ELSEVIER

Contraception 76 (2007) 282–286

Contraception

Original research article

Usefulness of FSH measurements for determining menopause in long-term users of depot medroxyprogesterone acetate over 40 years of age☆

Cassia Teatin Juliato, Arlete Fernandes, Nadia Maria Marchi, Sara Castro, Bruna Olivotti, Luis Bahamondes*

Human Reproduction Unit, Department of Obstetrics and Gynecology, School of Medicine, Universidade Estadual de Campinas (UNICAMP), Caixa Postal 6181, 13084-971 Campinas, SP, Brazil

Received 16 April 2007; accepted 28 May 2007

Abstract

Objective: To assess the usefulness of follicle-stimulating hormone (FSH) measurements for determining menopause in 40–55-year-old users of depot medroxyprogesterone acetate (DMPA).

Study Design: FSH levels were measured in 355 blood samples from 82 amenorrheic women during an 18-month period. Blood was collected every 90 days immediately prior to DMPA administration.

Results: Using FSH values >35 mIU/mL as being in the post menopausal range, 32 women (39.0%) presented at least one FSH measurement in the postmenopausal range and 14 of them (43.7%) had more than one elevated FSH measurement and were considered postmenopausal. In five users (15.6%), only the last FSH measurement was within the postmenopausal range, and in 13 women (40.6%), FSH returned to normal values following one measurement that was within the postmenopausal range.

Conclusions: The menopausal status in DMPA users in amenorrhea should be determined based on at least two consecutive high FSH evaluations, since, as shown here, 40.6% of the women with high FSH had a low FSH in the subsequent determination. FSH measurements should be done only in women ≥50 years old because there is a greater possibility of being in postmenopause. However, we do not recommend the interruption of DMPA use prior to the quantification of FSH.

Keywords: Depot medroxyprogesterone acetate; Follicle-stimulating hormone; Menopause

1. Introduction

Although fertility declines with age during the menopausal transition, there remains a risk of pregnancy during this phase and a need for contraception. Depot medroxyprogesterone acetate (DMPA) is a highly effective contraceptive method used worldwide, with few side-effects and few restrictions to its use, including women in their last reproductive years [1].

DPMA acts mainly by inhibiting ovulation through suppression of the hypothalamic pituitary axis. However, DMPA also causes profound hypoestrogenism [2,3], with estradiol levels falling below 100 pg/mL in the first 4 months of use, while at the sixth month, the levels are similar to those seen following menopause [3]. Although almost 70% of DMPA users are in amenorrhea after 1 year of use, there is no correlation between the hypoestrogenic status and climacteric symptoms such as hot flashes [3]. Because of the amenorrhea and infrequent climacteric symptoms in users of this method, the diagnosis of menopause can be complicated, making it difficult to determine the moment at which the use of a contraceptive method is no longer necessary.

Some physicians instruct their patients to interrupt use of DMPA in order to determine whether the menstrual pattern has been restored. This interruption is followed by the measurement of follicle-stimulating hormone (FSH) since DMPA has been reported to suppress FSH levels, even after menopause [4–6]. However, in postmenopausal users of DMPA, FSH is not believed to be suppressed to the levels seen during the reproductive age [6]. If an evaluation of FSH is necessary, the measurements should be done for as long as

☆ This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (grant no. 03/08391-7).

* Corresponding author. Tel.: +55 19 3289 2856; fax: +55 19 3289 2440.
E-mail address: bahamond@caism.unicamp.br (L. Bahamondes).

0010-7824/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2007.06.005

Table 1
Number of blood samples collected and number of samples with high FSH levels (FSH cutoff ≥35 mIU/mL)

	Evaluation						Total
	1st	2nd	3rd	4th	5th	6th	
Number of samples	82	82	72	60	44	15	355
Number with high FSH level (%)	14 (17.1)	15 (18.3)	10 (13.9)	15 (25.0)	15 (34.1)	6 (40.0)	100

possible after the last injection or immediately prior to the next DMPA injection [6].

In a recent study, 28.2% of DMPA users over 40 years of age had FSH levels at the postmenopause range (>25.8 mIU/mL) according to the criteria defined by the authors [7]. A second measurement of FSH in some of these women during the following injection cycle confirmed FSH levels above 25.8 mIU/mL at the post menopause [7]. The authors concluded that FSH levels are a good marker for establishing menopausal status in DMPA users. However, their study did not assess the variation in FSH levels during the use of DMPA, particularly with regard to the possibility that a high FSH level could be followed by a low value at the subsequent measurement. In view of the uncertainty surrounding FSH measurements in DMPA users during their final reproductive years, the aim of this study was to measure the FSH levels every 3 months for 18 months in amenorrheic women over 40 years of age who were long-term users of DMPA in order to assess the usefulness of these measurements for determining menopausal status in these women.

2. Materials and methods

This study was done in the Human Reproduction Unit, Department of Obstetrics and Gynecology, School of Medicine, Universidade Estadual de Campinas (UNICAMP). The protocol was approved by the Institutional Review Board, and all of the women signed an informed consent form prior to enrollment in the study.

All users of DMPA in amenorrhea and ≥40 years of age were invited to participate in the study. Eighty-two women who were long-term users of the injectable contraceptive containing 150 mg of DMPA (Depo-Provera®, Pfizer, São Paulo, Brazil) were enrolled in the study. A blood sample was collected at the recruitment visit immediately prior to an administration of DMPA and 90 days following the previous injection. A further blood sample was collected 90 (±5) days after each visit, immediately before a further injection of DMPA. The serum was separated, frozen and stored at −20°C until assayed.

2.1. FSH assay

FSH levels were measured in duplicate using commercial kits (DPC FSH Immunolite®, Los Angeles, CA, USA). The lower detection limit of the assay, representing the lowest FSH level that could be distinguished from zero, was <0.10 mIU/mL. This limit was calculated as the concentration lying two standard deviations (S.D.) above that of the lowest standard. The upper limit of quantification was 170 mIU/mL. Values above this figure were reported as >170 mIU/mL. All of the samples analyzed in this study were >0.1 and <170 mIU/mL. The within-assay coefficient of variation was 3.0±0.6% (mean±S.D.). Repeated samples from each subject were analyzed in the same FSH assay to minimize interassay variation. FSH levels ≥35 mIU/mL were considered to be in the menopausal range.

2.2. Statistical analysis

The results were expressed as means±S.D. The relationship between the ages of the women and the occurrence of high and normal FSH levels was assessed using Student's *t* test. The correlation between age and elevated FSH was analyzed using a receiver operating characteristic (ROC) curve with two cutoff points for FSH (>35 and >40 mIU/mL) according to previous results from Randolph et al. [8].

3. Results

Three hundred fifty-five blood samples were obtained from the 82 women. The mean duration of DMPA use was 6.3±4.3 years (range, 9 months to 18 years), and the mean age of the users was 46.0±3.6 years (range, 40–55 years). The mean age of users with at least one FSH result within the postmenopausal range (>35 mIU/mL) was 48.9±2.8 years (range, 43–55 years), compared to a mean age of 44.2±2.7 years (range, 40–50 years) for the 50 users in whom all of the FSH results were within the normal range ($p<.0001$).

The number of women at each blood sampling interval throughout the study and the number of samples in which FSH values were within the postmenopausal range are shown in Table 1. The number of women ranged from 82 at the enrollment visit (first blood sampling) to 15 at the 18-month follow-up visit. The percentage of blood samples in which FSH measurements were within the postmenopausal range varied from 17.1% at the first evaluation to 40% at the sixth measurement (18 months after recruitment). However, this figure was probably influenced by the small number of women remaining in the study at the sixth follow-up visit.

Assuming that FSH values ≥35 mIU/mL were within the postmenopausal range according to a previous study [8], 50 women had values below the menopausal range. In the remaining 32 women (39.0%), at least one FSH measurement was within the postmenopausal range. The mean age of these women was 48.9±2.8 years (range, 43–55 years). Of these, 14 women (43.8%) were considered to have reached menopause since all of their FSH measurements, or at least more than one sequential measurement, were within