THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 10

RESEARCH ARTICLE

The Effect of Hormonal Contraceptive Use on Vitamin B12 Levels among Adult Females in Saudi Arabia

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OPEN ACCESS

PUBLISHED
31 October 2025

CITATION
Jnaid, H., Butt, S., et al., 2025. The Effect of Hormonal Contraceptive Use on Vitamin B12 Levels among Adult Females in Saudi Arabia. Medical Research Archives, [online] 13(10). https://doi.org/10.18103/mra.v13i10.7059

DOI
https://doi.org/10.18103/mra.v13i10.7059

ISSN
2375-1924

ABSTRACT

We investigated the impact of hormonal contraceptive use on vitamin B12 serum in Saudi Arabian and non-Saudi Arabian adult women in this retrospective cohort study. Prior studies suggested that using hormonal contraceptives may lower B12 levels. Still, the therapeutic significance of this finding remains unknown. This study involved 752 adult women who were followed up at King Faisal Specialist Hospital and Research Center from February 2022 to November 2023. Contraceptive users had smaller median increases in B12 serum than non-users, even though there was no statistically significant difference in their levels at the end of follow-up. According to the study, women in general good health do not appear to have a substantial change in their B12 levels when using hormonal contraceptives. These results confirm the current global evidence that any decrease will often be slight and clinically insignificant. These findings underscore the importance of environment-specific research and offer valuable insights into the health of Saudi Arabian women.

Purpose:
In Saudi Arabia, where dietary and cultural norms may affect contraceptive practices and baseline vitamin status, this study aims to assess the impact of hormonal contraceptive use on serum vitamin B12 levels in adult women, especially those who receive medical care.

752 women aged 18 and older who had been using hormonal contraceptives for at least three months were included in this retrospective cohort study from February 2022 to November 2023. Our team collected the information from family medicine clinics at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh, Saudi Arabia. Patients with pre-existing B12 deficits, disorders impacting B12 metabolism, or certain chronic diseases were excluded. We considered clinical and demographic factors and checked baseline and follow-up levels of folate, vitamin B12, methylmalonic acid, and vitamin B6.

Results:
A total of 752 women participated in this trial, 299 of whom (39%) used hormonal contraception, mainly oral contraceptives. While users and non-users had higher levels of B12 following a follow-up, the median increase for non-users was marginally greater (36 vs. 25 units). However, there were no statistically significant differences ($p = 0.262$). There was a statistically significant decrease in B12 levels among those who used contraceptives for contraception($p=0.028$). Other comparisons showed no discernible changes. Overall, the relationship between vitamin B12 level and the usage of contraceptives is not clinically significant.

Conclusion:
Using hormonal contraceptive medications does not significantly correlate with reduced B12 levels in Saudi Arabian adult women. B12 levels were somewhat lower in several subgroups, but these differences were inconsistent or clinically insignificant. This result supports various worldwide studies concluding that hormonal contraceptives may modify B12 metabolism without resulting in a functional deficit. Furthermore, a longitudinal study of multiple populations is necessary to ascertain possible long-term impact.

Keywords: Hormonal contraceptives, Vitamin B12, Women's health, Saudi Arabia, Nutritional biomarkers.

Introduction

Hormonal contraceptive medications, with their versatile forms, in particular oral contraceptive pills (OCs), are extensively used by women of reproductive age and have significantly contributed to reproductive autonomy and public health advancement[1]. However, evidence indicates that their use may impact micronutrient metabolism, specifically affecting the serum concentrations of vitamin B12 (cobalamin)[2,3,4]. Considering the crucial roles of vitamin B12 in DNA synthesis, neurological function, and blood cell formation, especially during the reproductive years, understanding how hormonal contraceptives influence B12 status is a priority[3,4,5].

Moreover, hormonal contraceptives may influence homocysteine, which is an indicator of cobalamin deficiency and metabolism. Homocysteine has wider clinical consequences, including raising the risk for thromboembolic events and decreased bone mineral density (BMD)[4,5,6]. Several observational and controlled studies reported lower serum vitamin B12 levels among OC users than non-users[3,4]. However, variability in contraceptive formulations, study design, and confounding nutritional factors makes the clinical significance of these changes debatable[2,7].

Decreases in total serum vitamin B12 and holo-transcobalamin (holoTC), the biologically active form of cobalamin, have been documented with combined oral contraceptives[3,4]. However, functional biomarkers of vitamin B12 deficiency, such as methylmalonic acid (MMA) and homocysteine (Hcy), are not always elevated, as expected in vitamin B12 deficiency[3]. This leads to questions about the physiological significance of this biochemical alteration[3].

Suggested mechanisms include hormonal effects on cobalamin-binding proteins, such as transcobalamin I (TCI), and changes in intestinal absorption processes[3]. Additionally, differences in estrogen dosage, the type of progestin used, adherence to contraceptive use, and dietary habits may affect the degree of vitamin B12 disruption[2,3].

Several studies have documented that suppression of cobalamin levels is likely dose-dependent concerning ethinyl estradiol, the synthetic estrogen commonly used in contraceptives[8]. Men treated with high doses of estrogens for prostate cancer have also shown similar reductions in serum B12 levels, further supporting the hormonal link to altered cobalamin metabolism[1,8].

Low-dose oral contraceptives typically deliver at least 20 µg of ethinyl estradiol daily. In contrast, the combined contraceptive vaginal ring releases approximately 15 µg of ethinyl estradiol per day. Thus, recent research suggested evaluating serum concentrations of cobalamin among hormonal contraceptive users to assess biochemical changes and the prevalence of related nutrient deficiencies[8].

Furthermore, the measured levels of vitamin B12 are highly affected by supplement use and dietary intake. For example, some populations may have lower baseline vitamin B12 levels due to low intake of animal products. Thus, more studies are needed for culturally centered research, especially in geographical regions such as the Kingdom of Saudi Arabia, where traditional dietary patterns, supplement behaviors, and contraceptive preferences differ from those in Western contexts[11].

Material and Methods:

SUBJECT IDENTIFICATION AND DATA ABSTRACTION:

A retrospective cohort study was conducted at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh, Saudi Arabia, from February 2022 to November 2023. All adult patients aged 18 years and older who were using hormonal contraceptives for at least three months and followed up at Family Medicine clinics at KFSHRC in Riyadh, Saudi Arabia, were included in the study. Patients with normal levels of vitamin B6, B12, and folate before using contraceptive medications were included in the study.

The study excluded patients with a history of vitamin B12 deficiency, pernicious anemia, hormonal disorders (Addison's, Cushing's, thyroid, or parathyroid diseases), renal-hepatic diseases, irritable bowel syndrome, celiac disease, and pregnancy during the last 20 weeks prior to study initiation. Patients with trauma, cuts, fractures, bleeding, burns, or other events in the past three months resulting in unconsciousness and hospitalization were excluded. Patients infected with HIV, mononucleosis, tuberculosis, viral hepatitis, or pneumonia in the past two weeks were excluded. Furthermore, patients using medications that could affect folate or cobalamin metabolism, vitamin supplements, or estrogen/progesterone/androgen therapy in the last six months were excluded. Malabsorption predisposing conditions like bariatric

surgery were excluded and adjusted in the analysis[8,11].

VARIABLES:

Data recorded included socio-demographic information (age, Saudi or non-Saudi), BMI value, smoking, single medication dose, combined formulation dose, and laboratory results (folate, vitamin B12, vitamin B6, and plasma methylmalonic acid level) before and after using contraceptives. Furthermore, it included the received contraceptive medication (type, dose, and duration) and covered patients' past medical history, history of hormonal therapy, and chronic disease (GI malabsorption and anemia). As a privacy and confidentiality measure, the patient's identification information, such as name and MRN, was replaced with a Unique Patient Number (UPN).

Statistical Analysis

Our team analyzed the data using the CERNER version of the electronic health records. We used percentages and frequencies to show the categorical variables. The medians with interquartile ranges (IQR) were used to report the continuous variables because of their non-normal distribution.

THE COMPARISON ANALYSIS WAS CARRIED OUT AS FOLLOWS:

Mann-Whitney U test: The median values of continuous variables (such as age, BMI, and serum B12 levels) were compared between two independent groups (contraceptive users and non-users) using the U test.

Chi-square test: used to assess correlations between categorical factors such as smoking, anemia, marital status, and usage of contraceptives.

Kruskal-Wallis test: used to analyze changes in blood vitamin B12 levels between more than two groups, such as oral contraceptives, single methods, and double methods.

P-value: a statistically significant value was defined as less than 0.05.

KEY STATISTICAL FINDINGS:

BMI: Contraceptive users had a significantly higher median BMI (28.5 vs. 27.5; p=0.007).

Marital Status: Contraceptive use was more common among married women (p=0.001).

Metformin Use: Considerably more prevalent among those who utilize contraceptives (p=0.001).

Anemia: Considerably more common in non-users (p=0.001).

Change in Vitamin B12 Levels: There was no statistically significant variation in vitamin B12 levels between forms of contraception (p=0.125) or between non-users and users (p=0.262). Those who took contraceptives for contraception were an exception, as their rise in B12 levels was significantly less than that of non-users (p=0.028).

Results

Between February 2022 and November 2023, a total of 752 female patients seen at the Family Medicine and Polyclinics Department at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh were reviewed retrospectively. Table 1 displays the baseline characteristics of the study population. The median age was 40 years (IQR 22), and the median BMI was 27.9 (IQR 8.6). Most participants were non-smokers (96.4%) and married (62.4%), with the majority being Saudi nationals (76.7%).

Contraceptive use was reported in 39.9% of the participants. Among those, oral contraceptives were the most common method used (60.1%), followed by other single methods (31.3%) and double methods (5.6%). The primary indication for contraceptive use was contraception (4.9%), followed by hormone replacement therapy (2.9%) and other indications (7.5%).

Regarding comorbidities, 12.3% had diabetes mellitus, 6% were on metformin, 11.5% had hypertension, and 27.1% were anemic. The median serum vitamin B12 level was 249.5 (IQR 155).

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (N = 752)

Baseline characteristics	N (%)
Age, Median (IQR)	40 (22)
BMI, Median (IQR)	27.9 (8.6)
Smoking	
No	721 (96.4)
Yes	27 (3.6)
Marital status	
Single	259 (34.5)
Married	468 (62.4)
Divorced	17 (2.3)
Widowed	6 (0.8)
Nationality	
Non-Saudi	175 (23.3)
Saudi	575 (76.7)
Contraceptive use	
No	451 (60.1)
Yes	299 (39.9)
Contraceptive type	
Oral	451 (60.1)
Another single Method	235 (31.3)
Double Methods	42 (5.6)
Indication of contraceptive use	
Contraception	37 (4.9)
Hormone replacement therapy (HRT)	22 (2.9)
Other indications	56 (7.5)
Diabetes Mellitus	92 (12.3)
Metformin use	45 (6)
Hypertension	86 (11.5)
Anemia	203 (27.1)
Vitamin B12, Median (IQR)	249.5 (155)

Note: Data are presented as median (interquartile range, IQR) for continuous variables and number (percentage) for categorical variables. BMI = Body Mass Index; IQR = Interquartile Range; HRT = Hormone Replacement Therapy; KFSH&RC = King Faisal Specialist Hospital and Research Centre, Riyadh.

Statistically significant differences were observed in several variables in table 2. Participants who used contraceptives had a slightly higher median BMI (28.5 vs. 27.5, p = 0.007). Marital status was significantly associated with contraceptive use (p = 0.001), with a higher proportion of married women among users. Additionally, metformin use, and anemia were both significantly different between the two groups. A greater proportion of contraceptive users were on metformin (p = 0.001), while anemia was more prevalent among non-users (p = 0.001). No significant differences were found in smoking status, nationality, diabetes, hypertension, or median vitamin B12 levels.

Table 2. Comparison of Baseline Characteristics by Contraceptive Use Among Study Participants (N = 752)

Variables	Contraceptive Use		P
	No	Yes	
Age, Median (IQR)	40 (26)	40 (15)	0.030*
BMI, Median (IQR)	27.5 (8.78)	28.5 (7.8)	0.007*
Smoking			
No	437 (60.6)	284 (39.4)	0.194
Yes	13 (48.1)	14 (51.9)	
Marital status			
Single	211 (81.5)	48 (18.5)	
Married	221 (47.2)	247 (52.8)	0.001 *
Divorced	14 (82.4)	3 (17.6)	
Widowed	5 (83.3)	1 (16.7)	
Nationality			
Non-Saudi	102 (58.3)	73 (41.7)	0.569
Saudi	349 (60.7)	226 (39.3)	
Diabetes Mellitus	63 (68.5)	29 (31.5)	0.081
Metformin use	7 (15.6)	38 (84.4)	0.001*
Hypertension	54 (62.8)	32 (37.2)	0.593
Anemia	150 (73.9)	53 (26.1)	0.001*
Vitamin B12, Median (IQR)	251 (152)	249 (162)	0.994

Note: Data are presented as median (interquartile range, IQR) for continuous variables and number (percentage) for categorical variables. $p < 0.05$ was considered statistically significant.
BMI = Body Mass Index; IQR = Interquartile Range; KFSH&RC = King Faisal Specialist Hospital and Research Centre, Riyadh.

Although women who did not use contraceptives had a higher median increase in B12 levels compared to users (36 vs. 25 units), the difference was not statistically significant ($p = 0.262$). When comparing different contraceptive types, users of other single methods experienced the most significant median increase (60.5 units), while those using double methods showed the smallest (11 units); however, the overall difference across groups did not reach statistical significance ($p = 0.125$).

Notably, a statistically significant difference was observed when comparing B12 level changes by contraceptive indication for contraception, where users showed a markedly lower median increase than non-users (8 vs. 32 units, $p = 0.028$). No significant differences were found in B12 changes among users of hormonal contraceptives for hormone replacement therapy, other medical indications, or by metformin use as illustrated in table 3.

Table 3. Median Change in Vitamin B12 Levels After Follow-Up by Contraceptive Use and Related Variables:

Vitamin B12 Difference After the Follow-up	Median units (IQR)	P
Contraceptive use		
No	36 (132)	0.262
Yes	25 (181)	
Contraceptive type		
None	36 (132)	
Oral	19 (206)	0.125
Other single Method	60.5 (118.3)	
Double Methods	11 (512.8)	
Contraception		
No	32 (151.5)	0.028*
Yes	8 (170.5)	
Hormone replacement therapy (HRT)		
No	31 (151.8)	0.809
Yes	40.5 (190)	
Other indications		
No	32 (150.3)	0.212
Yes	6.5 (230.5)	
Metformin use		
No	31 (152)	0.657
Yes	32 (173.5)	

Note: Data are presented as median (interquartile range, IQR). Statistical comparisons were performed to assess differences between groups, with $p < 0.05$ considered statistically significant.

HRT = Hormone Replacement Therapy; IQR = Interquartile Range; KFSH&RC = King Faisal Specialist Hospital and Research Centre, Riyadh.

Discussion

We explored how hormonal contraceptive use affects vitamin B12 levels among adult Saudi and non-Saudi women. Despite abundant international studies, local data remain scarce, despite widespread use of hormonal contraceptives and the essential role of B12 in neurological and hematological health. Our analysis included 752 women who had used hormonal contraceptives for at least three months at KFSH&RC. We observed no significant difference in B12 levels between users and non-users[1]. This suggests that in generally healthy women, hormonal contraceptive use does not substantially influence B12 status, providing valuable local evidence for clinicians.

Earlier investigations examined how combined oral contraceptives (OCPs) influence B12 metabolism. Shojania reported slightly lower serum B12 concentrations in OCP users, but no metabolic impairment or deficiency[3]. Hjelt et al. found reduced serum cobalamin and binding capacity in users, yet hematological indices and RBC folate remained stable[4]. Riedel et al. confirmed that total serum B12 decreased marginally, but functional markers such as methylmalonic acid and homocysteine stayed normal[27]. Similarly, Green et al. observed a 40% reduction in total B12 among OCP users, without clinical symptoms or hematologic abnormalities[5].

Recent research shows transient B12 reductions following contraceptive use with no clinically meaningful effects[12–14]. Longitudinal analyses show initial decreases stabilize after several months[6,15]. Estrogen-containing contraceptives may alter hepatic synthesis of transcobalamin, resulting in harmless serum declines[16–18].

Berenson and Rahman monitored OCP and DMPA users over three years, observing early reductions

of 13–20% within six months that plateaued without adverse outcomes[6]. McArthur et al. noted lower average serum B12 in OCP users compared to non-users[7], yet no clinical deficiency. Reviews and observational studies confirm these changes are reversible and rarely require intervention[19,20]. Newer formulations such as the vaginal ring and biphasic OCs appear to have minimal impact[8,9,21]. Some reports show more pronounced reductions. In a cohort of 219 women, B12 levels were significantly lower among contraceptive users[10], and a trial of low-dose OCPs showed a similar trend[11]. Variability may relate to formulation, dosage, nutrition, and duration[22–27]. Low consumption of animal-derived foods or genetic variants affecting cobalamin metabolism can intensify serum B12 decreases[28–30]. Women with marginal baseline B12 or long-term contraceptive exposure may experience greater biochemical changes[31,32].

The disparity between our results and studies showing significant B12 decline likely reflects contextual factors: healthy participants with adequate nutrition, short-term contraceptive use (≥3 months), regional formulation differences, and lab methodology variations.

Current evidence, including our findings, indicates hormonal contraceptive use can produce small, reversible decreases in B12 but seldom leads to clinically significant deficiency[12–32]. These changes likely result from altered binding dynamics rather than actual depletion. For most healthy women, routine monitoring is unnecessary unless additional risk factors exist.

In conclusion, we found no significant difference in serum B12 levels between hormonal contraceptive users and non-users among adult Saudi and non-Saudi women. Minor decreases observed elsewhere appear transient and physiologically inconsequential. Discrepancies reflect formulation, usage duration, diet, and ethnicity. Our findings provide region-specific evidence and highlight the need for additional research exploring functional B12 markers and long-term outcomes in diverse populations.

Conclusion:

In summary, most studies, including this one, report minimal or no clinically significant effects of contraceptive use on B12 level.

The variations in study design, population characteristics, and the contraceptive type May explain the conflicting results between different studies. More research is needed to explore possible long-term impact.

Conflict of Interest Statement:

None.

Funding Statement:

This research received no external funding.

Acknowledgements:

The authors would like to thank all those who contributed to this work, especially Mr. Yaser Alendijani for his support in statistical analysis.

Disclosure

The author(s) report no conflicts of interest in this work.

Abbreviations:

AUC, area under the curve; LS, least squares; NE, not estimable, OC, oral contraceptives.

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