Published in final edited form as:
Contraception. 2012 November ; 86(5): 481–487. doi:10.1016/j.contraception.2012.02.015.

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

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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 units 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

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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 EE and 0.15 mg desogestrel as well as DMPA over 3 years on B12 level, and the role of B12 on the 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 ethinyl estradiol taken for 21 days, followed by 2 days of placebo and 5 days of 10 mcg ethinyl estradiol); 240 chose DMPA; and 218 chose a 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) accurate to the nearest 0.001 m. 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 (DXA; 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® (Siemans Healthcare Diagnostics Inc., Deerfield, IL) 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 chi-square test for categorical variables were 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), 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 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 dataset. The primary outcomes were serum B12 levels and BMD at the spine and femoral neck. To examine the overall effect of method, race, and time, our models included contraceptive method (OC/DMPA/NH), race/ethnicity, and duration of contraceptive use (time) as main effects after adjusting for other covariates. Interaction terms (method x race/ethnicity; method x time) were then included in the model. To generate adjusted estimates, variables which were statistically significant at baseline by contraceptive methods were included in the final models. All analyses were performed using Stata 11 (Stata Corporation, College Station, TX).

3. Results

The mean age of the entire sample was 24 (SD: ± 5) years. Twenty-nine percent of the sample (n = 200) was non-Hispanic black, 36% (n = 256) were Hispanic (predominately Mexican American), and 35% (n = 247) were non-Hispanic white. The number of women in each racial/ethnic group and in each age category (16–24 y and 25–33 y) did not significantly differ by contraceptive method (Table 1). Furthermore, there were no significant differences between contraceptive groups in mean baseline height, weight, BMI, total fat mass, percent body fat, age at menarche, and previous use of birth control pills. Three differences were observed between groups at baseline: NH users had a higher mean parity, OC users were less likely to have used DMPA in the past, and DMPA users were more likely to smoke. No difference was observed among the three contraceptive groups with regard to mean serum vitamin B12 level or BMD of the spine or femoral neck at baseline.

Over 3 years, all three groups experienced a decrease in mean B12. These patterns differed by type of contraception. Among both OC and DMPA users, a marked decrease in mean B12 was observed during the first 6 months of use (OC: 97 pg/mL and DMPA: 64 pg/mL) (20% and 13% of their baseline values, respectively). In contrast, NH users had a mean 14 pg/mL (3% of baseline value) decrease during the first 6 months of follow-up.

The mean B12 level of OC users remained almost flat over the next 30 months while DMPA users experienced a further decrease of 22 pg/mL and NH users had a 17 pg/mL decrease during this same period of time. When the entire 36 months of follow-up was examined, it was observed that OC users had a greater decrease in mean B12 levels than DMPA users ($p=.004$). However, both DMPA and OC users experienced greater decreases in mean B12 level than NH users ($p<.001$; Table 2, Fig. 1).

Racial differences were also observed as non-Hispanic black and Hispanic women had higher levels of mean B12 at baseline and after 36 months of use than white women, irrespective of contraceptive methods. Black women had a higher mean B12 level at baseline compared to white and Hispanic women (white; 437 pg/mL, black: 556 pg/mL, and Hispanic: 484pg/mL; $p<.001$ for both) while Hispanic women had significantly higher B12 levels than whites ($p<.01$) (Fig. 2). Similar significant differences in mean B12 levels by ethnicity were also observed after 36 months, irrespective of contraceptive use. Women of all racial/ethnic groups who had a higher B12 level at baseline were more likely to have a higher level after 36 months. No other covariates were significantly associated with B12 levels over 36 months of contraceptive use.

We also examined the effect of B12 on BMD changes at the lumbar spine and femoral neck over 3 years using the mixed model regression analysis after adjusting for age, whole body lean mass, duration of use, contraceptive methods, race/ethnicity, parity, smoking status, and previous use of DMPA. No significant associations were observed between mean B12 levels (continuous data) and mean BMD at the spine ($p=.107$) or femoral neck ($p=.877$) after adjusting for different covariates.

Very few participants had abnormally low (<180 pg/mL) levels of B12 (NH 1, DMPA 2, OC 0) at baseline which remained low at subsequent visits. Overall, 4 NH users (2% of total NH users at baseline) developed an abnormally low level of B12 during the follow-up period. Two became normal at a subsequent visit, while the other two had abnormally low levels at 30 and 36 months only and then were lost to follow-up. Study stopped at 36 months. Two DMPA users (1% of total DMPA users) had abnormally low B12 levels at baseline, of which one became normal at a later visit and the other was lost to follow-up after an abnormal result at 18 months. With regards to OC users, 9 (4% of total OC users) had abnormally low B12 levels during the follow-up period of which 4 became normal at a later visit, 4 were lost to follow-up, and one remained abnormally low over the 36 months of follow-up.

4. Discussion

In this study, we observed that use of both OC and DMPA resulted in lower mean serum levels of vitamin B12. However, levels still remained in the normal range for almost all users. By and large, these findings agree with previous cross-sectional and case-control studies on the effect of OC on serum B12 levels [1–15]. This longitudinal study adds to the literature by demonstrating a cause and effect relationship between OC use and serum B12 levels. In addition, we observed lower B12 levels among DMPA users, which has not been previously reported in the literature.

It is important to note that even though B12 levels decreased, very few OC or DMPA users demonstrated abnormally low B12 levels during the 3-year follow-up period. We observed only 4% of OC users had an abnormal B12 level during follow-up, of which almost half demonstrated a return to normal at a subsequent visit. This is much lower than reported in the case-control study conducted by Sütterlin et al. [14], which similar to our study, also examined third generation OC users. In that study, 13% of OC users had frank B12 deficiency (<180 pg/mL) while another 15% demonstrated subnormal (180–223 pg/mL) B12 levels, although none in either group developed clinical symptoms. It is possible that dietary differences in the populations studied could have contributed to differences in findings between their study and ours. Differences in assay methods (intrinsic factor-coated micro-particle enzyme immunoassay vs. direct chemiluminescent immunoassay in our study) and types of OC used by participants might also have played some role.

Our findings among DMPA users were even more reassuring. We observed frank B12 deficiency (<180 pg/mL) in <1% of DMPA users during the follow-up interval, which was comparable to our control group of NH users. Furthermore, none showed any clinical signs or symptoms, so the clinical significance of this laboratory abnormality is uncertain. Overall, these data do not justify routine measurement of B12 in OC and DMPA users.

The mechanism by which hormonal contraception causes a decrease in serum B12 has yet to be elucidated. One possible mechanism is a deficiency in the level of serum B12 binders resulting in a false low B12 level in OC users [8, 11, 15, 30–32]. However, several studies [1, 6] have shown no difference in the level of mean unsaturated B12 binders between OC users and nonusers, suggesting that absorption is not affected and that redistribution of B12 throughout the body could be responsible [1]. However, the mechanism of this redistribution is unknown. Furthermore, the mechanism of suppression of B12 levels among DMPA users, which was less severe than that observed among OC users in our study, has not been determined.

Our finding that the level of B12 was not associated with BMD, irrespective of contraceptive use, is in contrast to the findings of several cross-sectional studies [19–24]. All but one of these prior studies, however, focused on postmenopausal women, who may react differently. The one study which did include reproductive-age women was limited to European adolescents who adhered to a specific diet plan (one group consumed a macrobiotic diet for up to 6 years followed by a vegetarian/omnivorous diet while the other group ate an omnivorous diet throughout their life). Furthermore, it differed from the current study in that it was cross-sectional in design and included males as well as females. These differences could explain the variation in findings between their study and ours.

Our observations that non-Hispanic white women had the lowest mean B12 levels (437 pg/mL) while non-Hispanic blacks (556 pg/mL) had the highest levels are consistent with a large national study (460 pg/mL, 566 pg/mL and 484 pg/mL, respectively) of 20–39 year old women [33]. Other studies with smaller sample size have also noted similar disparities [34–37]. The reason for this disparity, however, has yet to be elucidated. Elevated serum transcobalamins (B12 binding protein) and higher unsaturated cobalamin binding capacities in non-Hispanic blacks compared to whites have been suggested as possible reasons [36, 38, 39]. Furthermore, it has been speculated that genetic factors, such as differences in transcobalamin II gene frequencies (40), might be responsible for the elevated transcobalamin levels in blacks [37, 38].

This study has several limitations. First, we did not randomly assign women to a contraceptive method because the three types under study have different efficacies and randomization could have led to unintended pregnancies. Second, we studied only one formulation of OC, so our findings cannot be generalized to other types of oral contraceptive pills with different amounts of estrogen or other progestins. Together, these limitations could impact the overall generalizability of our findings, and selection bias cannot be ruled out. Finally, we are unable to shed light on the mechanism by which OC and DMPA altered B12 levels.

Overall, this longitudinal study demonstrated that women receiving OC/DMPA may experience a suppression of their B12 level, but this decrease is rarely clinically significant and does not warrant regular measurement of B12 levels among users. Thus, data from this longitudinal study are overall reassuring about the effects of these two contraceptives on serum B12.

Acknowledgments

Dr. Berenson's work was supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development (R01HD039883, PI: Berenson and K24HD043659, a Midcareer Investigator Award In Patient-Oriented Research Award PI: Berenson), and the General Clinical Research Centers program (5M01RR000073-43-8696), National Center for Research Resources, National Institutes of Health (NIH). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NICHD or the NIH.

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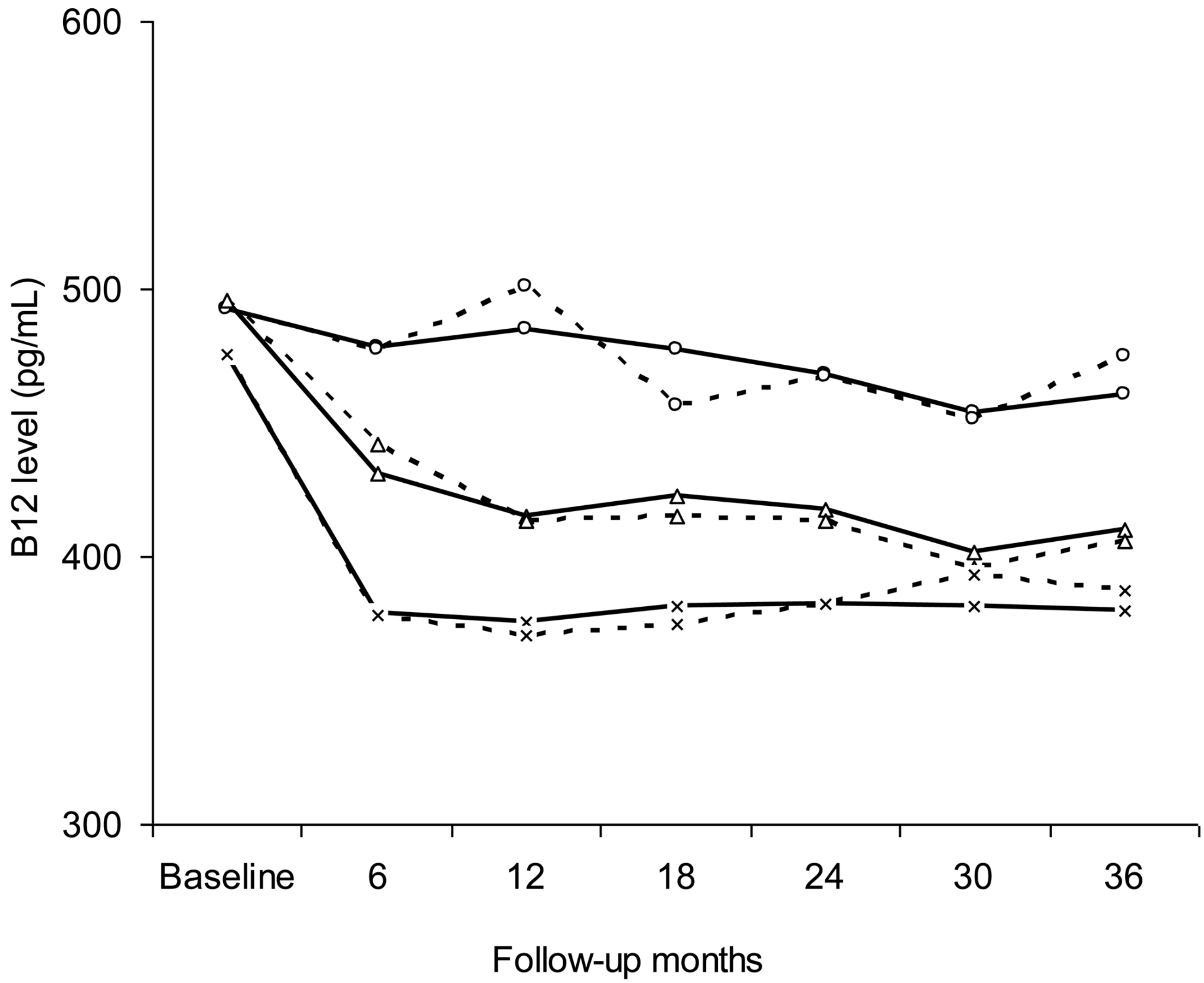

Fig. 1.

Modeled mean change of B12 from baseline across 36 months by contraceptive method. Empty circles: NH contraceptives; X shape: OC, and empty triangles: DMPA Solid lines represent the estimated mean changes, and dotted lines represent the unadjusted values.

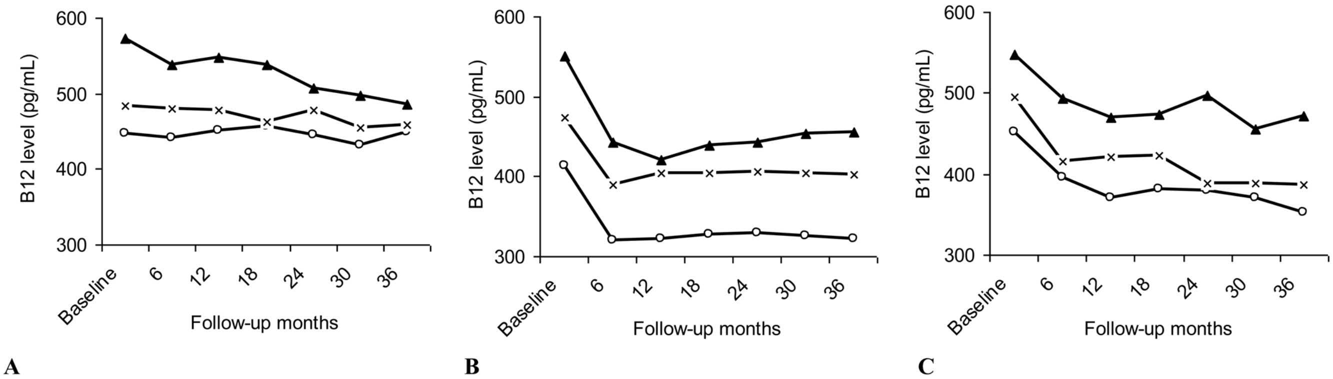

Fig. 2.

Modeled mean change of B12 level from baseline across 36 months by race/ethnicity and contraceptive method: **(A)** B12 level – NH method; **(B)** B12 – level OC; and **(C)** B12 – level DMPA.

Empty circles: white women; solid triangles: black women; X shape: Hispanic women. Adjusted by baseline value of B12, BMI weight status [(time varying variable; normal weight (BMI: <25 kg/m^2), overweight (BMI: 25–29.9 kg/m^2), and obese (BMI: 30 or above kg/m^2)], age (16–24 years vs. 25–33 years), race/ethnicity (white, black, and Hispanic), parity (continuous), smoking status (current smoker vs. not current smoker), and previous use of DMPA.

Table 1

Sample characteristics according to contraceptive method selected at baseline

Characteristic	OC (n = 245)	DMPA (n = 240)	NH (n = 218)
Age, %			
16–24 years	54.3	56.7	45.9
25–33 years	45.7	43.3	54.1
Race, %			
Black	29.8	30.0	25.2
White	33.5	34.2	38.1
Hispanic	36.7	35.8	36.7
Current smoker, %	23.3§	36.3†	22.0
Weight-bearing exercise >120 min/wk,%	43.2	36.3	37.5
	Mean (SD)		
Weight, kg	73.3 (17.7)	71.8 (19.2)	73.2 (18.6)
BMI, kg/m^2	27.9 (6.4)	27.2 (6.9)	28.3 (7.0)
Age at menarche, years	12.2 (1.5)	12.5 (1.7)	12.2 (1.6)
Previous use of pill (months)	21.9 (31.8)	16.9 (29.6)	17.7 (28.6)
Previous use of DMPA injection (#)	1.4 (3.5)‡	3.5 (6.5)§ †	2.6 (5.2)
Alcohol use, g/day	1.6 (8.7)	1.2 (6.1)	2.3 (14.5)
Parity	0.9 (1.1)‡	1.1 (1.2)†	1.6 (1.5)
Serum B12 level	476.0 (191.0)	495.8. (190.0)	492.4 (229.7)
Spine BMD, g/cm^2, mean (SE)	1.065 (0.109)	1.055 (0.112)	1.051 (0.100)
Femoral neck BMD, g/cm^2, mean (SE)	0.921 (0.124)	0.912 (0.132)	0.900 (0.114)

OC = oral contraceptive; DMPA = depot medroxyprogesterone acetate; NH = nonhormonal contraception; BMI = body mass index; SD = standard deviation

One-way analysis of variance with Bonferroni correction was used for continuous variables and chi-square tests were used for categorical variables. To identify specific pairwise differences for categorical variables, we created separate 2x2 tables for each of the pairs and used chi square tests. To adjust for multiple comparison, p<.017 (.05/3) was used to indicate the statistical significance between any two contraceptive groups.

§Significant difference was found between OC and DMPA after bonferroni adjustment.

†Significant difference was found between DMPA and NH contraception after Bonferroni adjustment.

‡Significant difference was found between OC and NH contraception after Bonferroni adjustment.

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Table 2

Estimated changes in mean B12 level across 36 months by contraceptive method[a,b,c]

	NH		DMPA		OC		p value
	N	Mean	N	Mean	N	Mean	
Baseline	215	492.4	238	495.8	238	476.0	NH vs. OC: <.001
6 mo	146	478.1	171	431.5	162	378.8	
12 mo	128	484.5	133	415.3	140	375.4	NH vs DMPA: <.001
18 mo	131	477.6	94	422.5	114	381.2	
24 mo	112	468.2	69	417.5	104	382.5	OC vs. DMPA: =.004
30 mo	89	454.2	55	401.8	81	381.6	
36 mo	79	460.9	31	409.9	67	379.9	

OC = oral contraceptive; DMPA = depot medroxyprogesterone acetate; NH = nonhormonal contraception.

[a]Adjusted by baseline value of B12, BMI weight status [(time varying variable; normal weight (BMI: <25 kg/m^2), overweight (BMI: 25–29.9 kg/m^2), and obese (BMI: 30 or above kg/m^2)], age (16–24 years vs. 25–33 years), race/ethnicity (white, black, and Hispanic), parity (continuous), smoking status (current smoker vs. not current smoker), and previous use of DMPA.

[b]Mixed-model regression analyses were used for the adjustment.

[c]B12 level was not available for some participants although other follow-up data were available (12, 0, 11, 4, 2, 4, and 2 at baseline and other follow-up visits, respectively)