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Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously

Penina Segall-Gutierrez[a,*], DeShawn Taylor[a], Xinwen Liu[b], Frank Stanzcyk[a], Stanley Azen[b], Daniel R. Mishell Jr [a]

[a]*Department of Obstetrics and Gynecology, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*
[b]*Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA*

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Abstract

Background: Subcutaneous depo-medroxyprogesterone acetate (DMPA-SC) has not been studied in the extremely obese population (BMI ≥40 kg/m^2). The purpose of this 26-week prospective experimental study was to determine incidence of ovulation and follicular development among women with Class 1, 2 and 3 obesity after receiving DMPA-SC.

Methods: Five normal-weight, five Class 1-2 obese, and five Class 3 obese women received subcutaneous injections of 104 mg DMPA-SC at baseline and 12 weeks later. Weekly progesterone levels, bimonthly estradiol (E_2), and monthly medroxyprogesterone acetate (MPA) levels were measured by immunoassay methods for a total of 26 weeks in each subject.

Results: Ovulation did not occur in any subject more than 1 week after the first injection. There was large intersubject and intrasubject variability in E_2 levels, and fluctuating E_2 levels were more frequent among obese women than normal-weight women. Median MPA levels remained above the level needed to prevent ovulation but, compared with normal-weight subjects, were lower among Class 1-2 obese and lowest among Class 3 obese subjects.

Conclusion: Fluctuating E_2 levels reflective of follicular development occurred more often among Class 1, 2 and 3 obese women than normal-weight women after DMPA-SC injections. Median MPA levels were consistently lowest among Class 3 obese women but remained above the level needed to inhibit ovulation. Further studies should more fully address the pharmacokinetics of DMPA-SC in extremely obese women.

Keywords: Depomedroxyprgesterone acetate; Contraception; Injection; Obese; Class 3 obese; Follicular development; Ovulation

1. Introduction

Depo-medroxyprogesterone acetate (DMPA) is a progestin-only contraceptive method, which is administered as a 150-mg intramuscular (DMPA-IM) or 104-mg subcutaneous (DMPA-SC) dose every 3 months. The main mechanism of action of DMPA is complete suppression of ovulation [1]. DMPA is an extremely effective method of contraception, with the percentage of women experiencing an unintended pregnancy within the first year of use estimated to range from 0.3% for perfect use and 3.0% for typical use [2]. In 2002, DMPA was used by 4.8% of women ages 15–44 years at risk for unintended pregnancy in the United States, making it the contraceptive method of choice for over 2 million American women. The World Health Organization Medical Eligibility Criteria for Contraceptive Use 2008 Update lists DMPA as Class 1 for obese adult women [body mass index (BMI) ≥30 kg/m^2], meaning it can be used without any restriction [3]. There have not been specific recommendations for contraceptive use for Class 2 obesity (BMI 35–39.9 kg/m^2) or Class 3 obesity (extreme, BMI ≥40 kg/m^2).

DMPA became FDA-approved as "Depo-Provera IM" in 1992, at which time the prevalence of obesity was 10–14% in California [4]. The prevalence of obesity in California increased to 23.7% in 2008, just as it has alarmingly increased throughout the United States [4]. Trends in Class 3

* Corresponding author. LAC+USC Medical Center, Los Angeles, CA 90033, USA. Tel.: +1 323 226 5408; fax: +1 323 226 3424.
E-mail address: psegall@usc.edu (P. Segall-Gutierrez).

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obesity are similar. Among women in the United States, the prevalence of extreme obesity in women of reproductive age continues to rise, reaching 8% among 20–39-year-old women in the United States in 2004 [5].

While obesity has substantial adverse long-term health effects for all individuals, the immediate importance of obesity and extreme obesity for women of reproductive age is profound. Complications of pregnancy occur more frequently in obese than normal-weight women [6].

While DMPA is commonly used and is extremely effective in normal-weight and overweight women, little is known about its use in obese women. Several studies have found that DMPA-IM effectively suppresses ovulation in overweight women and normal-weight women [7–10]. While Jain et al. [11,12] demonstrated no difference in contraceptive efficacy or return to ovulation in normal-weight, overweight, and obese DMPA-SC users, there was a trend towards decreasing trough medroxyprogesterone acetate (MPA) levels as the BMI increased. It is possible that DMPA may not provide as effective contraception in women with Class 3 obesity as in obese women with a lower BMI.

There have been no published studies specifically determining the incidence of ovulation and follicular development in Class 3 obese women during DMPA use. In the present report, we compare estradiol (E_2), progesterone (P_4) and MPA levels among normal-weight, obese and extremely obese women receiving DMPA-SC, to determine the incidence of ovulation and follicular development among Class 3 obese women receiving 104 mg of DMPA-SC.

2. Materials and methods

2.1. Subjects

The study was conducted at the Los Angeles County +University of Southern California (LAC+USC) Medical Center. Subjects were recruited from all outpatient gynecology clinics at Women's and Children's Hospital, LAC+USC Medical Center, via flyers posted in clinic waiting areas and letters sent to providers requesting referrals. Potential subjects were screened at the Reproductive Research Clinic during a 7-month period for the following eligibility criteria: willingness to use DMPA for contraception, absence of chronic disease, age 18–35 years, BMI either between 18.5 and 24.9 (for normal-weight control) or ≥30 kg/m^2, no use of DMPA for at least 6 months and no use of other hormonal methods of contraception for at least 3 months prior to enrolment, intact uterus and ovaries, normal Pap smear within prior 12 months and no intent to become pregnant or undertake major lifestyle changes for at least 6 months. The major exclusion criteria for all subjects included: hemoglobin A1c (HbA1c)>6%, fasting blood sugar ≥126 mg/dL, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, elevated fasting lipid profile as evidenced by (1) total cholesterol ≥240 mg/dL, (2) low-density lipoprotein (LDL) ≥160 mg/dL or (3) LDL ≥130 mg/dL with ≥1 risk factor for coronary artery disease (including family history of early myocardial infarction or high density lipoprotein <40 mg/dL), history of thromboembolism, current breastfeeding, ovarian pathology (including benign cysts), concomitant treatment with cytochrome P450 3A4-inducing medications, genital bleeding of undetermined etiology, smoking >15 cigarettes/day, hemoglobin <10.5 mg/dL and body weight ≥300 lb. Subjects were not excluded if they had a history of irregular menses.

This was a 6-month open-label trial. Subjects were recruited for 3 BMI categories [Class 3 obese (BMI ≥40 kg/m^2), Class 1–2 obese (BMI=30–39.9 kg/m^2), and normal-weight controls (BMI=18.5-24.9 kg/m^2)] until there were 6 subjects in each category or until the 7-month recruitment period ended, whichever came first. No overweight women (BMI=25–29.9 kg/m^2) were enrolled. Once informed consent was obtained from women who appeared to be eligible after screening, a medical history and physical examination and a vaginal ultrasound were performed. At that time, it was verified that subjects did not plan to become pregnant or make major lifestyle changes in the next 6 months. Fasting blood was obtained for measurement of serum glucose; a metabolic panel; a lipid panel; HbA1c, E_2 and P_4 levels and a urine pregnancy test (QuickVue One-Step hCG urine test, Quidel, San Diego, CA, USA). Women who remained eligible after this additional screening and received their first injection of DMPA were entered into the study. The study was approved by the USC Health Science Campus Institutional Review Board. Informed consent was obtained from all subjects prior to their participation.

2.2. Procedures

Once pregnancy was excluded, and the subject did not have a dominant follicle (follicle>10 mm) on transvaginal ultrasound, each subjects received a subcutaneous injection of 104 mg of DMPA-SC in the right thigh at the first visit. Consistent with clinical protocols, the injection was administered on the day of presentation irrespective of menstrual cycle day. Subjects with dominant follicles at the time presenting for first DMPA-SC injection were asked to return to the clinic 2 weeks later for a urine pregnancy test and transvaginal ultrasound. Once no dominant follicle was seen and pregnancy was excluded, the first DMPA-SC injection was given. The subjects returned weekly for 26 weeks for the remainder of the 6-month study period. The first cycle of DMPA-SC included 12 weeks of follow-up. Twelve weeks following the first injection, another DMPA-SC injection was administered, after verification of a negative urine pregnancy test. The second cycle of DMPA-SC included 14 weeks of follow-up.