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Does Unilateral Oophorectomy Lead to Early Menopause?

ABSTRACT & COMMENTARY

By Jeffrey T. Jensen, MD, Editor

Synopsis: *In a large Norwegian population-based cohort study, women with a history of unilateral oophorectomy experienced a slightly earlier onset of menopause compared to women with both ovaries, but this finding does not suggest a clinically important effect.*

Source: Bjelland EK, et al. Is unilateral oophorectomy associated with age at menopause? A population study (the HUNT2 Survey). *Hum Reprod* 2014;29:835-841.

TO DETERMINE WHETHER REMOVAL OF ONE OVARY IS ASSOCIATED WITH AN early onset of menopause, Bjelland et al performed a retrospective cohort study of 23,580 Norwegian women who were included in the population-based HUNT2 Survey. All individuals ≥ 20 years of age living in Nord Trøndelag County, Norway, during the years 1995-1997, were invited to participate in the survey. Data on gynecologic surgery and age of menopause were collected at enrollment using two self-administered questionnaires. Cox proportional hazard models were used to estimate relative risks of menopause according to unilateral oophorectomy status with and without adjustment for birth cohort, parity, smoking, body mass index (BMI), and age at menarche.

Overall, women in the unilateral oophorectomy cohort were about 1 year younger at menopause (mean, 49.6 years; 95% confidence interval [CI], 49.2-50.0) than women without unilateral oophorectomy (mean, 50.7 years; CI, 50.6-50.8). The crude relative risk of menopause was 1.28 (CI, 1.15-1.42) and remained elevated after adjustment for potential confounders (relative risk aversion [RRA], 1.27; CI, 1.14-1.41).

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To put this risk in perspective, the impact of unilateral oophorectomy was similar to that of nulliparity (49.7 vs 50.7 years; RRa, 1.25; CI, 1.16-1.36) and greater than that attributable to smoking (1.18; CI, 1.13-1.24). In contrast, there was a modest increase in the age of menopause associated with increasing BMI (RRa, 0.88; CI, 0.82-0.94) for BMI \geq 30 kg/m² compared to BMI < 25 kg/m².

Given that the overall effect of unilateral oophorectomy on age at onset of menopause is small, and similar to other established risk factors like smoking and nulliparity, the authors concluded that mechanisms must exist that compensate for the large loss of follicles with ovarian surgery.

■ COMMENTARY

This is a nice study because the authors put the findings into real clinical perspective. The main result that unilateral oophorectomy increases the risk of early menopause by 27% could make for a great alarmist headline. Although the tight confidence interval around the relative risk estimate demonstrates statistical significance, the finding is clearly not clinically important. Although large database and retrospective cohort studies are capable of producing impressive small confidence intervals, the clarity of the statistical results should not cloud the interpretation of the clinical relevance of these results. In general, risk estimates that do not exceed a minimum threshold of 2.0 (or 0.5 for protection) are highly suspect, and should be largely ignored.¹ In addition, the authors of this study acknowledge inherent weakness of the study design (e.g., self-reported outcomes, misclassification bias) that

should reduce confidence in the strict interpretation of the findings. Nevertheless, we can still learn from this study.

Since the age of menopause has reproductive and health implications for women, research addressing factors that might influence the onset is a legitimate area of inquiry. Results from well-designed studies can be useful to clinicians counseling their patients. The findings of Bjelland et al illustrate a principle of mammalian reproductive biology. Menopause occurs due to the loss of ovarian follicles. This process begins in fetal life and accelerates through the reproductive years. Although many environmental and genetic conditions likely contribute to the age of menopause, the process of follicle atresia and apoptosis occurs rather steadily in most women until the pool of oocytes is exhausted.² Radiation therapy and chemotherapy during cancer treatment accelerate the loss of follicles and are associated with an early onset of menopause, and the same effect has been noted on a population consisting of atomic bomb survivors.³ But treatment with hormonal contraceptives that block ovulation does not prevent follicular atresia or postpone the age of menopause.⁴ Thus, the loss of follicles occurs slowly and steadily throughout life, with ovarian failure occurring in the early 50s for most women.

If the timing of menopause was related only to follicle number, the effect of oophorectomy should be substantial, as surgery results in loss of approximately half the remaining ovarian follicles. Given that women are born with a finite number of follicles, Faddy and Gosden estimated that if the absolute rate of follicle atresia remained the same after oophorectomy, the age of menopause should be 5-10 years earlier.⁵ Since the epidemiologic data do not support this hypothesis, other explanations must exist. Some experts believe that the ovary is capable of producing new primordial follicles. There have been recent reports of mitotically active germ cells in the ovaries of women capable of producing new "oocyte-like structures."⁶ However, these findings are highly speculative and have not been confirmed.⁷

The most likely explanation for the stable age of menopause after oophorectomy is that the rate of follicle atresia is relatively constant in each ovary and independent of ovulation. In other words, each ovary has an independent clock and fate. Although the two ovaries influence each other to favor maturation and ovulation of a single oocyte each cycle, the background rate of follicle loss occurring in each ovary is independent of ovulation. When one ovary is missing, the other does not speed up the rate of follicle loss. Consider two blocks of ice side by side. Removal of one block may slightly influence the rate of melting of the other, but to a large extent, they melt independently.

So the clinical message from this report is reassuring for women facing the decision regarding a unilateral oophorectomy. Among women desiring future fertility, every effort should be made to conserve ovarian tissue.

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Questions & Comments

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However, if unilateral oophorectomy is indicated, consideration of menopause should not factor into the clinical decision making. I don't see the value in performing a difficult ovarian cystectomy procedure on a 40-year-old woman who is not interested in future pregnancies. ■

References

1. Schulz KF, Grimes DA. *The Lancet Handbook of Essential Concepts in Clinical Research*. New York: Elsevier; 2006.
2. Fritz MA, Speroff L. *Clinical Gynecologic Endocrinology and Infertility*. 8th Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
3. Sakata R, et al. *Radiat Res* 2011;176:787-795.
4. Pokoradi AJ, et al. *Am J Obstet Gynecol* 2011;205:34.e1-13.
5. Faddy MJ, Gosden RG. *Hum Reprod* 1996;11:1484-486.
6. Tilly JL, Sinclair DA. *Cell Metab* 2013;17:838-850.
7. Hanna CB, Hennebold JD. *Fertil Steril* 2014;101:20-30.

Mobility Impairment and Urinary Incontinence in Elderly Women

ABSTRACT & COMMENTARY

By Chiara Ghetti, MD

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

Synopsis: In a large population of older community-dwelling women, there was a strong association between limited motor and balance skills and urge incontinence.

Source: Fritel X, et al. Mobility impairment is associated with urge but not stress urinary incontinence in community-dwelling older women: Results from the Ossébo study. *BJOG* 2013;120:1566-1572.

THE OBJECTIVE OF THIS STUDY WAS TO EVALUATE THE association between urinary incontinence and mobility impairment in elderly women. This was a cross-sectional observational study of 1942 community-dwelling women and an ancillary analysis of a larger parent study, a randomized controlled trial of physical exercise for prevention of falls in elderly women. The main outcome measures were mobility, balance, and urinary incontinence symptoms. Mobility and balance were assessed using a set of standardized functional tests (validated for the pre-

diction of falls and fractures) and incontinence symptoms measured by the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF), which assesses frequency, quantity, and type of urine loss and degree of bother over the last 4 weeks. Mobility and balance results were compared between continent and incontinent women by severity and type of incontinence. Logistic regression modeling was used to investigate the association between mobility and balance and urinary incontinence by adjusting for age, body mass index, and testing center.

Women aged 75-85 years were recruited by mail using electoral rolls. A total of 19,360 invitations were mailed. The study recruited 1940 women who were examined at one of nine study centers between January 2008 and June 2009 in several large French cities. Participants' mean age was 79.3 (\pm 2.9) years. Urinary incontinence was reported by 815 (42%), for whom 305 (37%) reported slight severity, 397 (49%) reported moderate severity, 97 (12%) reported severe, and 16 (2%) reported very severe. Of women with incontinence, 194 (24%) reported symptoms of stress incontinence, 251 (31%) reported urgency incontinence, 302 (37%) reported mixed symptoms, and the remainder reported leakage for other reasons. Bivariate analysis revealed worsening mobility and balance scores with increased urinary incontinence severity, with worse scores in women with urge or mixed incontinence compared to continent women. Multivariable logistic regression using single mobility and balance test results found a strong association between deterioration of mobility testing and presence of urgency incontinence.

■ COMMENTARY

More than one-half of women will be affected by urinary incontinence over their lifetime.¹ Urinary incontinence significantly decreases a woman's quality of life and overall functional status. Estimates suggest that by 2030, 1 in 5 adults in the United States will be 65 years of age or older.² The prevalence of incontinence increases with age, and as the population ages, urinary incontinence will be an even more significant public health issue. Elderly women are also greatly impacted by cognitive impairment, depression, gait, and balance disturbances.

This study accentuates the interrelationship between function and urinary incontinence in the elderly, a major quality-of-life issue in the aging population.³ The study reminds clinicians caring for elderly women that physical activity is one of the most important factors affecting functional ability in the elderly, and that our elderly patients should be encouraged to remain active. Asking our elderly patients with incontinence about falls and about their gait and quietly watching them as they enter or leave our exam rooms may reveal mobility deficits of which we may not be aware. Mobility is an important consideration before prescribing the anticholinergic medications used to treat

urinary incontinence, as these medications can have significant cognitive and functional side effects in the elderly.

As an observational study, this study has limitations and by design cannot establish causality. While the link between impaired mobility and urge urinary incontinence is not clear, the authors do explore possible mechanisms to explain this relationship. It is possible that impaired mobility could increase leakage due to difficulty getting to the bathroom. It is also possible that the physiology leading to decline in cognitive function and to gait may be linked to the development or worsening of urgency incontinence. The small differences the authors found in mobility testing are significant enough to be predictive of physical abilities and risk of falls. These findings highlight the important role of physical and occupational therapy in our elderly patients,⁴ as improving mobility and balance may be beneficial in reducing falls and may play a role in decreasing symptoms of urinary urgency incontinence. ■

References

1. Fantl JA, et al. Urinary Incontinence in Adults: Acute and Chronic Management. Clinical Practice Guideline 2. Rockville, MD: HHS, Agency for Health Care Policy and Research; 1996.
2. U.S. Department of Health and Human Services. Administration on Aging AOA-Older Americans 2010: Key Indicators of Wellbeing. Available at: http://www.agingstats.gov/agingstatsdotnet/Main_Site/Data/2010_Documents/docs/OA_2010.pdf. Accessed April 28, 2014.
3. Tinetti ME, Williams CS. *N Engl J Med* 1997;337:1279-1284.
4. Gillespie LD, et al. *Cochrane Database Syst Rev* 2009;CD007146.

'An aspirin a day keeps the ovarian cancer away...'

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

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

Synopsis: In this pooled analysis of more than 7700 ovarian cancer patients and nearly 12,000 controls, low-dose aspirin and high-dose non-aspirin NSAID use was associated with a risk reduction for invasive epithelial ovarian cancer of 20-34% relative to non-

users. Acetaminophen use was not associated with a risk reduction, irrespective of dose or frequency.

Source: Trabert B, et al; Ovarian Cancer Association Consortium. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst* 2014;106:djt431.

INCREASING EVIDENCE IS EMERGING TO LINK REGULAR ASPIRIN use and reduced risks of several malignancies. However, the association to invasive ovarian cancer has been inconclusive, largely attributed to low prevalence and small sample sizes. To better understand this relationship, Trabert and colleagues collected individual case data from 12 population-based, case-control studies of ovarian cancer. The study sample consisted of 7776 case patients and 11,843 control subjects who were accrued between 1992 and 2007. Exposure data were collected regarding use, dose, duration, and frequency. Outcomes were limited to invasive epithelial ovarian, fallopian tube, and primary peritoneal cancer. Patients with low malignant potential and non-epithelial tumors were excluded. In addition, while all histologies were analyzed, a sensitivity analysis of type of serous cancer (high grade vs low grade) was conducted due to the underlying biology of these two lesions. Adjustments were made for important confounding factors affecting ovarian cancer risk such as family history, steroidal contraception use, parity, body mass index, race, and age, as well as, history of endometriosis, tubal ligation, hysterectomy, and estrogen replacement use. Further sensitivity analyses were conducted removing potential factors that were incompletely reported or collected between the various studies. Odds ratios (ORs) for associations of medication use with invasive epithelial ovarian cancer were estimated in individual studies using logistic regression and combined using random effects meta-analysis. Associations between frequency, dose, and duration of analgesic use and risk of ovarian cancer were also assessed. All statistical tests were two-sided. The authors reported that aspirin use was associated with a reduced risk of ovarian cancer (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.84-0.99). Results were similar but not statistically significant for non-aspirin NSAIDs, and there was no association with acetaminophen. In seven studies with frequency data, the reduced risk was strongest among daily (regular) aspirin users (OR, 0.80; 95% CI, 0.67-0.96). In three studies with dose information, the reduced risk was strongest among users of low-dose aspirin (< 100 mg; OR, 0.66; 95% CI, 0.53-0.83), whereas for non-aspirin NSAIDs, the reduced risk was strongest for high dose (\geq 500 mg) usage (OR, 0.76; 95% CI, 0.64-0.91). The authors concluded that aspirin use was associated with a reduced risk of ovarian cancer, especially among daily users of low-dose aspirin.

■ COMMENTARY

The relationship between aspirin use and disease has been demonstrated in both retrospective studies and in prospective randomized clinical trials. The benefits have long been known for cardiovascular risk, and recently the beneficial effects have extended to several solid tumors including colorectal cancer, esophageal cancer, bladder cancer, endometrial cancer, liver and lung cancer, and female breast cancer.¹ The risk reduction in ovarian cancer is not surprising as there is a biological/pharmacological link: inflammation.² Aspirin and non-aspirin NSAIDs are potent inhibitors of COX, particularly COX-1. Aspirin is an irreversible inhibitor of COX-1 and NSAIDs reversibly inhibit both COX-1 and COX-2 and are distinguished from acetaminophen, which is a more effective inhibitor of COX-2. The observations from the current study would suggest COX-1 is more important to cancer risk reduction. In addition, it is becoming clear the macrophage infiltration is an important survival mechanism for cancer cell support and subsequent angiogenesis.³ The impact on local micro-environment effects by many pharmacological agents is aggressively being investigated as options for tumor control and, as in the current case, for cancer prevention.

Large population-based studies such as this where data are dependent on recall and personal estimation of use over time are very difficult to interpret. One confounding variable is recall, where cancer patients are more likely to link exposure to outcome relative to controls. However, other factors are more difficult to tease out, such as intermittent regular use or the development of a condition that might increase the risk for ovarian cancer but is mitigated by increased and episodic use of pharmacological agents to treat the effects of that disorder (e.g., endometriosis). The authors admit they could not clearly evaluate this aspect in the study. However, multiple sensitivity analyses were performed to judge the robustness of the finding and suggest the link is consistent.

It is somewhat curious that low-dose regular use of aspirin is more efficacious than high-dose aspirin, yet high-dose non-aspirin NSAIDs are more efficacious than low-dose NSAIDs, particularly since the mechanism of action is directed to COX inhibition. In addition, the use of regular high-dose NSAIDs, particularly COX-2 inhibitors, has been associated with increased cardiovascular risks making it a poor choice for chemoprevention.⁴ Nevertheless, low-dose regular aspirin use appears to clear a safety margin that also provides extensive protection against a variety of ailments. This is an extremely important consideration because institution of a chemoprevention strategy risks exposure of large numbers of unaffected individuals who will never attain a benefit from treatment. Ovarian cancer, which has a low annual incidence and overall lifetime risk, is very difficult to study in the general population. Targeting high-risk populations (such as BRCA mu-

tation carriers or Lynch syndrome patients) may improve the therapeutic index and make prospective trials to document its efficacy a feasible adventure. ■

References

1. Rothwell PM, et al. *Lancet* 2012;379:1602-1612.
2. Thun MJ, et al. *J Natl Cancer Inst* 2002;94:252-266.
3. Altinoz MA, Korkmaz R. *Neoplasma* 2004;51:239-247.
4. Mukherjee D, et al. *JAMA* 2001;286:954-959.

The Best Emergency Contraceptive? The Copper IUD

ABSTRACT & COMMENTARY

By *Rebecca H. Allen, MD, MPH*

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

Synopsis: *In this prospective cohort study, women who used the copper IUD for emergency contraception had lower unintended pregnancy rates in the following 12 months compared to women who chose the oral levonorgestrel pill.*

Source: Turok DK, et al. Emergency contraception with a copper IUD or oral levonorgestrel: An observational study of 1-year pregnancy rates. *Contraception* 2014;89:222-228.

THE AUTHORS CONDUCTED A PROSPECTIVE COHORT STUDY comparing the copper T380A intrauterine device (IUD) and oral levonorgestrel (1.5 mg LNG) for emergency contraception (EC) among 542 women at two family planning clinics in Salt Lake City, Utah, between November 2009 and July 2010. Participants were aged 18-30 years, had unprotected intercourse within 120 hours of presenting, and chose the method they desired free of charge. Exclusion criteria were uterine infection within 3 months and gonorrhea or chlamydia infection in the past 60 days. IUDs were placed by nurse practitioners who were experienced providers. Women were followed with phone calls at 1, 3, 6, 9, and 12 months to determine pregnancy rates. The primary outcome was the rate of unplanned pregnancy in the 12 months after presenting for EC.

Of the 542 women studied, 215 (40%) chose the IUD and 327 (60%) chose oral LNG. Women in the IUD group were slightly older (23.1 years vs 22.0 years; $P < 0.001$) and more likely to have heard of the IUD for contraception (94% vs 73%; $P = 0.014$). In both groups, approximately one-third of women were not using any method of con-

trapection at the time of presentation (IUD group 35%, oral LNG group 42%) and a little more than half were nulliparous (IUD group 59%, oral LNG group 53%). In the IUD group, there were 42 insertion failures; therefore, 173 women actually received the device. There were four pregnancies (1%) in the oral LNG group from EC failure and none in the copper IUD group. The 12-month follow-up rate was overall 82% with no significant differences in each arm. Ninety-five women continued the IUD with only one pregnancy, there were 17 IUD expulsions with one pregnancy, and 37 IUD removals with subsequently seven pregnancies. In the oral LNG group, there were 40 pregnancies over the following 12 months. The risk of pregnancy in the IUD group at 12 months was less than half that of the oral LNG group (hazard ratio, 0.42; 95% confidence interval [CI], 0.20-0.85).

■ COMMENTARY

In the United States, approximately half of pregnancies are unintended and 40% of these end in abortion.¹ EC is intended to reduce the risk of pregnancy after unprotected intercourse or method failure and can play an important role in reducing unintended pregnancies. While this has been demonstrated on an individual level, the population effect of EC on the national unintended pregnancy rate has been disappointing.² This is likely due to the fact that women underestimate their risk of pregnancy and do not take EC as often as they should. The effectiveness of EC depends on the mechanism of action of the method and when the method is used after unprotected intercourse. Ideally, EC should work at various points in the menstrual cycle and for 5 days after unprotected intercourse, the lifespan of the sperm in the female reproductive tract. In addition, given that many women have repeated acts of unprotected intercourse in the same cycle, a method that provides ongoing contraception would be beneficial.³

Oral LNG (1.5 mg, Plan B OneStep, Teva Pharmaceuticals) is available over-the-counter in the United States and is effective up to 72 hours after intercourse. Ulipristal acetate (30 mg, Ella, HRA Pharma) is available by prescription and is effective up to 120 hours after intercourse.⁴ In one study, among women who took EC within 72 hours of unprotected intercourse, the pregnancy rate was 1.8% for ulipristal acetate (UPA) and 2.6% for LNG. When taken between 72-120 hours after unprotected intercourse, UPA prevented pregnancy more effectively than LNG ($P = 0.037$).⁵ Overall, the risk of pregnancy was reduced by half among women using UPA compared to LNG. The reason that UPA is superior to LNG is its greater effect preventing ovulation.⁶ Of note, breastfeeding should be avoided for 36 hours after using UPA.⁴

Risk factors for failure of oral EC are body weight, intercourse during the fertile time of the cycle, and re-

peated acts of unprotected intercourse in the same cycle.⁷ Preliminary data are concerning regarding the efficacy of oral EC in overweight and obese women. One study found that obese women have a three times greater risk of pregnancy following use of oral EC compared to normal weight women (odds ratio, 3.60; 95% CI, 1.96-6.53; $P < 0.001$).⁷ LNG performs worse than UPA in overweight and obese women, losing efficacy when body mass index (BMI) exceeds 26 kg/m², while UPA appears to retain effectiveness up to a BMI of 34 kg/m².³ Of course, the most effective method of EC is the copper T 380A IUD, which has failure rates of < 1 per 1000 and is not affected by body weight.⁴ In addition, as a long-acting reversible contraceptive, it has few contraindications and high continuation and satisfaction rates.

This study, while not perfect, attempted to estimate the unintended pregnancy rates of women who chose the copper IUD or oral LNG for EC. They found that, when offered, a significant proportion of women were willing to use the copper IUD for EC. While the failed insertion rate was higher than normal, the authors speculate that the women, not having anticipated IUD insertion that day, may have experienced more anxiety and pain with the insertion process causing providers to abort the procedure. It is not surprising that women who received the copper IUD reported fewer pregnancies at 1 year than those receiving a one-time dose of LNG, given that 64% of those who received an IUD retained it at 12 months. In my opinion, the main benefit of this study is to show that the copper IUD for EC was well received by the participants. To date, the copper IUD has not been as popular for EC as the oral methods for obvious reasons: cost, logistics, and access. However, given the evidence, providers should strive to offer the copper IUD to their patients who request EC and have timely appointments available for insertion. Research is currently underway evaluating the LNG IUD for EC, given that most women prefer the bleeding profile of the LNG IUD to that of the copper IUD. Hopefully, the LNG IUD will also prove effective for EC and we will have more options to offer women. ■

References

1. Finer LB, Henshaw SK. *Perspect Sex Reprod Health* 2006;38:90-96.
2. Raymond EG, et al. *Obstet Gynecol* 2007;109:181-188.
3. Gemzell-Danielsson K, Trussell J. *Contraception* 2013;88:585-6.
4. Faculty of Sexual and Reproductive Health Care Clinical Guidance. Available at: <http://www.fsrh.org/pdfs/CEUGuidanceEmergencyContraception11.pdf>. Accessed April 28, 2014.
5. Glasier AF, et al. *Lancet* 2010;375:555-562.
6. Brache V, et al. *Contraception* 2013;88:611-618.
7. Glasier A, et al. *Contraception* 2011;84:363-367.

Racial Differences in Women with PCOS

ABSTRACT & COMMENTARY

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

Synopsis: A retrospective cohort study of 519 women diagnosed with polycystic ovary syndrome demonstrates that black adolescents and reproductive-aged adults have a higher risk for metabolic syndrome and cardiovascular disease compared to their white counterparts.

Source: Hillman JK, et al. Black women with polycystic ovary syndrome (PCOS) have increased risk for metabolic syndrome and cardiovascular disease compared with white women with PCOS. *Fertil Steril* 2014;101:530-535.

THIS STUDY CONSISTS OF 519 TOTAL WOMEN WITH POLYCYSTIC ovary syndrome (PCOS) who were stratified into adult and adolescent groups. Criteria for PCOS was different depending on the group. In the adults, two of three components were necessary to secure the diagnosis of PCOS. These adult criteria included: biochemical or clinical hyperandrogenism, oligomenorrhea, or polycystic appearing ovaries on ultrasound. This is based on the well-accepted Rotterdam criteria.¹ However, in the adolescents, PCOS was diagnosed using a previously published modified criteria (of Rotterdam) that is specific for adolescents, which included irregular menstrual cycles with nine or fewer per year for at least 2 years after menarche, polycystic ovaries on transvaginal ultrasound (volume ≥ 10 cm³), and either biochemical hyperandrogenism (total testosterone ≥ 55 ng/mL) or clinical hyperandrogenism (Ferriman-Gallaway score ≥ 8).²

Physical examination and laboratory testing, including fasting glucose and lipids, were performed on all participants. Black adolescents (relative risk [RR], 2.65; 95% confidence interval [CI], 1.29-5.4) and adults (RR, 1.44; 95% CI, 1.21-2.6) were noted to have an increased incidence of metabolic syndrome compared to white girls or women with PCOS. Overall, black PCOS patients had a higher systolic blood pressure (127.33 ± 13.3 vs 121.49 ± 13.3 mmHg), diastolic blood pressure (74.88 ± 8.76 vs 72.04 ± 9.75 mmHg), insulin (23.25 ± 22.31 vs 12.45 ± 14.11 mcU/mL), glucose (88.6 ± 18.8 vs 83.3 ± 11.6), and body mass index (BMI) > 30 kg/m² (72.3% vs 47%), but lower values for total cholesterol (179.07 ± 38.51 vs

184.49 ± 34.26 mg/dL), high-density lipoprotein (HDL; 49.24 ± 17.19 vs 55.05 ± 15.91 mg/dL), and triglycerides (100.38 ± 83.92 vs 115.47 ± 67.15 mg/dL). When controlling for age and BMI, black adults with PCOS had higher fasting concentrations of low-density lipoproteins and glucose as well as lower HDL in comparison to their white counterparts.

■ COMMENTARY

PCOS is the most common endocrine disorder in reproductive-aged women with an incidence of 8-12%. Though various diagnostic criteria have been postulated to establish a diagnosis, the classic features of PCOS are hyperandrogenism, oligomenorrhea, and a sonographic finding of a polycystic ovarian morphology. Although the Rotterdam Consensus group in 2004 allowed a diagnosis of PCOS with only two of the three classic criteria,¹ many of the experts argued that hyperandrogenism could not be eliminated when making a “definitive” diagnosis.³ Despite these minor diagnostic differences, an association between PCOS and cardiovascular comorbidities (insulin resistance, abnormal glucose metabolism, obesity, and dyslipidemias) has been recognized.⁴ Metabolic syndrome is a strong predictor of cardiovascular disease and encompasses a constellation of components including abdominal obesity, dyslipidemia, hypertension, and insulin resistance.⁵ Although the National Health and Nutrition Examination Survey (NHANES) showed no differences in non-Hispanic black men or women compared to non-Hispanic white men or women,^{6,7} a population of PCOS adolescents and young adults women was not the focus of the study.

This study highlights the racial differences in PCOS patients. Though it was known that PCOS patients are at higher risk for metabolic syndrome and cardiovascular disease, these cardio-metabolic risk factors are much worse in adolescent and adult black women compared to white women. A smaller study examined the potential metabolic differences in black and white women who had PCOS.⁸ These investigators examined 32 black and 94 white women and noted that the black women had higher HDL cholesterol concentrations and lower non-HDL and triglyceride values. A case-control study of 120 women with PCOS noted that the black cohort also had a more favorable lipid profile than their white counterparts.⁹

However, these previous studies did not address the issue of overall metabolic differences between the races. Dyslipidemias are only one aspect of metabolic syndrome, which also includes an assessment of abdominal obesity, blood pressure, and insulin resistance. This trial used BMI as a surrogate marker for abdominal obesity, which is one of the potential limitations that the authors expressed.

This study was the first to demonstrate that not all

PCOS patients are the same; although white women and girls with PCOS are at risk for increased cardiovascular disease, blacks at all ages are at much higher risk. These black adolescents and adults also demonstrated a higher incidence of obesity, lower HDL cholesterol concentrations, and higher fasting insulin and glucose levels. This is a long-term recipe for cardiovascular events (stroke, myocardial infarction, etc.) or premature death.

The study highlights the need for adequate recruitment of racially diverse populations in trials. Focused attention should be given to recruiting and maintaining women of African, Hispanic, or Asian descent to have a better assessment of their risk. Though this current investigation recruited only from one clinical center, a study from multiple sites should be undertaken to confirm or refute these findings.

Whether aggressive weight loss and dietary intervention at an early age in those diagnosed with PCOS will result in benefit remains to be seen. The National Institutes of Health's Reproductive Medicine Network is considering funding an aggressive weight loss program for patients diagnosed with PCOS.

It is my hope that racial differences can be assessed during this prospective trial. ■

References

1. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. *Fertil Steril* 2004;81:19-25.
2. Carmina E, et al. *Am J Obstet Gynecol* 2010;203:201.e 1-5.
3. Azziz R, et al. *J Clin Endocrinol Metab* 2006;91:4237-45.
4. Wild RA, et al. *J Clin Endocrinol Metab* 2010;95:2038-2049.
5. Trevisan M, et al. *Am J Epidemiol* 1998;148:958-966.

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6. Ervin RB. *Natl Health Stat Rep* 2009;5:1-7.
7. Walker SE, et al. *Nutr Metab Cardiovasc Dis* 2012;22:141-148.
8. Koval KW, et al. *J Clin Endocrinol Metab* 2010;95:E49-53.
9. Ladson G, et al. *Fertil Steril* 2011;96:224-229.

CME Questions

1. **In the Norwegian HUNT2 study, what is the take-home message?**
 - a. Since unilateral oophorectomy was associated with an approximately 1 year earlier onset of menopause, clinicians should advise women to avoid oophorectomy to avoid premature menopause.
 - b. Since unilateral oophorectomy was associated with only a 1 year earlier onset of menopause, oophorectomy should be recommended as a routine procedure during benign gynecologic surgery to reduce cancer risk.
 - c. Since unilateral oophorectomy was associated with an approximately 1 year earlier onset of menopause, clinicians can reassure patients that this procedure will have little effect on menopause, and base the decision for oophorectomy on other clinical indications.
2. **Which of the following statements best describes the findings in the study on aspirin and ovarian cancer?**
 - a. Acetaminophen provide a modest risk reduction in ovarian cancer risk.
 - b. Aspirin dose is associated with a greater beneficial effect as compared to aspirin frequency.
 - c. NSAID use significantly reduced the risk of ovarian cancer.
 - d. The analysis set was a collection of summarized patient data from randomized controlled trials.
3. **In the study by Turok et al, the risk of pregnancy in the 12 months after using emergency contraception was:**
 - a. twice as high in the IUD group compared to the oral levonorgestrel group.
 - b. the same in both the IUD group and the oral levonorgestrel group.
 - c. half as much in the IUD group compared to the oral levonorgestrel group.
4. **What is a component in the diagnosis of metabolic syndrome?**
 - a. Body mass index
 - b. Neck circumference
 - c. Elevated blood pressure
 - d. Hyperthyroidism
5. **Which of the following statements about mobility impairment and urinary incontinence in elderly women is false?**
 - a. The prevalence of urinary incontinence increases with age.
 - b. There is no relationship between mobility and urinary incontinence.
 - c. Anti-cholinergic medications can have significant side effects in the elderly.
 - d. Providers caring for elderly patients should screen for falls and gait issues.

In Future Issues:

Passive Smoking Exposure and Preeclampsia