ELSEVIER

Contraception 86 (2012) 481–487

Contraception

Original research article

Effect of hormonal contraceptives on vitamin B12 level and the association of the latter with bone mineral density

Abbey B. Berenson*, Mahbubur Rahman

Department of Obstetrics and Gynecology and Center for Interdisciplinary Research in Women's Health, The University of Texas Medical Branch, Galveston, TX 77555, USA

Received 23 December 2011; revised 22 February 2012; accepted 28 February 2012

Abstract

Background: The study was conducted to estimate the effect of depot medroxyprogesterone acetate (DMPA) and oral contraceptives (OC) containing 20 mcg ethinyl estradiol on serum B12 and whether observed changes impact bone mineral density (BMD).
Study Design: Serum B12 and BMD at the lumbar spine and femoral neck were measured on 703 women using OC, DMPA or nonhormonal (NH) birth control at baseline and every 6 months thereafter for 3 years.
Results: OC and DMPA users experienced greater decreases in B12 than NH users ($p<.001$). A sharp decrease in B12 was observed during the first 6 months of hormonal contraceptive use (OC: 97 pg/mL and DMPA: 64 pg/mL) in contrast to 14 pg/mL among NH users (20%, 13% and 3% of their baseline values, respectively). Over the following 30 months, B12 levels of OC users remained almost flat, while DMPA users had a further 22-unit decrease. Very few women demonstrated B12 deficiency. Moreover, B12 levels were not associated with BMD.
Conclusion: Hormonal contraception causes B12 levels to decrease, but this does not appear to be clinically significant or affect BMD.

Keywords: Depot medroxyprogesterone acetate; Depo-Provera; Oral contraceptive pills; Contraception; Birth control; Bone density; Vitamin B12

1. Introduction

Use of oral contraceptive pills has been associated with lower serum levels of B12 [1–15]. For example, Sütterlin et al. [14] observed in a case–control study conducted in Western Europe significantly lower B12 levels in oral contraceptive (OC) users than in controls. A cross-sectional study from the same geographic region also observed similar results [15]. Other studies, however, have failed to find an association between OC and B12 levels, making it difficult to determine if a relationship does exist [16–18]. Moreover, these studies were all cross-sectional in design, and thus, a cause and effect relationship could not be examined. In addition, studies have not examined the effects of another popular form of birth control, depot medroxyprogesterone acetate (DMPA), on B12 levels. Thus, it is not known whether a progestin-only contraceptive would have similar effects as those reported with use of OC.

If hormonal contraceptive use does lead to lower B12 levels, this could have important clinical implications as several studies on postmenopausal women have shown an association between low B12 levels and low bone mineral density (BMD) [19–23]. A similar association was also shown in one study on adolescents, demonstrating that this may also occur during the reproductive years [24]. However, two other studies did not observe any association between B12 and BMD levels [25,26]. Thus, it is unclear whether changes in B12 levels which may occur during contraceptive use would actually affect bone density.

To examine the interplays among hormonal contraceptive use, BMD and serum B12, a longitudinal study examining use of these two popular methods with an adequate follow-up period is essential. The purpose of this study was to estimate the effects of OC containing 20 mcg ethinyl estradiol (EE) and 0.15 mg desogestrel as well as DMPA over 3 years on B12 level, and the role of B12 on the

* Corresponding author.
E-mail address: abberens@utmb.edu (A.B. Berenson).

0010-7824/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.contraception.2012.02.015

association between hormonal contraceptives and BMD using longitudinal data with a control group.

2. Methods

As part of a larger study, 805 non-Hispanic black, non-Hispanic white and Hispanic women between 16 and 33 years of age were recruited between October 9, 2001, and September 14, 2004. The methods for the larger study are reported in detail elsewhere [27–29]. Briefly, recruitment was conducted to achieve a sample that was balanced by age group (16–24 years and 25–33 years), race (black, white, Hispanic) and contraceptive method: nonhormonal (NH), OCs and DMPA. Of the 805 women who signed a consent form for the larger study, 5 withdrew prior to completing their first visit and 97 were excluded due to abnormal laboratory or bone scan results. Thus, 703 women were invited to participate in the longitudinal study. Those excluded (n=102) did not differ from women included in the longitudinal study (n=703) on age, marital status, parity or education (all p>.05). Written, informed consent was obtained from all participants, and parental consent was obtained for participants <18 years of age. All procedures were approved by the Institutional Review Board at the University of Texas Medical Branch at Galveston.

Following counseling on the different types of contraception available and their efficacies, women were allowed to select one of three types of birth control: 245 chose OC (0.15 mg desogestrel+20 mcg EE taken for 21 days, followed by 2 days of placebo and 5 days of 10 mcg EE); 240 chose DMPA; and 218 chose an NH method (barrier method: 53%, tubal ligation: 33%, copper T: 10% and partner had vasectomy: 4%). Both DMPA and OC were dispensed every 3 months. NH contraceptive users also attended clinic every 3 months and were offered a supply of condoms at each visit. All participants received free well-woman care and contraception during the study as well as monetary compensation. Those who did not return for scheduled visits were reminded by phone and certified letters.

At each 6-month visit, weight was measured with a digital scale accurate to the nearest 0.1 kg while women were wearing light indoor clothing. Height was measured using a wall-mounted stadiometer (Heightronic, Snoqualmie, WA, USA) accurate to the nearest 0.001 m. Body mass index (BMI) was calculated as weight (kg)/height (m^2). At baseline and every 6 months thereafter for 36 months, BMD of the lumbar spine (L1–L4) and femoral neck was measured using dual-energy X-ray absorptiometry (Hologic QDR 4500W Elite fan-beam densitometer). A detailed description of how the bone densitometry was performed has been reported previously [27].

Serum levels of vitamin B12 were also measured at baseline and every 6 months thereafter. All blood samples were collected between 7:00 a.m. and 10:00 a.m. after an overnight fast. Assays were performed on the Siemens Advia Centaur Immunoassay system® (Siemens Healthcare Diagnostics Inc., Deerfield, IL, USA) using the Bayer Advia Centaur direct chemiluminescent immunoassay and the manufacturer's instructions, reagents and calibrators. Calibration was performed every 28 days per manufacturer's recommendation along with daily quality control for any B12 samples processed. Total %-coefficients of variation ranged from 3.8% to 10.4%. Samples were assayed in batches at the University of Texas Medical Branch laboratory between March and November 2009 after the study was completed.

During the 36-month study period, 257 women were lost to follow-up, 137 women stated they desired a different contraceptive method, and 123 women did not complete the study due to other reasons. Thus, 428 (NH 126, DMPA 145, OC 157), 294 (NH 86, DMPA 95, OC 113) and 186 (NH 51, DMPA 58, OC 77) completed 12, 24 and 36 months of follow-up, respectively. There were differences with regard to reasons for discontinuation among the three contraceptive groups: NH users were more likely to be lost to follow-up (NH 44%, DMPA 35%, OCP users 32%; p<.018), whereas DMPA users were more likely than their counterparts to seek a different contraceptive method (DMPA 36%, OC 15%, NH 6%; p<.001). Furthermore, OC users had a higher frequency of discontinuation due to pregnancy or a desire to become pregnant than DMPA users (7% compared with 2%, p<.006), but a similar rate to NH users (7% compared with 5%, p<.281).

2.1. Statistical analysis

One-way analysis of variance with Bonferroni correction for continuous variables and χ^2 test for categorical variables was performed to compare the three contraceptive groups at baseline. We used longitudinal analyses to compare changes in vitamin B12 for each contraceptive method, along with their predictors over time. In addition, effect of B12 (exposure variable) as a continuous and categorical variable (quartile) on bone density at the spine and femoral neck (outcome variables) was also examined using the similar model after adjusting for baseline values of bone density. To accommodate the repeated measurements, the data were modeled with the use of a mixed-effects regression procedure (xtmixed module; Stata Corporation, College Station, TX, USA), which allowed us to obtain regression coefficients for various predictors while adjusting for the estimated errors for the repeated measurements. This class of model also allows inclusion of time-dependent covariates and accommodates subjects with incomplete data because of variation in number and spacing in observations over the period of follow-up, which frequently occurs in longitudinal studies. During the course of study, women who were lost to follow-up, chose the contraceptive method other than that chosen at baseline and discontinued the study for some other reasons were considered as missing observations in the longitudinal data set. The primary outcomes were serum B12