborative Reanalysis study from 1996.[1] The rapid disappearance of excess risk after discontinuation of use among women who used hormonal contraception for short periods is what you would expect to see if early detection is occurring with short-term use. The same effect is seen in the results with levonorgestrel-releasing IUDs; the increase was significant with short-term use and failed to reach statistical significance with use greater than 10 years. This raises other questions regarding attribution of risk. The analysis assumed that a woman used the LNG IUS for four years unless she received a prescription for a different hormonal method, potentially increasing exposure.

Leon pointed out that the authors' conclusion that the risk increased with longer durations of use is especially vulnerable to the unknown effect of non-assessed confounders. To reach this conclusion, they relied on a "bias analysis" that assumed confounders not assessed were highly prevalent in the population and strongly associated with breast cancer. This convenient assumption lacks rigor. The database design simply does not permit us to adequately assess the effect of unmeasured confounders strongly associated with breast cancer risk: the degree of positive family history (number of first-degree relatives), the presence of inherited mutations, early menarche, breast feeding, and alcohol consumption.[4] As mentioned earlier, data on BMI were available only for parous women. Although the authors stated that risk increased with duration of use, these results only achieved statistical significance among older women (> 35 years, see supplemental tables). Attempting to parse out the effects of various treatments over many years without rigorous control for confounding renders this conclusion particularly weak. We also believe the authors missed an opportunity to report the risk of breast cancer diagnosis during and following pregnancy among nonusers of hormonal methods.

In our summary of the results above, we pointed out our confusion with the lack of dose response with estrogens and progestins, and the absence of any effect with contraceptive implants and low androgenic progestins, such as drospirenone and desogestrel. The results showing some of the highest risk estimates with LNG products deserves comment. We find it ironic that the Lidegaard group repeatedly has made the case for the cardiovascular safety of LNG pills using the same database. Could the negative press regarding thrombosis risk have resulted in a prescription bias driving women at higher risk for breast cancer to the use of progestin-only LNG products? A well-recognized phenomenon is preferential prescribing. Clinicians tend to prescribe newer products or perhaps progestin-only products to patients with known risk factors. The effect of this phenomenon was not and probably could not be assessed in this study, but it may

explain the high point estimate seen with the estradiol valerate/dienogest pill.

The authors recognize that their numbers, if real, translate into a very low number of additional cases of breast cancers in users of hormonal contraception. When the statistical conclusions of analyses are in the risk range of 1 to 2, clinicians should be skeptical that there is real clinical meaning in the numbers. Add to this the uncertainty in this study regarding adjustment for the effect of all factors that influence breast cancer risk, we see no reason to change current practice or patient recommendations.

Clinicians and patients also should find reassurance in the long-term safety data published last year from the UK Royal College of General Practitioners' Oral Contraception Study that began in the late 1960s and involves up to 44 years of follow-up.[5] In this cohort, ever use of oral contraceptives was associated with reduced colorectal, endometrial, ovarian, and lymphatic/hematopoietic cancers. An increased risk of lung cancer was seen only among ever users who smoked at recruitment. An increased risk of breast and cervical cancer was seen only in current and recent users, and not in past users. These data strongly support that the overall risk of cancer is not increased with the use of hormonal contraception. ■

REFERENCES

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713-1727.
2. Shelton J. Scientists and the media must give a balanced view. *Nature* 2011;479:7.
3. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet* 2002;359:248-252.
4. Kim HJ, Jung S, Eliassen AH, et al. Alcohol consumption and breast cancer risk in younger women according to family history of breast cancer and folate intake. *Am J Epidemiol* 2017;186:524-531.
5. Iversen L, Sivasubramaniam S, Lee AJ, et al. Lifetime cancer risk and combined oral contraceptives: The Royal College of General Practitioners' Oral Contraception Study. *Am J Obstet Gynecol* 2017;216:580. e1-e9.

ABSTRACT & COMMENTARY

Does Hysterosalpingography With Oil-based Contrast Increase Fertility?

By Robert W. Rebar, MD

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

Dr. Rebar reports that he chairs Data Safety Monitoring Committees for Myovant Sciences, Inc.

SYNOPSIS: A multicenter, randomized trial in the Netherlands documented higher rates of ongoing pregnancy and live births among infertile women who underwent hysterosalpingography with oil-based contrast compared to those who underwent the procedure with water-based contrast.

SOURCE: Dreyer K, van Rijswijk J, Mijatovic V, et al. Oil-based or water-based contrast for hysterosalpingography in infertile women. *N Engl J Med* 2017;376:2043-2052.

Hysterosalpingography to assess tubal patency often is regarded as an essential part of the initial evaluation of the infertile couple. Because of numerous suggestions and smaller studies indicating a possible fertility-enhancing effect of hysterosalpingography with the use of oil contrast, investigators in the Netherlands conducted a multicenter, randomized, controlled trial in 27 Dutch hospitals to compare ongoing pregnancy rates in women with infertility undergoing hysterosalpingography with either oil- or water-based contrast. In all, 1,119 spontaneously menstruating women between the ages of 18 and 39 years with infertility of at least one year's duration were included in the trial, with 557 women assigned to hysterosalpingography with oil-based contrast and 562 women assigned to water-based contrast. The researchers excluded individuals with a high risk of tubal disease (based on a history of pelvic inflammatory disease), previous chlamydia infection (generally on the basis of testing for antichlamydial antibodies), or known endometriosis. Hysterosalpingography showed bilateral tubal patency in 86.1% of women assigned to oil-based contrast and in 88.6% of those assigned to water-based contrast. After the procedure, couples received expectant management (58.3% of the oil-based contrast group and 57.2% of those assigned to water-based contrast) or the women underwent intrauterine insemination, either with or without "mild ovarian hyperstimulation" with either clomiphene citrate or exogenous gonadotropins to cause development of two or three ovarian follicles.

On an intention-to-treat basis, ongoing pregnancy — defined as a positive fetal heart beat on ultrasonographic examination after 12 weeks of gestation with the first day of the last menstrual period for the pregnancy occurring within six months of randomization — resulted in 39.7% of the women randomly assigned to oil-based contrast and in

29.1% of those randomly assigned to water-based contrast (rate ratio, 1.37; 95% confidence interval [CI], 1.16-1.61; $P < 0.001$). The median time to the onset of pregnancy was 2.7 months in the oil group and 3.1 months in the water group; 38.8% in the oil group and 28.1% in the water group had a live birth (rate ratio, 1.38; 95% CI, 1.17-1.64; $P < 0.001$).

■ COMMENTARY

The possibility that oil-based contrast material used for hysterosalpingography increases the likelihood of pregnancy has been suggested for many years.[1,2] This randomized trial would seem to confirm the advantages of oil-based contrast in certain select populations. However, the real question is whether these data are relevant to the U.S. population and couples routinely seen for infertility in the United States.

The authors have suggested that the use of oil contrast combined with expectant management may be an inexpensive treatment for some women with infertility. While this is true, it is interesting to note that the specific contrast material utilized (Lipiodol, Ultra-Fluid, Guerbet) is several-fold more expensive in the United States than it is in the Netherlands.

The authors noted that the trial involved infertile women with a low risk of tubal disease. The prevalence and incidence of chlamydia admittedly is low in the Netherlands. That is not the case in the United States. Data from the Centers for Disease Control and Prevention website indicate that 50% of women in the United States may have had chlamydia by the age of 30. In the absence of definitive data, the risk of hysterosalpingography with oil-based contrast material to result in acute pelvic inflammatory disease always has been believed to be higher than that with water-based contrast material because of the length of time the contrast material remains in the pelvis. Older practitioners like myself long have been familiar with publications indicating that administration of doxycycline prophylactically appears to reduce the risk of acute disease.[3] Although the risk of acute pelvic inflammatory disease appears low, as detailed in that study, it is very real. The ability of acute disease to further increase the risk of infertility is such that I find it difficult to support the routine use of oil-based contrast in all women evaluated for infertility.

In low-risk women it may be justifiable to consider hysterosalpingography with oil-based contrast material. However, the authors concluded their paper with the observation that new tests for assessment of tubal patency in the office setting using ultrasound have been introduced. Oil-based contrast in such settings and for tubal flushing has not been evaluated. Until such time as more data are available, I find little reason to switch to the more expensive oil-based contrast material routinely in the evaluation of infertile women. ■

REFERENCES

1. Weir WC, Weir DR. Therapeutic value of salpingograms in infertility. *Fertil Steril* 1951;2:514-522.
2. Mohiyiddeen L, Hardiman A, Fitzgerald C, et al. Tubal flushing for subfertility. *Cochrane Database Syst Rev* 2015; May 1;CD003718. doi:10.1002/14651858CD003718.pub4.
3. Pittaway DE, Winfield AC, Maxson W, et al. Prevention of acute pelvic inflammatory disease after hysterosalpingography: Efficacy of doxycycline prophylaxis. *Am J Obstet Gynecol* 1983;147:623-626.

ABSTRACT & COMMENTARY

Intrauterine Device String Checks: Are They Necessary?

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 is a Nexplanon trainer for Merck.

SYNOPSIS: Two-thirds of women complied with the recommendation for a six-week follow-up visit after intrauterine device (IUD) insertion. Among these women, 19.8% had their IUD removed in the first year compared to 12.6% among women who did not attend the follow-up visit. The majority of removals occurred outside the six-week follow-up period.

SOURCE: Bernard A, Satterwhite CL, Reddy M. Frequency of 6-week follow-up appointment scheduling after intrauterine device insertion. *BMJ Sex Reprod Health* 2017. [Epub ahead of print].

This is a single-institution, retrospective cohort study from the University of Kansas from January to June 2015. Women who underwent intrauterine device (IUD) insertion were identified, and subsequent follow-up visits and outcomes in the first year of placement were described. The primary outcome was the proportion of women who attended a six-week follow-up visit for IUD string check. Data on demographics, parity, IUD type, and IUD removals in the first year were collected.

A total of 380 women underwent IUD insertion during the six-month period. Mean age was 29.3 years (standard deviation, 6.4). One-third of women (35.2%) were nulliparous. For IUD types, 88.4% of women chose the

52 mg levonorgestrel device, 2.1% chose the 13.5 mg levonorgestrel device, and 9.5% chose the copper IUD. In the majority of cases (91.3%), the provider recommended a six-week follow-up visit, and 253 women (66.6%) complied. At the follow up-visit, bleeding concerns were documented in 26.9% of visits and string concerns in 9.1% of visits. Sixteen ultrasounds to document IUD location were ordered, presumably because strings were not visualized. Two ultrasounds showed malposition and one showed a small perforation. At the six-week visit, three IUDs were noted to have been expelled (one was replaced) and 11 IUDs were removed (four for malpositioning [two replaced], one because of the presence of a septate uterus, and the remaining for various complaints such as pelvic pain or desire for pregnancy). Of the 380 women who had an IUD placed, 66 (17.4%) had their IUD removed within one year. Type of IUD was not associated with removal rates. Among women who attended the six-week visit, 19.8% had their IUD removed compared to 12.6% who did not attend a six-week follow-up visit ($P = 0.08$). When removals at the six-week visit were excluded from the analysis, visit attendance was not associated with subsequent IUD removal rates within the first year (36/239 removals vs. 16/127 removals, $P = 0.52$).

■ COMMENTARY

Long-acting reversible contraceptives (LARC), including IUDs and implants, are highly effective and have continuation rates as high as 70% at three years of use.[1] The use of LARCs in the United States has increased dramatically in the past decade, with the most recent data reporting 11.6% of contracepting U.S. women opting for LARC in 2012.[2] IUDs are placed in the office setting and, traditionally, a six-week visit to check the IUD strings and ensure proper placement of the IUD has been recommended. The rationale for this interval was that the patient would have had a menstrual period during this time and also would have resumed sexual intercourse if sexually active. The follow-up visit also then would be an opportunity to discuss any patient complaints or questions regarding the IUD. Furthermore, although rare, if the patient had developed pelvic inflammatory disease from the insertion process, this could be detected. This recommendation is present on the manufacturers' prescribing information for Mirena, Liletta, Skyla, Kyleena, and Paragard.

Nevertheless, this clinical recommendation does not have a strong evidence base. Unfortunately, the existing studies are limited and of poor quality. In a review, Steenland et al found two studies addressing this question and were unable to determine whether a specific follow-up visit after insertion improved continuation rates.[3] Based on this review, the Centers for Disease Control and Prevention's U.S. Selected Practice Recommendations for Contraceptive Use (USSPR) does not recommend a mandatory six-week follow-up visit. However, the USSPR does add a caveat that the recommendations refer to general situations and might vary for different users and different situations, such as adolescents or persons with certain medical conditions or characteristics.[4]

The authors of this study concluded that their data support the fact that the six-week IUD check is unnecessary given that removal rates did not differ significantly between those who attended the visit and those who did not. They felt that the complaints addressed at the six-week visit (bleeding and string-related) could have been handled over the phone. One critique of this study is the lack of documentation regarding provider experience at the time of insertion (resident vs. attending) and whether any of those women who did not attend the visit were lost to follow-up in terms of tracking outcomes at one year. This is also a single institution study, which decreases generalizability.

The interpretation of this study depends on what one considers the goal of the six-week visit. If the goal of the visit is to increase IUD continuation rates, then I agree that this study demonstrates the six-week visit does not seem to make a difference. However, if the goal of the visit is to detect complications with the IUD, it seems that this was accomplished. After all, three expulsions and four malpositioned IUDs were discovered, and 16 ultrasounds were ordered to confirm IUD placement because the strings were not visualized. These women could have had silent expulsions, and one perforation actually was found. The authors reported that nulliparous women ($P = 0.015$) and women receiving their first IUD ($P = 0.004$) were more likely to attend the follow-up visit. Therefore, certain women actually may seek the reassurance of a follow-up visit if they are uncomfortable checking for the strings themselves.

As IUDs become more and more popular, we owe it to our patients to ensure that they have a good experience with the IUD and catch any issues if they arise. I have no problem offering women a six-week follow-up visit if they desire it; however, I also would not make it mandatory if the patient found it inconvenient to attend and was able to check for strings herself and call for any issues. That being said, I work in an ob/gyn resident continuity clinic, and most of the IUDs are inserted by residents. For their patients, we do mandate six-week follow-up visits because these providers are less experienced. The bottom line is that, as with any guidelines, providers should practice medicine in a way with which they are comfortable when treating individual patients. The absence of evidence supporting six-week IUD checks does not prove that they are useless; it only proves that proper studies have not yet been carried out. ■

REFERENCES

1. Diedrich JT, Zhao Q, Madden T, et al. Three-year continuation of reversible contraception. *Am J Obstet Gynecol* 2015;213:662.e1-8.
2. Kavanaugh ML, Jerman J, Finer LB. Changes in use of long-acting reversible contraceptive methods among U.S. women, 2009-2012. *Obstet Gynecol* 2015;126:917-927.
3. Steenland MW, Zapata LB, Brahmi D, et al. The effect of follow-up visits or contacts after contraceptive initiation on method continuation and correct use. *Contraception* 2013;87:625-630.
4. Curtis KM, Jatlaoui TC, Tepper NK, et al. U.S. Selected Practice Recommendations for Contraceptive Use, 2016. *MMWR Recomm Rep* 2016;65:1-66.

ABSTRACT & COMMENTARY

The Debate Continues on Salpingectomy

By Molly A. Brewer, DVM, MD, MS

Professor and Chair, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Connecticut Health Center, Farmington

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

SYNOPSIS: The role of routine salpingectomy during vaginal hysterectomy is controversial.

SOURCE: Cadish LA, Shepherd JP, Barber EL, Ridgeway B. Risks and benefits of opportunistic salpingectomy during vaginal hysterectomy: A decision analysis. *Am J Obstet Gynecol* 2017;217:603.e1-603.e6.

The question of whether routine salpingectomy should be done at the time of hysterectomy or adnexal surgery to prevent ovarian cancer is controversial. There are not convincing data whether the fallopian tube is always, sometimes, or occasionally the site of the high-grade serous carcinomas of the ovary. Multiple studies have determined that women with a deleterious BRCA mutation who undergo prophylactic bilateral salpingo-oophorectomy (BSO) and who have microscopic carcinoma actually have cancers that arise from the fallopian tubes 75% of the time and only 25% of the time from the ovary.[1-3] Studies in patients with ovarian cancer who are not known to carry a deleterious BRCA mutation vary in terms of the origin of their cancer. Cancers arising from the ovary compared to the fallopian tube vary from 75% to 20%, and some even think that all ovarian cancers arise from the tubal epithelium.[4] In addition, ovarian cancer is a rare but deadly cancer, and although there is only a 1.5-1.7% lifetime risk of ovarian cancer, the death rate is approximately 50% or higher. This warrants reasonable prophylactic approaches to prevent cancer, particularly in those women at increased risk of ovarian cancer due to a deleterious mutation. In addition, the morbidity from removal of the ovaries in premenopausal women is considerable and is associated with all of the effects of early menopause including osteoporosis, heart disease, and urinary issues. For these reasons, bilateral oophorectomy in premenopausal women is reserved for those in whom the benefit outweighs the risk.

This study was a decision analysis to determine the efficacy and cost of combining vaginal hysterectomy with bilateral salpingectomy. The authors used TreeAge Pro, an interactive database in which researchers input estimates of the rate of complications, readmissions, fallopian tube carcinoma, and effectiveness of the intervention in prevention of cancer. In addition, estimates of the cost of the additional surgery, the cost of treating ovarian cancer, and the cost of complications to balance the effectiveness of the intervention also are considered. The authors used the Falconer study, which was a large population-based study that measured the rate of ovarian cancer in women who underwent hysterectomy, hysterectomy and BSO, BSO, and unilateral and bilateral salpingectomy to estimate the prevention associated with salpingectomy.[5] The Falconer study has been criticized because the rate of bilateral salpingectomy was low, the data on oral contraceptive use were not included, and the hazard ratio for ovarian cancer was much lower with hysterectomy and BSO (0.06 at 10 years) than it was for bilateral salpingectomy (0.37 at 10 years). That being said, it gave Cadish and colleagues an estimate of the rate of ovarian cancer with bilateral salpingectomy. Using these data, they estimated that the risk of ovarian cancer was reduced from a probability of 0.01300 to 0.00455, a reduction of 55%, while a hysterectomy with BSO reduced the risk of ovarian cancer to 0.00078, a reduction of 94%.

Cadish et al found that planned salpingectomy was only slightly worse than hysterectomy alone in terms of complications, with a rate of 7.68% in the vaginal hysterectomy alone group and a rate of 7.95% in the hysterectomy with salpingectomy group. The authors estimated that there were three additional complications for each five cases of cancer. Salpingectomy was less expensive than not performing it, even when the cost of cancer care was excluded. They concluded that bilateral salpingectomy at the time of vaginal hysterectomy was a reasonable and cost-effective approach with minimal morbidity. A second study found that salpingectomy at the time of vaginal hysterectomy was feasible in most women and increased the operating time by only 11 minutes and blood loss by 6 mL, both of which are trivial.[6]

A commentary in the same journal by Kho suggests that it is time for a "policy" regarding salpingectomy at the time of hysterectomy.[7] She concluded that given the cancer prevention benefit that results from bilateral salpingectomy and the low morbidity, removal of the tubes at the time of hysterectomy should become standard practice as opposed to just a clinical recommendation.

So, as clinicians, how should we counsel our patients? Bilateral salpingectomy reduces reoperation for benign adnexal surgery from 12.6% to 4.2%.[8] This reduction is substantial and is a reasonable rationale for doing bilateral salpingectomy at the time of any hysterectomy. It may reduce the probability of ovarian cancer from 0.013 to 0.00045, about a 55% reduction, suggesting that approximately 55% of the ovarian cancers start in the fallopian tube. The rate of salpingectomy for sterilization has increased from 0.4% to 35.5% from 2011 to 2016.

Interestingly, by 2016, salpingectomy was done in 78% of the interval tubal sterilization procedures.[9] This is also a reasonable approach, as the efficacy of sterilization is better and the morbidity is not increased substantially.

So what is the risk of routine salpingectomy for cancer prevention? Clinicians may be counseling their patients that it will prevent ovarian cancer. We should be careful about promising cancer prevention when it may provide only about a 55% reduction in the probability of developing ovarian cancer, approximately the same rate as oral contraceptives. ■

REFERENCES

1. Powell CB, Chen LM, McLennan J, et al. Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: Experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer* 2011;21:846-851.
2. Callahan MJ, Crum CP, Medeiros F, et al. Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol* 2007;25:3985-3990.
3. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. *Gynecol Oncol* 2006;100:58-64.
4. Labidi-Galy SI, Papp E, Hallberg D, et al. High grade serous ovarian carcinomas originate in the fallopian tube. *Nat Comm* 2017;8:1093.
5. Falconer H, Yin L, Gronberg H, Altman D. Ovarian cancer risk after salpingectomy: A nationwide population-based study. *J Natl Cancer Inst* 2015;107: pii: dju410. doi: 10.1093/jnci/dju410.
6. Antosh DD, High R, Brown HW, et al. Feasibility of prophylactic salpingectomy during vaginal hysterectomy. *Am J Obstet Gynecol* 2017;217:605.e1-605.
7. Kho RM. Prophylactic bilateral salpingectomy at vaginal hysterectomy: Time for a "policy"? *Am J Obstet Gynecol* 2017;217:503-504.
8. Vorwergk J, Radosa MP, Nicolaus K, et al. Prophylactic bilateral salpingectomy (PBS) to reduce ovarian cancer risk incorporated in standard premenopausal hysterectomy: Complications and reoperation rates. *J Cancer Res Clin Oncol* 2014;140:859-865.
9. Powell CB, Alabaster A, Simmons S, et al. Salpingectomy for sterilization: Change in practice in a large integrated health care system, 2011-2016. *Obstet Gynecol* 2017;130:961-967.

CME/CE QUESTIONS

1. **In the Danish Registry study, a statistically significant increased risk of invasive breast cancer was associated with current use of:**
   a. the levonorgestrel intrauterine system.
   b. contraceptive implants.
   c. drospirenone oral contraceptives.
   d. depo medroxyprogesterone acetate.
2. **In the study by Bernard et al, what proportion of women came for their six-week IUD string check?**
   a. 20%
   b. 35%
   c. 66%
   d. 80%
3. **Which of the following is true about prophylactic salpingectomy at the time of vaginal hysterectomy?**
   a. It will prevent reoperation for benign indications substantially.
   b. It will prevent 90% of ovarian cancer.
   c. It is associated with significant morbidity.
   d. None of the above

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]

The Latest in Genetic Screening for Gynecologic Malignancies

Oxytocin Discontinuation