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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Is an Even Safer Combined Oral Contraceptive Pill Available?

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, and she has served on advisory boards for Bayer and Pharmanest.

SYNOPSIS: In this large prospective cohort study, the estradiol valerate/dienogest oral contraceptive pill had a similar or even lower cardiovascular risk compared to combined oral contraceptive pills containing ethinyl estradiol and other progestins.

SOURCE: Dinger J, Do Minh T, Heinemann K. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. *Contraception*. June 2016. [Epub ahead of print].

This Phase IV, prospective cohort study of combined oral contraceptive (COC) users, titled the International Active Surveillance Study on the Safety of Contraceptives and the Role of Estrogens (INAS-SCORE), was conducted in the United States and Europe. The primary objective of the study was to assess the risks of short- and long-term use of a new COC formulation containing estradiol valerate (EV) and dienogest (DNG) compared to other COC formulations. The DNG/EV pill is marketed as Natazia in the United States and is approved for contraception and heavy menstrual bleeding by the FDA. Women were recruited from 2009 to 2013 in participating physicians' offices. The main clinical outcomes were venous and arterial thromboembolic events: deep vein thrombosis, pulmonary embolism, myocardial infarction, and stroke. Study participants could be starters (new pills users), switchers (women switching from one COC to another), or restarters (women who restarted COCs with a break of at least four weeks). All women who opted for COCs were offered participation in the study. There were no specific inclusion or exclusion criteria. Robust baseline data on cardiovascular risk factors (age, body mass index [BMI], smoking, hypertension, high cholesterol, diabetes, family history, cancer) were collected, and women were followed every six months for the first two years and annually thereafter. A group of medical experts confirmed all reported serious adverse events by contacting study participants and their treating physicians as well as evaluating medical records. A blinded, independent adjudicator reassessed these judgments. The

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researchers compared three exposure groups: users of DNG/EV pills, users of all other COCs (oCOC), and users of levonorgestrel-containing COCs (LNG).

A total of 50,203 women enrolled in the study and were analyzed, 60% from Europe and 40% from the United States, contributing 105,761 women-years (WY) of observation. Average follow-up was 1.6 years in the United States because of a later recruitment start than anticipated and 2.4 years in Europe. Women were allowed to change COC types or discontinue COC use during the study. Ultimately, there were 12,512 WY for DNG/EV and 63,539 WY for oCOC, of which 10,071 WY were LNG users. Only 3.1% of study participants were lost to follow-up, and these women were balanced across the groups. Participants in the DNG/EV group were older at enrollment (median age 31 vs. 26 years). BMI and other cardiovascular risk factors were equally distributed among the three groups. American women had a higher BMI but lower smoking rates than European women. The authors observed 77 venous thromboembolic events (VTE): DNG/EV, nine cases for 7.2 VTE per 10,000 WY; oCOC, 58 cases for 9.1 VTE per 10,000 WY; and LNG, 10 cases for 9.9 VTE per 10,000 WY. After controlling for age, BMI, current duration of use, and family history of VTE, the adjusted hazard ratio was 0.5 (95% confidence interval [CI], 0.2-1.0) for DNG/EV vs. oCOC, and 0.5 (95% CI, 0.2-1.3) for DNG/EV vs. LNG. When only the European data were analyzed, the adjusted hazard ratio for DNG/EV vs. oCOC was 0.4 (95% CI, 0.2-1.0) and was statistically significant. A total of 18 arterial thromboembolic events (ATE) were observed: four myocardial infarctions, 10 ischemic strokes, two transient ischemic attacks, and two peripheral artery thromboses. This corresponds to DNG/EV, one case for 0.8 ATE/10,000 WY; oCOC, 15 cases for 2.4/10,000 WY; and LNG, one case for 1.0/10,000 WY. For comparison, there were two ATE in women not using contraception at the time.

■ COMMENTARY

Until now, the most common estrogen component of COCs has been ethinyl estradiol. Ethinyl estradiol is a potent synthetic estrogen with similar metabolic effects (e.g., liver protein production) regardless of the route of administration because of the long half-life of ethinyl estradiol and slow metabolism.[1] In contrast, EV is a synthetic hormone that is immediately metabolized to estradiol and valeric acid before reaching the systemic circulation.[2] Estradiol is identical to endogenously produced 17 ß-estradiol. Data from menopausal use have shown that transdermally and vaginally administered estradiol is not associated with an increased production of liver proteins and, therefore, has a lower risk for thrombosis.[3] Whether the same will hold true of oral administration for contraceptive purposes has not been studied until now. A daily dose of 2 mg of EV has biological effects on the uterus, ovary, and hypothalamic-pituitary-ovarian axis similar to those of a 20 mcg dose of ethinyl estradiol.[2] Natazia — the first estradiol-containing pill available in the United States — is a 28-day formulation that delivers 3 mg of EV on days 1 and 2, 2 mg of EV and 2 mg of DNG on days 3 to 7, 2 mg of EV and 3 mg of DNG on days 8 to 24, 1 mg of EV on days 25 and 26, and placebo on days 27 and 28. This four-phasic regimen was developed to minimize the unscheduled bleeding seen in earlier versions of EV-containing oral contraceptives. In a study comparing the DNG/EV oral contraceptive with a monophasic oral contraceptive containing ethinyl estradiol and LNG, the DNG/EV pill had a well-tolerated bleeding profile and decreased episodes of withdrawal bleeding.[4]

This study was conducted at the request of the European Drug regulatory authorities after the introduction of the DNG/EV pill to the market. The study has many advantages, including ascertainment of important confounding variables, validation of outcomes and exposure, comprehensive long-term follow-up, and a low rate of loss to follow-up. In addition, the study population was not restricted and is representative of COC users in normal clinical practice. The DNG/EV group was older than the oCOC group, especially in the European population (difference in mean 6.2 years). The authors speculated that this reflects prescribing patterns in Europe, where gynecologists use estradiol-containing hormone replacement therapy preparations preferentially, and, therefore, may have associated the DNG/EV oral contraceptive pill with older women. In addition, during the study, the DNG/EV pill had approval for heavy menstrual bleeding in Europe but not yet in the United States.[5] Therefore, it may have been chosen preferentially for older women in Europe.

The authors highlighted the fact that the European data showed a statistically significant lower risk of VTE for DNG/EV vs. oCOC pills and that incidence rates were lower for DNG/EV vs. oCOC and LNG. The authors focused on the European-only data, as only

4% of the DNG/EV group was American and there were no VTE events in the American DNG/EV participants. These are certainly promising data about EV that will need to be confirmed with further studies. These results were unchanged when VTE outcomes were restricted to only "idiopathic" VTE (e.g., not associated with pregnancy, surgery, trauma, immobilization, chemotherapy, or long-haul air travel). It would be interesting to know in future analyses if the risk of VTE changed when comparing DNG/EV users to users of COCs containing only 20 mcg of ethinyl estradiol. However, at the very least, there is good evidence that the DNG/EV is as safe as existing pills containing ethinyl estradiol and other progestins. Personally, I have not prescribed Natazia, since it is a brand-name pill that is more expensive than generics in the United States. Nevertheless, the safety data for this new formulation are reassuring. ■

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ABSTRACT & COMMENTARY

Genetic Testing: Who Should Be Tested and What Should They Be Tested For?

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 she receives grant/research support from the National Cancer Institute.

SYNOPSIS: Genetic testing has changed rapidly over the past three years, so to prevent cancer, it is critical that obstetricians-gynecologists take a complete family history, identify women at risk, and make appropriate referrals for genetic counseling with potential testing to prevent cancer.

SOURCE: Hall MJ, Obeid EI, Schwartz S, et al. Genetic testing for hereditary cancer predisposition: BRCA1/2, Lynch syndrome and beyond. *Gynecol Oncol* 2016;140:565-574.

A recent review paper outlined genetic testing for BRCA1/2, Lynch, and other recently identified genes that predispose women to gynecologic cancers.[1] Over the past three years since Myriad Genetics lost its patent on gene testing for BRCA1/2 mutations, there has been an explosion of companies doing genetic testing, with eight additional companies doing panels of genes. These gene panels have expanded testing beyond BRCA1/2 mutations significantly. Genetic testing for cancer predisposition is a relatively recent phenomenon and has only been available for about 20 years. Mary Claire King and her group initially discovered BRCA1 in 1990 and cloned it in 1994, leading to the patent by the company that would later become Myriad Genetics. BRCA2 was discovered in 1996, but widespread testing for this gene mutation took another 10 years. In 2002, Myriad Genetics launched a campaign of direct-to-consumer marketing to promote BRCA 1/2 testing to all physicians. There was considerable concern about the lack of genetic counseling that accompanied this testing, because the implications of a positive test, a negative test, and an uncertain result, a variant of uncertain significance (VUS), are very different. In addition, because of Myriad's patent, no other labs could offer commercial genetic testing until the patent was overturned in 2013. Prior to overturning the patent, the cost of open reading frame testing for BRCA1/2 was more than $4,000. With the development of next generation sequencing (Next-gen) and the revocation of the patent, the cost for multigene testing became much less than the earlier patent-protected testing.

The best known inheritable cancer syndrome is hereditary breast and ovarian cancer syndrome. First described in 1971 by Henry Lynch,[2] it is an autosomal dominant genetic disorder associated with a deleterious mutation in BRCA1 or 2 genes, which function as tumor suppressor genes. These mutations are associated with a significantly increased risk of breast cancer and ovarian cancer and are characterized by early onset cancers. BRCA1/2 mutations are responsible for 10% of breast cancers and 10-20% of ovarian cancers. Risk of ovarian cancer varies with mutation, but BRCA1 carries a 44-63% lifetime risk of ovarian cancer and BRCA2 carries a 27-31% lifetime risk by age 70 years.[3,4] These are extremely high compared to the baseline population risk of 1.5-1.7% lifetime risk.

Henry Lynch also described Lynch syndrome (hereditary nonpolyposis colorectal cancer). Initially, Lynch syndrome was described as an increased risk of colorectal cancer but

was soon extended to endometrial and ovarian cancers.[5] These cancers are due to deleterious mutations in mismatch repair genes MLH1, MSH2, MSH6 and PMS2. MLH1 and MSH2 are associated most strongly with early-onset colorectal cancer and endometrial cancer. MSH6 is associated with a higher risk of endometrial cancer.[6] At least 20% of ovarian cancers are linked to a deleterious mutation in BRCA1/2 or Lynch and another 5% are due to other mutations.[7,8]

Genes other than BRCA1/2 associated with an increased risk of ovarian cancer include BRIP1, RAD51C, RAD51D, and MRE11. BRIP1 has been reported to have a relative risk (RR) of 11-14 for ovarian cancer and RAD51D a RR of 6.3.[1] Other mutations include MRE11, NBS1, and RAD50, which all are associated with an increased risk of ovarian cancer.[9]

■ COMMENTARY

Why is it important to identify mutations associated with an increase in gynecologic cancer risk? Obstetrician-gynecologists are the optimal physicians to identify these women at risk. Family history remains the cornerstone of identifying women who should be referred for genetic counseling and testing.[10] By taking a careful family history, and referring patients for genetic testing and counseling, women who are identified as carrying a deleterious mutation can undergo either an increase in screening or prophylactic surgery to avoid many of these cancers.[10,11] In addition to identifying a risk of gynecologic cancers, women or their families may be at risk for other cancers, including breast cancer, colorectal cancer, prostate cancer, pancreatic cancer, and melanoma, and they also can be referred for appropriate screening.

Should obstetrician-gynecologists test for mutations that may predispose their patients to cancer? Unfortunately, most physicians do not understand the complexity of the new mutations nor do they understand the implications of a negative test, particularly if the patient who underwent genetic testing did not have cancer. They do have the background to understand the implications of a variant that has not been classified as deleterious or benign, which is called a VUS. With the genetic information changing so rapidly over the past three years, taking a complete family history, identifying women at risk, and making appropriate referrals for genetic counseling with potential testing is critical to our role as obstetricians-gynecologists to prevent cancer. ■

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ABSTRACT & COMMENTARY

Oligohydramnios: How to Best Diagnose It and What It Really Means

By John C. Hobbins, MD

Professor, Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Aurora

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

SYNOPSIS: A multicenter randomized, clinical trial involving large numbers of patients has shown that using the maximal vertical pocket instead of the amniotic fluid index to detect oligohydramnios more than halves the amount of inductions for the diagnosis of oligohydramnios without affecting the overall outcome.

SOURCE: Kehl S, Schlekle A, Thomas A, et al. Single deepest vertical pocket or amniotic fluid index as an evaluation test for predicting adverse pregnancy outcome (SAFE Trial): A multicenter, open label, randomized controlled trial. *Ultrasound Obstet Gynecol* 2016;47:674-679.

Oligohydramnios gets the attention of providers for good reason. It is seen more frequently in patients whose fetuses have intrauterine growth restriction (IUGR) and in those with ruptured membranes (PROM). In the IUGR, it has been thought that the fetus will adapt to intrauterine deprivation by sending more blood to the brain at the expense of renal plasma flow. In PROM, the etiology is obvious and, if dealing with prolonged severe oligohydramnios, there is great concern for fetal pulmonary hypoplasia. Since oligohydramnios has been noted to correlate with outcome in IUGR and, to some extent, in PROM, attempts to detect it have been expanded to include, seemingly, any high-risk patient. In fact, it has become the staple of every fetal surveillance regimen.

The two most common methods to evaluate the amount of amniotic fluid in the uterus are the amniotic fluid index (AFI) and the maximum vertical pocket (MVP). Even though most studies[1,2,3] and a Cochrane meta-analysis[4] have suggested the MVP to be the superior method, the AFI-leaning providers have not appeared to be swayed by the results of these studies.

In a recent multicenter study from Germany, the authors initiated a randomized trial in low-risk and high-risk patients who had ultrasound exams after 36 weeks and who delivered within one week of their last exams. One group of patients was randomly assigned to have MVPs as the method of choice in their assessments and the other group had AFIs. The patients were all managed according to the desires of the primary providers. However, oligohydramnios was used as a diagnostic trigger for induction. Neonatal outcomes were based on many variables.

Data were available for 498 patients in the AFI group and 504 patients in the MVP group. About 82% of the study group were labeled as low risk. Oligohydramnios was diagnosed more frequently by AFI (9.8% vs. 2.2%; relative risk [RR], 4.51; 95% confidence interval [CI], 4.8-1.50), resulting in more inductions of labor for oligohydramnios (12% vs. 3.6%; RR, 3.50; 95% CI, 1.76-6.96). Interestingly, although there was an increase in "abnormal cardiotocography" in the AFI group (36.3% vs. 26.2%; RR, 1.23; 95% CI, 1.02-1.50), there was no increase in the need for cesarean section for "fetal distress" (RR, 1.26; 95% CI, 0.88-1.79). Most importantly, there were no differences in any of the many neonatal outcomes investigated (newborn special care unit admissions, Apgar scores, blood gases, and meconium-stained amniotic fluid).

■ COMMENTARY

Amniotic fluid assessment is part of every ultrasound exam done throughout pregnancy and is an integral part of the biophysical profile (BPP), which is incorporated into surveillance protocols in late pregnancy. The BPP originally was developed by Platt and Manning in 1980.[5] The authors decided to use a vertical pocket of ≤ 1 cm to define oligohydramnios. However, it soon was clear that this cutoff was too stringent, so the MVP threshold was liberalized to 2 cm. It was then realized that even when there is an obvious paucity of amniotic fluid, it is possible with some creativity to get a thin slice of fluid in a vertical plane to measure > 2 cm. This led to the addition of a horizontal dimension to the definition of oligohydramnios (i.e., a pocket of < 2 cm × 2 cm, or < 2 cm × 1 cm, as was used in the above study).

Later, based on the concept of "if some is good, more is better," Phelen adapted the technique to use the sum of four vertical pockets in each of four quadrants of the uterus. The thresholds of concern were AFIs of < 5 cm for oligohydramnios and > 20 cm for polyhydramnios.[6]

Again, this study shows that by using MVP as a primary tool in fetal assessment, fewer patients are labeled as having oligohydramnios, thereby subjecting fewer patients to inductions. Although this study did not show an increase in cesarean sections with the AFI, other studies have shown an increase.[4,7] Of significant note was the fact that this increased intervention did not result in improvement in any of the adverse neonatal outcomes studied.

Although oligohydramnios can be very concerning, true oligohydramnios is not a usual feature of IUGR. The most common form of IUGR is late IUGR in which most surveillance tests, including umbilical artery waveforms, nonstress tests, and BPPs (including amniotic fluid assessment) are normal. Why? Although the supply line is sufficient to sustain these fetuses for many weeks, they simply get to a point, generally after 34 weeks, where they demand more than their partially challenged placentas can provide. To adapt, they begin prioritizing by sparing their brains. This shift in blood flow does not curtail urine production immediately, so by the time they get our attention, oligohydramnios has not yet had a chance to develop. If oligohydramnios does complicate IUGR, it is in the early, severe, forms of placental insufficiency in which there are many other worrisome clues that surface first.

I am amazed at how often providers quibble about the subtle differences in MVPs or AFIs. These methods represent indirect reflections of a dynamic process of amniotic fluid production and absorption that vary not just on a day-to-day basis, but on an hour-to-hour basis. In addition, the methods themselves have wide inter- and intra-observer variabilities. Now that amniotic fluid assessment has been applied to high-risk and low-risk patients, its value, if isolated, should be put into proper perspective. Even in conditions such as IUGR and PROM, oligohydramnios rarely should be a "game changer," by itself, with regard to intervention. ■

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SPECIAL FEATURE

PCOS and Hormonal Contraception: A Tale of Two Syndromes?

By Jeffrey T. Jensen, MD, MPH, Editor

SYNOPSIS: Emerging evidence supports that two metabolic phenotypes exist among women with polycystic ovary syndrome (PCOS). For metabolically healthy PCOS patients, managing menstrual symptoms, anovulation and androgen excess with combined oral contraceptives (COCs) provides a simple and well-tolerated treatment regimen. In contrast, PCOS patients with metabolic syndrome are at high risk for type 2 diabetes, and COC use may contribute to hyperinsulinemia, adverse lipid changes, and endothelial changes associated with adverse cardiovascular risk. The use of a levonorgestrel intrauterine device combined with spironolactone (to manage hyperandrogenism) and metformin (to manage hyperinsulinism) may offer advantages to metabolically unhealthy PCOS patients.

Recent advances in the treatment of polycystic ovary syndrome (PCOS) support therapeutic interventions that address the key disturbances of the condition: combined oral contraceptive pills (COCs) to suppress ovarian androgens and induce regular menstrual bleeding, metformin to treat hyperinsulinemia and improve glucose tolerance, and lifestyle modification of diet and exercise for weight loss. Although all of these have supportive data, not all patients present with the same complaints, and some treatments, such as contraception or prevention of metabolic disturbances, are better tolerated or offer additional benefits.

As a syndrome, PCOS encompasses a heterogeneous group of women who present with hyperandrogenism, anovulation, and polycystic ovarian morphology. Recently, the Endocrine Society recommended new guidelines for the diagnosis and treatment of PCOS.[1] For adults, a diagnosis of PCOS can be made if two of the three Rotterdam criteria are met: androgen excess, ovulatory dysfunction, or polycystic ovaries (PCO). Disorders that mimic the clinical features of PCOS (thyroid disease, hyperprolactinemia, and nonclassic congenital adrenal hyperplasia) must be excluded. In adolescents, the diagnosis must include the clinical or biochemical evidence of hyperandrogenism (after exclusion of other causes) in the presence of persistent oligomenorrhea. Since anovulation and polycystic appearance of ovaries on ultrasound occur commonly during adolescence, neither provides evidence for PCOS in the absence of hyperandrogenism. Although obesity and metabolic dysfunction are not included in the diagnosis of PCOS, both occur commonly. About one-third of adolescents with PCOS meet criteria for metabolic syndrome compared with only 5% without PCOS.[2] The risk of metabolic syndrome seems correlated with increasing androgen levels independent of obesity and insulin resistance.[2] Metabolic syndrome increases the risk of cardiovascular disease.

ROLE OF COMBINED ORAL CONTRACEPTIVES

COCs act to decrease gonadotropins that stimulate ovarian steroid hormone production. This results in a decrease in ovarian androgen production, a prime factor that drives the PCOS phenotype. Progestins also decrease the conversion of testosterone to the more potent and peripherally active 5-hydrotestosterone that is associated with acne and hirsutism. Drospirenone offers the unique property of inhibiting the androgen receptor directly. The estrogen competent of all combined pills provides an additional therapeutic effect by increasing sex hormone binding globulin, further lowering free androgen levels. A large literature supports the beneficial effect of COCs on the phenotypic symptoms of hyperandrogenism.[3] Although low androgen progestins result in the greatest decrease in free and total androgens,[4] the clinical benefit has not been shown in women with PCOS. A randomized study by Kriplani et al compared oral drospirenone/ethinyl estradiol (EE) to desogestrel/EE in Indian women with PCOS.[5] Both groups showed similar improvement in acne. Treatment with the drospirenone pill resulted in a reduction of body mass index (BMI) (-0.52 kg/m^2) and blood pressure compared to slight increases with desogestrel. The lipid profile improved, and fasting/postprandial blood sugar, insulin, and total testosterone all decreased compared to the desogestrel pill.

However, COCs also increase the risk of thrombosis, a risk also elevated by obesity. Some studies suggest that COCs increase the risk of insulin resistance and coronary heart disease. A cohort study of 31-year-old women from Finland found that after adjusting for BMI, income, and area of residence, users of COCs had higher systolic and diastolic blood pressure, increased levels of inflammatory indices (C-reactive protein), and impaired insulin sensitivity compared to users of the levonorgestrel-releasing intrauterine device.[6] This raises the question of safety for COC use in women with PCOS.

Mastorakos et al randomized adolescent girls with PCOS to treatment with a COC containing desogestrel 150 mcg plus EE 30 mcg or cyproterone acetate (CPA) 2 mg/EE 35 mcg.[7] CPA pills are commonly prescribed in Europe for acne and are considered to be non-androgenic. After 12 months of

treatment, insulin resistance increased significantly in both groups, but insulin levels increased only among teens using the CPA pill. Battaglia et al compared oral drospirenone/EE to the etonogestrel/EE vaginal ring (CVR).[8] Although fasting insulin, glucose, and C-peptide did not change with either treatment, the area under the curve (AUC) for both insulin and glucose significantly decreased in users of the CVR.
A recent study by Adeniji et al compared the metabolic response following initiation of triphasic norgestimate/EE COC in obese (BMI > 30 kg/m^2) women with and without PCOS.[9] The obese PCOS subjects were more insulin resistant, had higher fasting insulin and glucose levels, and had higher AUC insulin at baseline. After three months of COC use, glucose tolerance deteriorated further only in the PCOS group, but there was no additional increase in insulin resistance. This study confirmed the previously noted positive correlation of androgen levels to insulin resistance and cardiovascular risk.[10,11]

WHEN TO USE INSULIN SENSITIZERS

Metformin reduces hepatic glucose output and increases insulin-stimulated glucose uptake in skeletal muscle and adipocytes. It also has been used to improve fertility in women with PCOS. Although clinical pregnancy rates are improved for metformin (alone or with clomiphene) vs. placebo, a recent Cochrane review concluded that there was no evidence that metformin improved live birth rates.[12] Costello and colleagues reviewed the evidence comparing metformin to combined pills in non-diabetic women with PCOS and concluded that there is no evidence of a difference in effect between the two therapies on reducing fasting glucose levels, total cholesterol levels, or severe adverse events.[13] Among obese teenagers with PCOS, the addition of metformin did not add improvement to quality-of-life measures above those observed with lifestyle modification and COC treatment alone.[14] Taken together, these data do not support a role for metformin in the treatment of non-diabetic women with PCOS.

LIFESTYLE MODIFICATIONS

A growing literature supports the value of lifestyle modification with diet and exercise for women with PCOS. Hoeger and colleagues randomized obese adolescent women with PCOS to receive either metformin, a lifestyle modification program, a COC, or placebo.[15] They followed this study with a randomized combination trial of lifestyle modification and COC with and without metformin. In the single intervention study, both lifestyle modification (-59%) and COCs (-86%) significantly reduced the free androgen index, and COC use decreased BMI (mean decrease 1.4 kg/m^2). The addition of metformin to lifestyle modification and COCs in the combination trial resulted in a further reduction of total testosterone and central obesity, but did not enhance overall weight reduction.

Dokras et al evaluated quality of life in women with PCOS randomized to a continuous COC, intensive lifestyle modification, or a combination of both approaches.[16] All three interventions resulted in significant improvement in health-related quality of life. Orio et al randomized women with PCOS to a drospirenone/EE COC, a structured exercise program, or a multivitamin (control).[17] The primary outcome was change in intima-media thickness (IMT) and flow mediated dilation (FMD). After six months of treatment, the IMT was significantly lower and reduced from baseline in the exercise group, with no changes observed in the COC and control groups. FMD also significantly improved only in the exercise group. Similarly, BMI significantly reduced only in the exercise group, while menstrual regularity improved in both the exercise and COC group. Fasting glucose and AUC for glucose did not change with any of the treatments. Acne scores, free testosterone, and the free androgen index improved only with COC treatment.

THE LEVONORGESTREL INTRAUTERINE SYSTEM

The levonorgestrel intrauterine system provides reliable, long-acting, and highly effective contraception. For women with PCOS, intrauterine levonorgestrel provides protection from anovulation-related endometrial hyperplasia and carcinoma, and effective treatment for heavy menstrual bleeding.[18] The local mechanism of action results in a neutral metabolic profile[19] and no increase in thrombosis.[20] However, since gonadotropins generally are not suppressed with the levonorgestrel intrauterine system, there is no reduction in ovarian androgen production or treatment of androgen excess. Thus, effective treatment of androgen excess requires the addition of spironolactone or an alternative anti-androgen.

CLINICAL RECOMMENDATION

Women with PCOS should undergo detailed evaluation for signs of type 2 diabetes and metabolic syndrome. Growing evidence supports lifestyle modification, with diet and exercise as a cornerstone of therapy for both prevention and a primary treatment for metabolic syndrome and type 2 diabetes. Metformin is indicated as treatment for women with PCOS who have clinical diabetes. Healthy women with PCOS can safely use combined hormonal contraception. Combined hormonal contraception also will manage symptoms of hyperandrogenism effectively. Although there may be theoretical advantages to low-androgen progestins, there is an absence of supportive comparison studies in PCOS women. Since obesity is an independent risk factor for venous thrombosis, and greatly increases the risk of thrombosis with combined hormonal contraception, use of COCs is not recommended. The levonorgestrel intrauterine system provides endometrial protection for obese women with PCOS, but does not manage androgen excess. ■

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CME/CE QUESTIONS

1. On average, Dinger et al found which of the following to be true of the American cohort?
a. Americans had lower body mass index compared to the Europeans.
b. Americans had higher smoking rates compared to the Europeans.
c. Americans had lower smoking rates compared to the Europeans.
d. Americans made up the majority of the study cohort.

2. BRCA1/2 deleterious mutation is:
a. responsible for 50% of ovarian cancers.
b. responsible for 10-20% of ovarian cancers.
c. the only gene mutation associated with ovarian cancer.
d. not associated with ovarian cancer.

3. Kehl et al did not find a significant increase in cesarean section rate when amniotic fluid index was used instead of the maximum vertical pocket, but other studies have found such an association.
a. True
b. False

4. Which of the following statements is true when considering treatment options for women with polycystic ovarian syndrome (PCOS)?
a. Obese women with PCOS should receive counseling on exercise and diet as a primary therapy.
b. PCOS is a contraindication to use of combined oral contraceptives.
c. The LNG IUS is an effective treatment for androgen excess.
d. Metformin is a first line agent for prevention of metabolic syndrome and obesity in adolescents with PCOS.