

DIALOGUES



IN CONTRACEPTION®

In This Issue

Depot Medroxyprogesterone Acetate and Bone Density

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Polycystic Ovary Syndrome: Management and Contraception

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Depot Medroxyprogesterone Acetate and Bone Density

Raquel D. Arias, MD, Andrew M. Kaunitz, MD, and Michael R. McClung, MD

Educational Objectives:

The health care provider should be able to:

- describe advantages and disadvantages of depot medroxyprogesterone acetate (DMPA) use by individual adolescent and adult women
- evaluate evidence regarding short- and long-term effects of DMPA on skeletal health
- counsel all reproductive-age women about importance of maintaining a healthy lifestyle to minimize risks of osteoporotic fractures later in life
- utilize an evidence-based approach to the recently approved black box changes in DMPA product labeling

Illustrative Case Study

Carol V: An 18-year-old Asian woman, who had an unintended pregnancy and termination at age 16, has been using depot medroxyprogesterone acetate (DMPA) for contraception ever since and is now amenorrheic. She is concerned about media reports that this contraceptive method should not be used for longer than 2 years because of increased risk of fractures later in life.

The 2002 National Survey of Family Growth reported that 5.3% of all US women aged 15 through 44 currently using contraception used DMPA.¹ Among contraceptors, 13.9% of those aged 15 to 19 and 10.1% of those aged 20 to 24 currently used DMPA compared with 1.6% of those aged 40 to 44.¹ Decreasing rates of adolescent pregnancy between 1995 and 2002 are considered to be due in part to increased use of some method of contraception, including DMPA, by this age group.²⁻⁵

Advantages of DMPA Use

DMPA provides high contraceptive effectiveness, with a first-year pregnancy rate of 0.3%.^{6,7} Contraceptive effectiveness begins within 24 hours after injection.⁸ However, women can still ovulate in the first 24 hours; therefore, backup protection is needed for the first 3 days of DMPA use. The contraceptive efficacy of DMPA is maintained for at least 14 weeks after administration, providing a margin of protection if reinjection is delayed.^{8,9} Use of DMPA is convenient and discreet, characteristics often desired by adolescents seeking contraception. The intramuscular or subcutaneous injection of DMPA is required only once every 3 months, the injection site is invisible, and the long-acting contraception provided by DMPA is not dependent on user action or partner cooperation at the time of intercourse. The reversible contraceptive action of DMPA is inhibition of ovulation, with ovulation resuming between 14 weeks to 9 months after method discontinuation.⁸

Physicians will read the newsletter and submit a Post-Test and Evaluation
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Dear Colleague:

As Executive Editor of *Dialogues in Contraception*®, I am pleased to introduce you to the latest volume of this long-established newsletter. As always, *Dialogues in Contraception* will continue to present timely, useful, and comprehensive articles on new developments and topical issues in contraception.

We are excited to tell you about some new features this year:

- In response to reader requests, we've changed the look of the publication to include larger type size and more "white space" for easier reading
- *Dialogues in Contraception* will continue to provide the best in evidence-based medicine, but the reference list supporting each article will now be found online at www.usc.edu/CME
- There will no longer be any fee for CME/CE credits: **All continuing education credit for *Dialogues in Contraception* is now FREE!**

Our Editorial Board is composed of distinguished leaders in this field, including Kathryn M. Andolsek, MD, MPH; Raquel D. Arias, MD; Ronald T. Burkman, MD; Philip D. Darney, MD, MSc; Andrew M. Kaunitz, MD; Sharon M. Schnare, RN, FNP, CNM, MSN, FAANP; Lee P. Shulman, MD; Deborah M. Smith, MD, MPH; Leon Speroff, MD; Carolyn L. Westhoff, MD, MSc; and Susan J. Wysocki, RNC, NP, FAANP. *Dialogues in Contraception* will continue to feature articles written by Board members as well as by guest experts in obstetrics and gynecology, epidemiology, public health, family medicine, and other medical specialties. We encourage readers to correspond with the authors and Editorial Board members with questions or comments on the articles in each issue.

The Board is committed to responding to the clinician's need for relevant and current information on women's health issues; therefore, we will incorporate into Volume 11 many of the topics suggested by your responses to our last Readership Survey. In light of that survey, the first issue of Volume 11 contains articles on polycystic ovary syndrome, depot medroxyprogesterone acetate and bone density, and emergency contraception.

Some of the other topics we'll be covering throughout the year include:

- Unscheduled bleeding with various contraceptive methods
- Obesity and contraceptive efficacy
- Advances in female sterilization
- Economics of contraception
- Socio- and multicultural issues
- Sexual satisfaction and mood changes with contraception

Finally, we will be conducting an Outcomes Study and a Readership Survey in which we hope you will participate; your feedback helps us make the newsletter an even better tool for your practice by focusing on the issues important to you and your fellow clinicians.

This newsletter series is sponsored by the Keck School of Medicine of the University of Southern California and produced by Health Learning Systems (HLS), part of Common-Health®, under an educational grant from Ortho Women's Health and Urology, a division of Ortho-McNeil Pharmaceutical, Inc.

We appreciate your continued support of and interest in *Dialogues in Contraception* and encourage you to complete the post-test in each issue to obtain FREE continuing education credit. Past issues of *Dialogues in Contraception* are available on the Keck School of Medicine Office of Continuing Medical Education Web site (www.usc.edu/cme). Also, as each print issue of Volume 11 is distributed, it is simultaneously posted to the Web site. Many readers download copies of the newsletter to use as teaching materials or to give out to colleagues and staff members. It's easy, convenient, and free of charge, so feel free to download extra copies to fit your needs.

Sincerely,

Daniel R. Mishell, Jr, MD
The Lyle G. McNeile Professor
Department of Obstetrics and Gynecology

Executive Editor
Dialogues in Contraception®

In addition, since DMPA is a progestin-only method, it is appropriate for many women in whom estrogen use is contraindicated. Ovarian estradiol production is reduced with DMPA use.^{8,10} For about one third of DMPA users, mean estradiol levels are similar to those in normal-cycling women during the early- to mid-follicular phase of the menstrual cycle, approximately 40 to 50 pg/mL.^{8,10} However, for most DMPA users estradiol levels vary after the DMPA injection and may reach levels found in postmenopausal women (mean 18.9 pg/mL).¹⁰ Vasomotor symptoms and vaginal dryness occur uncommonly in DMPA users.^{8,11} High-dose progestins suppress vasomotor symptoms.^{12,13}

DMPA Use and Bone Mineral Density (BMD)

BMD Decreases During DMPA Use

The decreased endogenous serum estradiol levels produced by DMPA use may increase the rate of bone resorption.^{14,15} Many studies have found that, in adult DMPA users, BMD decreases from baseline levels, and, in current adolescent DMPA users, BMD levels are reduced compared with nonusers.¹⁵⁻³² Methodology and study population demographics, as well as BMD levels and the extent of BMD decrease found in DMPA users, vary among studies. Not all studies have found statistically significant differences in BMD between DMPA users and nonusers³³⁻³⁵; some cross-sectional studies report that BMD levels among DMPA users are generally within 1 standard deviation (SD) of the mean BMD found in nonusers.^{21,31}

A systematic review of DMPA studies found that, in longitudinal studies of adult DMPA users, the rates of BMD reduction changed over the period of use and differed among studies, with most studies reporting overall BMD decreases of less than 1% per year of use.²¹ The same review found that, in adolescents, differences in BMD reflected both decreased BMD in DMPA users and increased BMD in nonusers.²¹ A 7-year prospective, matched-cohort study of women aged 25 to 35 initiating DMPA use or using nonhormonal contraception assessed BMD changes over periods up to 4.6 years and posttreatment follow-up of up to 1.8 years.³² After 4.6 years of DMPA use, the mean percentage BMD change from baseline in DMPA users was -5.16% (SD, 3.60%) in the total hip and -5.38% (SD, 3.57%) in the lumbar spine, whereas little change from baseline in the lumbar spine (increases of <0.5%) was observed in the nonhormonal contraceptive users.³² The rate of BMD decline was greater in DMPA users in the first year of use than in following years.³² Other studies of women initiating DMPA use found BMD decreases of about 2% to 3% per year during the first 2 years of use^{20,28}; however, almost all of the decrease in BMD occurs in the first 2 years of DMPA use, with little incremental BMD loss during additional years of use.^{17,28,32} There are no data on postmenopausal fracture rates in women who used DMPA as adolescents or adults; therefore, the clinical significance of DMPA-associated declines in BMD is unknown.

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BMD Recovers After DMPA Discontinuation

Most studies find that women regain BMD after discontinuation of DMPA use.²¹

Adults

Studies of adult DMPA users have found that decreases in BMD are reversed after discontinuation of DMPA use.^{21,36,37} The 7-year prospective study found that at 1.8 years after DMPA discontinuation, total hip BMD had returned almost to baseline levels (-0.20%) and lumbar spine BMD levels showed partial recovery (-1.19%).³² In a prospective cohort study, mean BMD in former DMPA users 30 months after discontinuation was similar to that of never-users at either hip or spine.¹⁷ Another study found that in the 2 years following discontinuation of long-term (median 10 years; range 3 to 17 years) DMPA use, BMD in the lumbar spine increased significantly ($p < .002$), with mean increases overall of 3% (0.4% to 5.6%) at 1 year and 6.4% (3.4% to 9.4%) at 2 years.³⁸ One longitudinal study found that after discontinuation of DMPA use by women aged 18 to 35 at initiation, recovery of BMD differed by anatomical site and length of DMPA use: in all women there was return to levels seen in nonuser controls by 76 months and return to baseline levels by 92 months.²⁸ A cross-sectional study of women aged 30 to 34 found significantly lower mean BMD in short-term (24 to 36 months) current DMPA users than in never-users of hormonal contraceptives, but no significant differences in BMD between long-term (more than 48 months) current users of DMPA and never-users.³¹

A cross-sectional study of postmenopausal former-users of DMPA and never-users found no significant differences in BMD between the groups.³⁹ Overall, the evidence indicates that former-users of DMPA postmenopausally have BMD nearly identical to that of never-users.

Adolescents

Because adolescence is a critical period of bone accretion,⁴⁰ recent evidence of BMD recovery in adolescents following discontinuation of DMPA use is also reassuring. In a population-based, prospective cohort study of DMPA users aged 14 to 18 (the only study of BMD changes following DMPA discontinuation by adolescents), mean BMD measured at all anatomical sites reached or exceeded the levels of never-users by 12 months after DMPA discontinuation.¹⁶ This finding indicates that there is a faster rate of BMD recovery after stopping DMPA use in adolescents than that observed in adult DMPA discontinuers. Mean annualized gains in BMD by adolescents following discontinuation of DMPA use in this study also were greater than those occurring in an older cohort (18 to 39 years) prospectively studied by the same investigators¹⁷ (hip, 1.34% vs 1.04% per year, respectively; spine, 2.86% vs 1.41%, respectively).¹⁶

Modification of lifestyle factors may help increase BMD in all adolescents, including DMPA users.^{3,41} All adolescents should be encouraged to perform weight-bearing exercise, not to smoke, and to follow an adequately nutritious diet including sufficient dietary calcium (1300 mg/day) and vitamin D (200-400 IU) daily. Although these strategies are important for all women to attain peak bone mass during adolescence, studies documenting the efficacy of lifestyle modifications on improvement of BMD in DMPA users have not been performed.

Lactation and BMD: Similarities to DMPA Use

Hypoestrogenemia normally occurs postpartum and is associated with decreases in BMD.⁴² In the first days postpartum, women have lower BMD than age-matched nonpregnant controls.⁴³ During 3 months or more of lactation, breastfeeding women experience progressive declines in BMD compared with nonbreastfeeding women, who progressively regain BMD.⁴³⁻⁴⁷

After weaning, BMD increases to postpregnancy levels or higher.^{42,43,45} BMD also recovers after the resumption of menses, whether or not lactation continues.^{42,44,45,47} In women aged 20 to 25 who became mothers as adolescents and breastfed their infants, BMD after weaning was 5% to 10% higher than among similarly aged women who had been non-breastfeeding adolescent mothers.⁴⁸ Mean BMD of the former women was equivalent to nulliparous women. Calcium supplementation has not been found to prevent BMD decreases during lactation and only slightly enhances the gain in BMD after weaning.^{44,46}

The changes in BMD—both decline and recovery—associated with DMPA use demonstrate similarities to the BMD changes that occur postpartum during and after breastfeeding (Figure).^{17,32,47} The magnitude of BMD decrease is greater with lactation than with DMPA, but the patterns of BMD recovery are parallel.⁴⁹ Prolonged duration of breastfeeding has not been found to be associated with an elevated risk of postmenopausal fractures. The decrease in BMD associated with DMPA use is similarly transient, and BMD in adults has been found to be at least as high in former adolescent DMPA users as in never-users.¹⁶

ACOG Guidelines. ACOG recommends that skeletal health concerns should not restrict use of DMPA in adult women. In adolescents, the advantages of DMPA use outweigh the theoretical concerns regarding BMD and fractures. Consideration of long-term use in adolescents should be individualized.⁵¹

SAM Position Paper. SAM states that, for the majority of adolescents, the benefits of DMPA use (ie, prevention of physical, social, and economic adverse effects of unintended pregnancy including possible attendant effects on bone) outweigh potential risks. The use of DMPA in adolescents can be continued without any restriction on duration of use. Counseling about the risks and benefits of DMPA use should be provided.¹⁴

WHO Recommendations. The WHO recommends that there should be no restriction on use or duration of use of DMPA in adult women otherwise eligible to use this method. Among adolescents, the advantages of DMPA use generally outweigh theoretical concerns regarding fracture risk. Overall risks and benefits for continuing DMPA use should be reconsidered over time with individual adolescent users.⁵²

Are Tests or Interventions Appropriate?

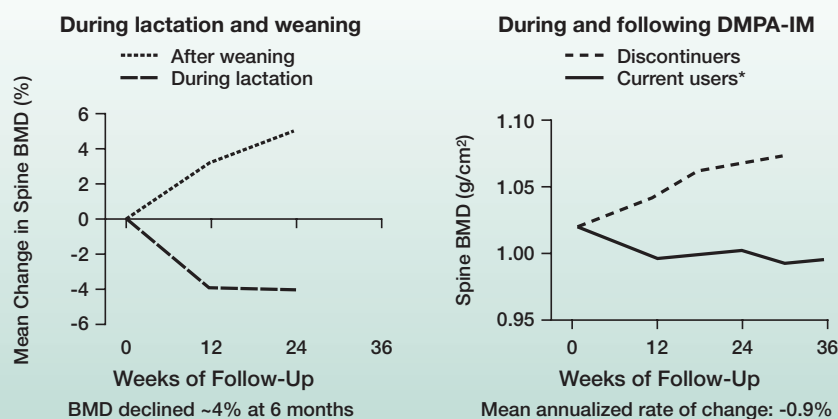
It should be axiomatic in clinical practice that testing of any type is not indicated if the test results will not influence management. The WHO provided diagnostic criteria for osteoporosis and low bone density (osteopenia) in postmenopausal Caucasian women based upon BMD values by dual energy x-ray absorptiometry.^{53,54} For determining the future probability of osteoporotic fractures, BMD is combined with other clinical risk factors, most importantly age and prior fracture history.⁵⁵ Much confusion surrounds the use of these WHO criteria in young women. The International Society for Clinical Densitometry has stated that the WHO criteria—which were developed for use in *postmenopausal* white women—cannot be applied to premenopausal women, who by definition cannot have postmenopausal osteoporosis.⁵⁶ Moreover, the use of T-scores is not appropriate for young women who have not reached skeletal maturity.⁵⁶ BMD testing is recommended only in adolescents or premenopausal women who have had fragility fractures or who have medical problems known to be associated with significant skeletal consequences.⁵⁶

The results of BMD tests in prospective or current DMPA users provide no more useful information than they would in lactating women. Therefore, in the absence of other indications, bone densitometry should not be performed either at initiation or for follow-up in apparently healthy women or adolescents using DMPA for contraception.^{14,49,51}

The results of BMD tests in prospective or current DMPA users provide no more useful information than they would in lactating women. Therefore, in the absence of other indications, bone densitometry should not be performed either at initiation or for follow-up in apparently healthy women or adolescents using DMPA for contraception.^{14,49,51}

(continued on page 9)

Figure. BMD changes with DMPA use and with lactation.^{17,47}



*Median duration of use, 11 months (range, 1 to 133 months)

BMD=bone mineral density; DMPA-IM=depot medroxyprogesterone-intramuscular.

Adapted with permission from: Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study. *Epidemiology*. 2002;13(5):581-587; and Kalkwarf HJ, Specker BL. Bone mineral loss during lactation and recovery after weaning. *Obstet Gynecol*. 1995;86(1):26-32.

DMPA Labeling

In 2004, the US Food and Drug Administration (FDA) mandated that a black box warning be added to DMPA labeling, stating that^{6,7,50} women who use DMPA may lose significant BMD; that bone loss is greater with increasing duration of use and may not be completely reversible; that it is unknown whether use of DMPA during adolescence or early adulthood will reduce peak bone mass or increase risk for osteoporotic fracture in later life; and that DMPA should be used as birth control for longer than 2 years only if other contraceptive methods are inadequate.

Professional Society Recommendations

After publication of these FDA labeling changes, and after review of the available evidence, the American College of Obstetricians and Gynecologists (ACOG), the Society for Adolescent Medicine (SAM), and the World Health Organization (WHO) endorsed guidelines differing from the DMPA product labeling.^{14,51,52}

Polycystic Ovary Syndrome: Management and Contraception

Leon Speroff, MD, and Daniel R. Mishell, Jr, MD

Educational Objectives:

The health care provider should be able to:

- evaluate signs and symptoms suggestive of polycystic ovary syndrome (PCOS)
- establish diagnosis of PCOS and any associated disorders through clinical findings and—when appropriate—diagnostic tests
- select and implement management strategies tailored to the individual characteristics of each woman with PCOS
- identify the benefit/risk profiles of various contraceptive methods for women with PCOS who wish to prevent pregnancy

Illustrative Case Study

Anne T: A 25-year-old overweight woman presents with visible hirsutism and oligomenorrhea. She is concerned by her facial hair and the irregularity of her menses. She does not want to become pregnant.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women, affecting approximately 1 in 15 (6.6%) women in the United States.^{1,2} Its etiology is not clearly understood, but studies suggest a genetic (autosomal-dominant) component³; clinicians should counsel the families of women diagnosed with PCOS that, theoretically, as many as 50% of sisters and daughters of affected women may also have PCOS characteristics. Women eventually diagnosed with PCOS typically present because of irregular bleeding, hirsutism, and/or infertility.^{4,5} PCOS is often accompanied by hyperinsulinemia, insulin resistance (IR), and glucose intolerance, which are correlated with high body mass index (BMI) and obesity.^{4,6}

Definitions/Diagnostic Criteria Controversy

Differing definitions of PCOS, including varying sets of diagnostic criteria, developed in recent years are in widespread use and have given rise to controversy.

National Institutes of Health: In 1990, an expert conference sponsored by the US National Institutes of Health (NIH) reviewed the available scientific literature and defined PCOS as a disorder characterized by evidence of hyperandrogenism **and** chronic anovulation when secondary causes of androgen excess (eg, adult-onset congenital adrenal hyperplasia, androgen-secreting neoplasms) have been excluded.⁷⁻⁹ Both the American College of Obstetricians and Gynecologists (ACOG) and the Androgen Excess Society agree that PCOS should first be considered a disorder of androgen excess or hyperandrogenism.^{7,9} Ultrasonographic documentation of polycystic ovarian morphology is not required for diagnosis under this definition. Polycystic ovaries (defined as at least one ovary with 12 or more follicles of 2 to 10 mm in a single plane or an ovarian volume greater than 10 mL in the absence of a dominant follicle greater than 10 mm, a corpus luteum, or a cyst¹⁰) are a common finding

(up to 25%) in women who are endocrinologically normal and neither hyperandrogenic nor anovulatory; such morphology does not commonly predispose to the development of PCOS and often resolves over time.¹⁰ Similarly, many women with oligoanovulation and hirsutism do not have polycystic ovarian morphology.¹¹

Rotterdam Conference: In 2003, the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine Rotterdam Conference agreed on a wider definition of PCOS. In this definition, PCOS is diagnosed when **at least 2** of the following 3 features are present: oligo-ovulation and/or anovulation; clinical and/or biochemical signs of hyperandrogenism; and polycystic ovaries seen by ultrasound.¹² Unlike the NIH definition, no single criterion is absolutely required for the diagnosis of PCOS; a diagnosis of PCOS can be made in the absence of evidence of hyperandrogenism if there is anovulation and polycystic ovarian morphology viewed by ultrasound.¹³ With these criteria, the frequency of diagnosis of PCOS is increased by about 65%, mainly due to the inclusion of women without hyperandrogenism¹³; however, the occurrence of obesity and carbohydrate disturbances was found to be considerably lower, supporting the hypothesis of a causal interrelationship between androgen excess and excess body weight.¹³

Generally, the NIH definition prevails in the United States, with the first criterion for PCOS being recognized as androgen excess with or without polycystic ovaries. Although approximately 75% of women with PCOS demonstrate polycystic ovarian morphology on ultrasonography, the false-positive rate is high,⁹ with up to 25% of an unselected group of women having this type of ovarian morphology.¹⁰ Ultrasonography to document the presence of polycystic ovaries is not necessary for the diagnosis of PCOS.

Diagnostic Evaluation

Clinical diagnosis of PCOS is based on signs of hyperandrogenism (eg, hirsutism, acne, androgenic alopecia⁹) and history of chronic anovulation. Laboratory tests are not routinely necessary for diagnostic purposes. Signs of hyperandrogenism can range from mild acne to severe hirsutism; clinicians should look for such signs of androgenicity, which may be concealed by makeup, hairstyle, bleaching, or hair removal. Hirsutism is the most common manifestation of the androgen component of PCOS⁴; acne, androgenic alopecia, and acanthosis nigricans can also be present.⁷ Other causes of androgen excess (eg, androgen-secreting neoplasms, exogenous androgens, adult-onset congenital adrenal hyperplasia) should be excluded.

Menstrual irregularities range from oligomenorrhea to amenorrhea; women with PCOS classically report a history of irregular menstrual cycles beginning soon after menarche, and generally report 6 or fewer episodes of spontaneous uterine bleeding per year.⁴ Obesity is not always present, but the majority of women with PCOS are obese and may also be insulin-resistant.⁸

Many—but not all—women with PCOS have elevated luteinizing hormone (LH) levels, increased LH/follicle-stimulating hormone ratios, elevated androstenedione levels, and mildly increased testosterone or dehydroepiandrosterone sulfate levels.¹⁴ However, routine laboratory assays for these serum levels are unnecessary if there is no evidence

of virilization,^{3,15} and the diagnosis of PCOS can be made by clinical presentation alone. Similarly, ultrasound examination of ovaries is not necessary for diagnosing PCOS since polycystic ovaries are a common finding in ovulatory women without hyperandrogenism.¹⁰

Testing for metabolic abnormalities, however, should be performed so that therapy can be instituted if necessary. IR is defined as a reduced glucose response to a given amount of insulin.³ All anovulatory and hyperandrogenic women should be tested for glucose tolerance and IR with measurement of 2-hour glucose and insulin levels after a 75-g glucose load; measurement of fasting glucose to fasting insulin ratio is not recommended because of its variability among ethnic groups and US population segments.^{3,16,17} A 2-hour glucose response of 140 to 199 mg/dL indicates impairment; 200 mg/dL and higher indicates non-insulin-dependent diabetes mellitus. A 2-hour insulin response of 100 to 150 U/mL suggests that IR is very likely, whereas 151 to 300 U/mL is diagnostic of IR, and greater than 300 U/mL denotes severe IR (*Table*).³ Lipid and lipoprotein levels should also be measured, as dyslipidemia is common in obese women and dyslipidemia is associated with IR.^{8,18} In addition, blood pressure, body weight, height, and waist circumference should be measured and BMI calculated.

Table. 2-Hour Glucose and Insulin Levels After 75-g Glucose Load³

2-hour Glucose Response

140–199 mg/dL: Impairment

≥200 mg/dL: Non-insulin-dependent diabetes mellitus

2-hour Insulin Response

100–150 U/mL: Insulin resistance likely

151–300 U/mL: Diagnostic of insulin resistance

>300 U/mL: Severe insulin resistance

Medical Effects of PCOS

Comorbid Conditions

Women with PCOS usually are obese and frequently have impaired glucose tolerance, IR, and dyslipidemia, each of which is a risk factor for both diabetes and cardiovascular disease (CVD).^{2,6,18,19} Glucose intolerance is significantly higher in obese women with PCOS (~30%) than in age-, ethnicity-, and weight-matched ovulatory control women (~10%).⁸ PCOS-related IR has been estimated to be associated with about 10% of cases of glucose intolerance in premenopausal women.⁸ Studies of women with PCOS have found increased (2- to 5-fold) risks of developing diabetes compared with controls.⁷

The prevalence of IR in women with PCOS is about 64%,²⁰ and IR in PCOS is worsened by abdominal obesity.²¹ Because IR can lead to hyperinsulinemia, which can then stimulate altered lipoprotein metabolism,²² women with PCOS often have abnormal lipoprotein profiles, including increased triglycerides, decreased high-density lipoprotein (HDL)-cholesterol, and increased low-density lipoprotein (LDL)-cholesterol.²³ Nearly 70% of women with PCOS have borderline or elevated cholesterol levels.^{7,23} Atherosclerosis from dyslipidemia increases risk for CVD, and studies of surrogate markers for CVD in women with PCOS have established the existence of classical risk factors for CVD.^{18,24,25} No prospective epidemiologic studies have been performed in older women with PCOS to determine whether or not they have an increased risk of CVD, but it is likely that CVD will be increased in older women with PCOS.

Other Sequelae of PCOS

Chronic anovulation, as occurs in many women with PCOS, results in unopposed high levels of endogenous estrogen, which have been shown to increase the risk of developing adenocarcinoma of the endometrium.^{26–28} Among a cohort of 1270 women with chronic anovulation followed for 14,499 woman-years, the relative risk (RR) of developing carcinoma of the endometrium compared with standard-population incidence rates was 3.1 (confidence interval [CI] 1.1–7.30).²⁷ A meta-analysis of 15 case-control studies (720 women with PCOS, 4505 women without PCOS) of pregnancy and neonatal outcomes in women with PCOS found a significantly higher likelihood of developing gestational diabetes (odds ratio [OR] 2.94, CI 1.70–5.08) among women with PCOS than among controls.²⁹ A number of studies have found high risks of spontaneous abortion in women with PCOS (25% to 73%) whether or not their pregnancies were facilitated by fertility induction treatment.^{30–34}

In selecting short- and long-term interventions for the treatment of PCOS manifestations, clinicians and women should be aware of health benefits associated with such interventions to help prevent development of diabetes and atherosclerosis. No pharmaceutical agents have been approved by the US Food and Drug Administration for the treatment of PCOS, but many off-label therapies for various aspects of PCOS have been found effective in both studies and wide clinical practice. For overweight and obese women with PCOS, lifestyle intervention including weight-reduction strategies (eg, calorie-restricted diet, enhanced physical activity) should be basic to any treatment program to help restore menstrual cyclicity and ovulation and to help decrease IR, glucose intolerance, and dyslipidemia.^{35–39} In 2 prospective studies of anovulatory obese women, average weight losses of as little as 10% from baseline resulted in resumption of ovulation in more than 80% of women, and pregnancies occurred in many of them.^{38,39} However, no studies have evaluated the duration of these beneficial effects, so whether the symptoms of PCOS recur over time is unknown.

Insulin-sensitizing agents (eg, metformin hydrochloride) can enhance weight-reduction efforts in obese, insulin-resistant women with PCOS and can increase insulin sensitivity to improve CVD risk factors associated with hyperinsulinemia in both obese and nonobese women with PCOS.^{40–42} The thiazolidinediones (eg, rosiglitazone, pioglitazone) have been found to produce improvements in IR, glucose intolerance, and hyperandrogenism in women with PCOS.^{43,44} However, the necessity to monitor liver enzymes during therapy with the thiazolidinediones may make these agents less acceptable.⁴⁵

Treatment of PCOS

Determination of appropriate therapeutic regimens for women with PCOS depends on whether each affected woman is primarily seeking to restore fertility or to avoid pregnancy while ameliorating her major PCOS symptoms.

Ovulation-inducing Strategies

Pharmacologic agents to induce ovulation in anovulatory women such as those with PCOS include clomiphene citrate and metformin hydrochloride. Two recent randomized controlled trials found that metformin alone is less effective in achieving ovulation and live births than clomiphene alone, and that metformin in combination with clomiphene is no more effective than clomiphene alone.^{46,47} In one of these trials, fecundity as determined by conception per ovulatory woman was significantly lower in the metformin-treated group (8.4%) compared with the clomiphene-treated group (39.5%) or combination-treated group

(46.0%; $p < .001$).⁴⁷ In ovulation induction of women with glucose abnormalities or insulin tolerance, adding metformin to the treatment regimen may be beneficial after failure to respond to clomiphene.⁴⁸ Laparoscopic ovarian drilling may be a secondary option for women who remain anovulatory after clomiphene and/or metformin therapy.⁴⁹

Contraception for Women With PCOS

Women with PCOS who do not wish to become pregnant need effective contraception because ovulation can occur at any time, even in women who have been persistently anovulatory.

Combination Hormonal Methods

Combination estrogen/progestin hormonal contraceptives (combination oral contraceptives [COCs], transdermal patch, vaginal ring) offer highly effective contraception while regularizing cyclic bleeding and providing beneficial effects on a variety of other PCOS manifestations. Combination hormonal contraceptives containing low-androgenic progestins are preferred for women with PCOS to avoid enhancing hyperandrogenism.

There has been some controversy as to whether or not combination hormonal contraceptives negatively affect glucose tolerance and insulin sensitivity and therefore whether or not their use should be avoided in women with PCOS.^{50,51} The majority of the evidence indicates that these agents have minimal, clinically insignificant effects on carbohydrate metabolism in nonsmoking women,^{52,53} even those with PCOS.⁵⁴ When women with PCOS and hyperinsulinism who used COCs for up to 10 years were compared with similar women not using COCs over the same period, glucose tolerance, basal insulin levels, and BMI improved over time in COC users while in nonusers hyperinsulinemia and IR worsened.⁵⁵ Metformin can be used concomitantly with combination hormonal contraceptives to improve insulin sensitivity in affected women with PCOS.⁵⁶ Use of COCs does not increase the risk of developing diabetes mellitus in women with prior gestational diabetes.^{57,58} No deterioration of lipid or biochemical markers for CVD was found in women with insulin-dependent diabetes using low-dose (≤ 35 mcg estrogen) COCs, and no increase in development of retinopathy or nephropathy was observed compared with nonusers with diabetes.⁵⁹

Combination estrogen/progestin hormonal contraceptives (combination oral contraceptives, transdermal patch, vaginal ring) offer highly effective contraception while regularizing cyclic bleeding and providing beneficial effects on a variety of other PCOS manifestations

Similarly, current or past use of low-dose estrogen-containing contraceptives does not increase the risk of stroke or myocardial infarction in reproductive-age, nonsmoking, normotensive women with no other risk factors for CVD.⁶⁰⁻⁶⁴ There is no evidence that women with PCOS who use combination hormonal contraceptives experience more CVD events than the general population.⁷ Clinicians should be aware that both obesity and estrogen-containing contraceptives are independent risk factors for venous thromboembolism (VTE).^{60,65} However, the overall absolute risk of VTE is low in women of reproductive age; the increased risk of VTE with combination hormonal contraceptive use remains low and is about half the risk associated with pregnancy. The risk of VTE in users of combination hormonal contraceptives is increased in obese women (BMI >30) compared with nonobese users (BMI <25 ; OR 3.47, CI 2.35-5.10).⁶⁵ For this reason, a family history of VTE in obese women is a concern but not a contraindication to use of combination hormonal contraceptives.⁶⁶

There has also been controversy regarding whether or not combination hormonal contraceptives may be less effective in preventing pregnancy in obese women than in nonobese women.⁶⁷⁻⁷⁴ However, several studies have found no effect of body weight on contraceptive efficacy.⁷²⁻⁷⁴ Decreased effectiveness of contraceptive steroids with increased body weight has not been conclusively demonstrated; even in those studies finding slightly reduced efficacy, these methods remain highly effective for most users regardless of weight, with very few pregnancies occurring even in the heaviest users and statistically significant differences attenuated by adjustment for socioeconomic factors and smoking.^{70,71}

In addition, combination hormonal contraceptives offer noncontraceptive benefits of particular relevance to women with PCOS. The estrogen component of these methods increases levels of sex-hormone binding globulin, which binds greater amounts of testosterone and reduces circulating levels of free testosterone, the cause of androgenicity.^{54,55,75} Reduction in LH reduces the amount of ovarian testosterone synthesis. The beneficial clinical effects of this process include improvements in hirsutism and acne.^{7,76,77}

Furthermore, anovulation and endometrial exposure to unopposed estrogen are associated with increased risk of endometrial hyperplasia and cancer.^{26,27,78} Hormonal contraceptives inhibit endometrial proliferation, protecting against the risk of endometrial cancer; in healthy women, ever-use of COCs reduces risk of endometrial cancer by at least 40% for at least 20 years after discontinuation of method use.⁷⁹⁻⁸⁴ There are no data regarding endometrial cancer risk and use of COCs in women with PCOS. Use of combination contraceptives also reduces the risk of dysfunctional uterine bleeding,⁸⁵ a condition which is common in women with PCOS.

Injectable Progestin-only Contraceptive

Depot medroxyprogesterone acetate (DMPA) is an option for contraception in women with PCOS who have contraindications to estrogen. However, DMPA may increase weight gain and/or appetite, and the possible impact of high-dose progestin on IR may also be a concern. Nevertheless, the progestin should reduce the effect of estrogen on the endometrium to reduce risk of hyperplasia.

Intrauterine Contraceptives (IUCs)

IUC use is appropriate for women with PCOS who wish to avoid pregnancy but are unable or unwilling to use hormonal contraception. Although both the copper IUC and the levonorgestrel (LNG)-releasing IUC are appropriate options, the LNG-IUC may be preferable because the progestin should reduce the impact of estrogen on the endometrium. The circulating levels of LNG provided by this method are not sufficient to suppress ovulation, and androgenic effects are uncommon.

Conclusions

Illustrative Case Study Resolution

Anne T: After a 75-g glucose load, measurement of 2-hour glucose and insulin levels results were 110 mg/dL and 75 U/mL, respectively, indicating no IR; therefore, an insulin-sensitizing agent was not prescribed. A strict exercise regimen and hypocaloric diet were developed to facilitate weight loss. A low-dose, low-androgenic-progestin COC was prescribed for contraception, to regularize bleeding, and to help ameliorate the hirsutism. After 6 months of COC use, Anne had lost 10 pounds, her withdrawal bleeding episodes were regular, and her hirsutism had begun to improve.

The first criterion for diagnosis of PCOS is androgen excess, with or without polycystic ovaries. The diagnosis of PCOS is a clinical one, based on presenting symptoms (such as oligomenorrhea) and signs of

(continued on page 10)

Emergency Contraception: An Update

Deborah M. Smith, MD, MPH

Emergency contraception (EC) is intended for use in preventing unintended pregnancy after a single unprotected or inadequately protected act of sexual intercourse but before pregnancy occurs; EC is not intended for use as an ongoing method of contraception.¹ The Table provides a brief timeline of EC development and use.

In August 2006, the US Food and Drug Administration approved a unique dual over-the-counter (OTC)/prescription status for levonorgestrel (LNG)-only EC.² This agent is now available for OTC pharmacy purchase, without a prescription, by women and men aged 18 and older.² Proof of age is required for purchase, and the product is stocked by pharmacies behind the counter to control approved access. For women aged under 18, LNG EC remains available on a prescription-only basis.

of pregnancy with LNG-only EC compared with combined regimen: 0.36, confidence interval [CI], 0.18–0.70).³ The overall background rate of expected pregnancy among women after a single act of midcycle unprotected intercourse is approximately 8%.⁴ WHO findings indicate that use of LNG EC can prevent 85% of expected pregnancies, thus reducing the expected pregnancy rate to approximately 1%.^{3,5} However, the effectiveness of LNG EC has never been assessed in a placebo-controlled trial, which would be neither ethical nor feasible.⁶

The copper intrauterine contraceptive, inserted within 7 days after unprotected intercourse, is also highly effective as EC but is not approved in the United States for this use.^{7,8}

reduced rates of unintended pregnancy.^{9–12} Similarly, elective abortion rates were not found to be reduced with widespread interventional provision of EC compared with rates in similar geographic areas during the same time period.¹³ Nevertheless, most studies have found that advance provision and/or direct access to EC increases prompt use of EC, and does not decrease ongoing use of regular contraception or increase frequency of unprotected intercourse, repeated use of EC, frequency of sexual activity by adolescents, or rates of sexually transmitted infections compared with EC prescription at the time of need.^{9–12,14–19} Use of EC also increases the likelihood of subsequent adoption of more effective methods of ongoing contraception.⁹

Most coital circumstances that increase risk of unintended pregnancy (eg, no or incorrect use of contraception, broken condom, dislodged barrier method) are instantly recognizable by the participants.⁹ Prompt use of EC has the potential to reduce an individual woman's risk of unintended pregnancy following a single act of intercourse compared with not using EC, and EC use is safe. Therefore, there is little reason why women should not avail themselves of this second chance to prevent unintended pregnancy. It is likely that the convenient OTC availability of EC may increase awareness and use, resulting in decreased rates of unintended pregnancy on a population level.

Table. Background History of EC

1960s:	use of high-dose estrogen as postcoital contraception for rape victims
1974:	Yuzpe regimen of estrogen-progestin COCs for EC first described
1984:	Yuzpe regimen approved in United Kingdom for EC; approval by other countries follows
1990s:	in the United States, off-label use of COCs for EC
1997:	US FDA approves use of various COC regimens as "safe and effective for postcoital emergency contraception"
1998:	prescription-only dedicated EE/LNG EC approved by FDA (no longer available)
1999:	prescription-only 2-tablet (0.75 mg each) LNG EC approved by FDA
2001:	petition to FDA requesting OTC status for EC
2006:	FDA approves LNG EC agent for OTC pharmacy sale to women and men aged 18 and older; same agent retains prescription-only status for women aged under 18

EC=emergency contraception; COC=combined oral contraceptive; FDA=Food and Drug Administration; EE=ethinyl estradiol; LNG=levonorgestrel; OTC=over-the-counter.

Although various high-dose regimens of combination oral contraceptives (COCs) or LNG-only OCs can also be used as EC (off-label applications), this *Dialogues in Contraception*® update focuses on the dedicated LNG EC. LNG EC was found in a World Health Organization (WHO) randomized controlled trial to be significantly more effective in preventing pregnancy than the combined OC regimen (pregnancy rates, 1.1% vs 3.2%, respectively; relative risk [RR]

Effects of Increased Access to EC: Study Findings

Studies of interventions to increase access to steroidal EC compared with control groups (eg, free advance provision vs information only or vs prescription access at time of need) have not found significantly

Mechanism of Action

EC is intended for use in preventing the occurrence of pregnancy after a single unprotected or inadequately protected act of sexual intercourse.¹ Ingested in the preovulatory (follicular) phase of a woman's cycle, LNG EC inhibits or delays ovulation by preventing or delaying the luteinizing hormone peak and inhibiting follicle rupture.^{20–25} Preovulatory and postovulatory administration of LNG EC does not impair corpus luteum function or endometrial morphology.^{20,21} LNG EC does not appear to affect implantation or endometrial development and is ineffective after ovulation.^{24,26} Importantly, LNG EC does not increase risk to an established pregnancy or a developing embryo.²⁷

Timing and Administration

Prescribing and package information for LNG EC advises ingestion of the first tablet within 72 hours (3 days) of a single act of unprotected intercourse, with the second tablet taken 12 hours after the first.⁵ Administered later than 72 hours postcoitus, LNG EC is slightly less effective but still capable of preventing a proportion of pregnancies. In a WHO multicenter randomized trial of various EC regimens, LNG EC prevented 79% to 84% of expected pregnancies (observed pregnancies, 1.34% to 1.69%) when taken within 1 to 3 days following intercourse, and 60% to 63% of expected pregnancies (observed pregnancies, 2.44% to 2.67%) when taken 4 to 5 days after intercourse.²⁸ Therefore, while EC should be used as soon as possible following the unprotected act of coitus for optimal effectiveness, women should be aware that EC taken up to 5 days following intercourse may still prevent an unintended pregnancy. In addition, randomized trials have found that taking both 0.75 mg LNG tablets at the same time is as effective in preventing pregnancy as taking the 2 tablets 12 hours apart.^{28,29} In the WHO randomized trial, the pregnancy rates with single-dose (1.5 mg) LNG and 2-dose LNG were 1.5% (20/1356) and 1.8% (24/1356), respectively.²⁸

For further information about EC, clinicians can direct women to the EC Web site, not-2-late.com, at <http://ec.princeton.edu/>.

Use of EC does not reduce the risk of pregnancy with coitus that occurs subsequent to EC administration; women should be aware that risk of pregnancy may even be increased with intercourse occurring in the first few days following EC treatment because of delayed ovulation.^{1,28,29}

Side Effects

Side effects with use of LNG EC are few, minor, and transient. Incidences of nausea and vomiting are decreased with LNG EC (23.1%, 5.6%, respectively) compared with combination EC (50.5%, 18.8%, respectively).³ A case-series study comparing bleeding patterns after use of LNG EC with modeled usual menstrual cycle lengths found that the first complete cycle following EC administration was significantly shorter than the usual cycle length ($p \leq 0.0001$) but the length of the second cycle was not significantly different from that expected.³⁰ Intermenstrual bleeding occurred in 8% or fewer of LNG EC users in each of these 2 cycles.³⁰ The overall safety of steroidal EC, including LNG EC, is reflected in WHO eligibility criteria for use: there are no medical conditions for which

the theoretical or proven risks outweigh the advantages of using EC.³¹

Summary

According to the most recent (2002) National Surveys of Family Growth, nearly half (49%) of all pregnancies in the United States are unintended, and more than half of those unintended pregnancies (52%) occur in women who use no contraception during the month of conception.³² Because many women are still unaware of the potential of EC to reduce risk of unintended pregnancy after a single act of unprotected or underprotected intercourse, this safe and effective method remains underutilized. Now that LNG EC is available both OTC to men and women aged 18 and older and by prescription to women aged under 18, the combination of increased access to and health education about EC should increase use. When contraception has not been used during coitus, or a condom breaks during intercourse, women usually immediately realize their heightened risk of unintended pregnancy. With education by clinicians, women can now become equally aware of their ability to reduce that risk by using EC as soon as possible after unprotected intercourse.

References are available online at www.usc.edu/cme

Depot Medroxyprogesterone Acetate and Bone Density (continued from page 4)

Even more uncertain is the role or effectiveness for young women of drugs approved to treat women with postmenopausal osteoporosis. There is no evidence that bisphosphonate therapy for young women with low BMD reduces fracture risk, and there is concern about the use of these agents in women who might subsequently become pregnant.^{57,58} The selective estrogen-receptor modulator raloxifene is contraindicated in women who may become pregnant⁵⁹ and would likely induce bone loss in premenopausal women as has been observed with tamoxifen.⁶⁰ With teriparatide injection in adolescents, there would be concern about osteosarcoma.⁶¹ None of these agents has been studied in healthy premenopausal women or in DMPA users.⁵⁹ In the absence of a strong clinical rationale (eg, long-term glucocorticoid therapy), no justification exists for prescribing drugs that treat osteoporosis to current DMPA users.

Regardless of use or nonuse of any contraceptive method, the US Recommended Adequate Intake daily for all adolescents to maximize bone formation are 1300 mg of calcium and 5 mcg (200 IU) of vitamin D.⁶² However, many clinicians recommend 400 IU daily for adolescents.

With rare exceptions (eg, immobilized adolescent), estrogen supplementation is not recommended for DMPA users because the

required daily user action and estrogenic side effects may complicate correct DMPA use.¹⁴

Long-Term DMPA Use

Studies of long-term (up to 27 years) current or former DMPA users, including postmenopausal women, have found little or no difference in BMD between these women and similarly aged controls,^{24,39,63} and there are no data reporting an increased incidence of fractures in these women. It is therefore reasonable for women who wish to do so to continue using DMPA until their mid-50s, when contraception is no longer necessary.

Subcutaneous DMPA is approved for management of endometriosis-associated pain,⁷ and intramuscular DMPA also has been found to be effective for this purpose (off-label application).⁶⁴ In clinical trials, DMPA has been found equivalent to leuprolide acetate in reducing endometriosis-associated pain with less short-term impact on BMD.^{36,37} With this chronic disease, clinicians also may use DMPA until menopause.

(continued on page 10)

Conclusions

Illustrative Case Study Resolution

Carol V: During annual contraceptive counseling, the clinician noted that Carol liked the convenience of DMPA use and was satisfied with the resulting amenorrhea. With regard to her concerns about skeletal health, the clinician explained that, although BMD declines during DMPA use, it recovers after discontinuation of contraceptive injections, and that there is no evidence of current or future increased fracture risk with DMPA use. Carol was reassured and elected to continue DMPA use.

The pattern of BMD decline and recovery associated with DMPA use is similar to that associated with lactation. There is no evidence of increased fracture rates with current or past DMPA use. Neither bone densitometry testing nor antiresorptive agents should be utilized in otherwise healthy adolescents or adults considering or using DMPA. Concerns about skeletal health should not restrict initiation, continuation, or duration of DMPA use at any age.

hyperandrogenism (eg, hirsutism, acne). Ultrasonography to document the presence of polycystic ovaries is unnecessary for diagnosis or treatment decisions. Similarly, in the absence of evidence of virilization, laboratory testing for serum androgen values should not be performed. In contrast, women with PCOS should be tested for glucose tolerance and IR with measurement of 2-hour glucose and insulin levels after a 75-g glucose load. If IR is present, use of metformin should be initiated. Lipid and lipoprotein levels should also be assessed.

Low-dose nonandrogenic combination hormonal contraceptive methods continue to be appropriate first-line choices for women with PCOS who do not wish to become pregnant. The use of such antidiabetic agents as metformin should be restricted to women with documented IR and may be used in these women concurrently with a combination hormonal contraceptive if pregnancy is not desired.

References are available online at www.usc.edu/cme

Post-Test

The following Post-Test contains 10 multiple-choice questions based on information contained in the *Dialogues in Contraception*[®], Volume 11, Number 1, newsletter. It is designed to enable practitioners to assess the knowledge they have gained from the newsletter and to identify areas for further study.

On the Answer Sheet, fill in all identifying information requested. Complete the Answer Sheet by circling the one response that most accurately answers each question.

- Women eventually diagnosed with polycystic ovary syndrome (PCOS) typically present because of which of the following?
 - irregular bleeding
 - hirsutism
 - infertility
 - any of the above
- The first criterion for PCOS is recognized in the United States as androgen excess with or without polycystic ovaries.
 - True
 - False
- The prevalence of insulin resistance in women with PCOS is about:
 - 24%
 - 44%
 - 64%
 - 84%
- The majority of the evidence indicates that combination hormonal contraceptives have minimal, clinically insignificant effects on carbohydrate metabolism in nonsmoking women, even those with PCOS.
 - True
 - False
- Levonorgestrel emergency contraception (LNG EC) is available for over-the-counter pharmacy purchase, without a prescription, by women and men aged 18 and older; for women aged under 18, LNG EC remains available only by prescription.
 - True
 - False
- In a World Health Organization multicenter randomized trial of emergency contraception (EC) regimens, the pregnancy rate with single-dose (1.5 mg) levonorgestrel EC was:
 - 0.5%
 - 1.0%
 - 1.5%
 - 2.0%
- In a prospective cohort study, mean bone mineral density (BMD) in adult former users of depot medroxyprogesterone acetate (DMPA) 30 months after discontinuation was:
 - significantly lower than in hormonal contraceptive never-users at hip only
 - higher than DMPA never-users at spine only
 - similar to that of never-users at either hip or spine
 - significantly lower than at baseline
- Overall, the evidence indicates that former users of DMPA postmenopausally have BMD nearly identical to that of never-users.
 - True
 - False
- In the absence of other indications, bone densitometry should not be performed either at initiation or for follow-up in apparently healthy adult or adolescent DMPA users.
 - True
 - False
- Prescription to current DMPA users of drugs approved to treat women with postmenopausal osteoporosis:
 - can reduce fracture risk
 - has been studied in healthy premenopausal women
 - has been studied in DMPA users
 - has no justification in otherwise healthy adolescents or adults in the absence of a strong clinical rationale

Post-Test Answer Sheet

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | c | d |
| 2. | a | b | | | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | | |
| 4. | a | b | | | 9. | a | b | | |
| 5. | a | b | | | 10. | a | b | c | d |

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Please indicate how well this activity addressed its objectives—circle your responses—on a scale of 1 to 5 (1=poor, 5=excellent)

- Polycystic Ovary Syndrome: Management and Contraception*
- Depot Medroxyprogesterone Acetate and Bone Density*
- Emergency Contraception: An Update*

Poor					Excellent
1	2	3	4	5	
1	2	3	4	5	
1	2	3	4	5	

Please rate the following in regard to this activity

- Overall quality of the activity
- Clarity of instructions for use of materials and how to register for and obtain CME/CE credit
- Organization of the materials
- Disclosure of faculty's relevant financial relationships
- Relevance to practice
- Quality of educational content
- Ease of use

1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5
1	2	3	4	5

Please rate the value of the activity to your professional level

- Knowledge
- Attitude
- Skills

1	2	3	4	5
1	2	3	4	5
1	2	3	4	5

Please list topics you would like to see addressed in future issues _____

- Do you agree with the following statements?
- | | | |
|---|------------------------------|-----------------------------|
| This activity was scientifically balanced | <input type="checkbox"/> Yes | <input type="checkbox"/> No |
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| Free of commercial bias | <input type="checkbox"/> Yes | <input type="checkbox"/> No |

If no to any of the above, please explain _____

Suggestions for improving the quality of the activity or additional comments _____

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