

SYSTEMATIC REVIEW


The role of adequate vitamin D levels in the menstrual cycle of reproductive-age women

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Article Info	ABSTRACT
<p>Received Nov 2, 2021 Revised May 17, 2022 Accepted Jun 20, 2022 Published Dec 1, 2022</p> <p>Corresponding author: Manik Retno Wahyunitisari manik-r-w@fk.unair.ac.id</p> <p>Keywords: Human & health Menstrual cycle Reproductive age Women Vitamin D</p> <p>This is an open access article under the CC BY-NC-SA license (https://creativecommons.org/licenses/by-nc-sa/4.0/)</p> 	<p>Objective: This study investigated the role of adequate vitamin D levels in the menstrual cycle of reproductive-age women.</p> <p>Materials and Methods: We systematically searched using certain key words in PubMed and ScienceDirect for English articles, full articles, published between August 2013 - August 2022 that evaluated the effect of vitamin D levels on the menstrual cycle of women in reproductive age. The results were analyzed qualitatively.</p> <p>Results: Eight studies from 653 recorded articles were eligible for review. Decreased vitamin D levels can cause menstrual cycle irregularities, which are related to a decrease in the hormone estradiol, affecting the menstrual cycle. In addition, lower levels of vitamin D lead to longer menstrual cycles.</p> <p>Conclusion: Vitamin D is vital in the menstrual cycle because it influences the frequency and duration of menstruation.</p>

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INTRODUCTION

Menstrual cycles are one sign of women's physiological well-being.¹ It occurs as a feedback process of the hypothalamus-pituitary-ovarian (HPO) axis.² The average menstrual cycle ranges from 18–35 days, and the intervals might differ for each.³ Approximately 64% of females have at least one menstrual issue. These issues include irregular menstrual cycle, oligomenorrhea, and menorrhagia.⁴ It is suggested that metabolic mechanisms play a role in disrupting menstrual regularity.⁵ Numerous physiological and metabolic processes rely on vitamin D as a crucial element.⁶ To

achieve ion-calcium balance and bone mineral metabolism, Vitamin D is necessary.⁷ Vitamin D's importance in calcium homeostasis and bone mineralization is generally acknowledged.⁸ Furthermore, it significantly impacts reproductive hormone regulation and the menstrual cycle.⁹ Inside reproductive organs, which includes, ovaries, endometrium, myometrium, uterus, and placenta there are sites/organs where vitamin D can also be found.^{10,11} Accordingly, a range of clinical reproductive consequences are associated with vitamin D inadequacy.^{8,12,13} Vitamin D is correlated with women-menstrual cycle, particularly

in its regularity and length, since it affects the metabolism of reproductive hormones.¹⁴

However, the mechanism whereby vitamin D impacts the menstrual cycle is still unclear.¹⁵ The hypothesis of significant correlation between vitamin D and Anti-Mullerian Hormone (AMH), insulin, androgen hormones, and other yet-to-be-identified key mechanisms have been studied.¹⁰ This association correlates with the active form of vitamin D, 25-hydroxyvitamin D (25(OH)D) which inducing menstrual problems if minimum amount of 25(OH)D is not reached. The correlated menstrual cycle problems are including menstrual cycle irregularities,¹⁰ endometriosis,¹⁶ menstrual cycle lengthening,¹⁷ and polycystic ovary syndrome (PCOS).¹⁸ Moreover, 25(OH)D insufficiency increases the symptoms of premenstrual syndromes, such as tenderness and pain.¹⁹ During the menstrual cycle, vitamin D level fluctuations might impact estradiol.^{14,20} Estradiol levels decrease when 25(OH)D is inadequate.^{1,20} Therefore, this study aimed to investigate the role of adequate vitamin D levels in the menstrual cycle of reproductive-age women.

MATERIALS AND METHODS

Search strategy

We performed systematic literature search on Pubmed and ScienceDirect for articles published from August 2013 to August 2022 that evaluated 25(OH)D level in the menstrual cycle of reproductive-age women following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.²¹ The following search term was constructed using Medical Subject Headings (MeSH) terms and Boolean operators: (“Menstrual Cycle” OR “Cycle, menstrual” OR “Menstrual cycles”) AND (“Adult” OR “Adolescent”) AND (“Woman” OR “Women” OR “Girls” OR “Female”) AND (“Ergocalciferol” OR “Cholecalciferol” OR “Calciferol” OR “25-Hydroxyvitamin D” OR “1,25-Dihydrocholecalciferol” OR “25-Hydroxycholecalciferol” OR “Vitamin D” OR “D3, Vitamin”). Potential studies were also found in the reference lists of the papers included in this investigation. The overall study selection process was conducted by two reviewers (AM and HS) and any disagreements or conflicts were accomplished through discussion with a third reviewer (BS) to determine the final resolution.

Eligibility criteria and quality assessment

Eligibility criteria was formulated using Population, Intervention, Comparison, and Outcome (PICO) framework as shown in Table 1. We included studies that: (1) investigated association between 25(OH)D

levels and menstrual cycle; (2) included women aged 12 to 55 years as subjects; and (3) published in English language. The exclusion criteria were: (1) duplicates; (2) studies with irretrievable full-text; or (3) review articles, case reports, case series, and conference abstracts. Afterwards we assessed the included methodological quality using the Joanna Briggs Institute (JBI) critical appraisal checklist^{22,23} conducted by two reviewers (AM and HS), and only studies with $\geq 50\%$ score will be further included.

Data extraction

Data extraction was conducted by two reviewers (AM and HS). The following data were extracted from each included study: (1) name of the first author and year of publication; (2) study design; (3) sample size; (4) age; (5) serum 25(OH)D level (ng/ml); and (6) study outcomes and results.

RESULTS AND DISCUSSION

Study selection

The initial search from the two databases returned 653 records and excluded 637 articles based on duplication, title, and abstract. In addition, a study was identified from citation searching. Ultimately, 16 eligible studies were assessed, and eight of these were included for a full review.^{14,17,20,24–28} Articles were excluded for the following reasons: duplicate paper, irrelevant title, wrong study design and population based on abstracts, and wrong outcomes based on full-text review. Figure 1 illustrates the overall process of the study selection.

Study characteristics and quality assesment

Six of the eight reviewed studies were observational studies.^{14,17,20,24,27,28} and the rest were randomized control trials (RCTs).^{25,26} The studies included a range of 60 to 1,133 women aged 12 to 55 years. This study assessed the correlation of study subjects' serum 25(OH)D levels on their menstrual cycles outcomes. Serum 25(OH)D level parameters were classified as deficient (<20–30 ng/ml) and sufficient (≥ 20 ng/ml). Seven studies measured serum 25(OH)D levels which are the deficiency or lower levels associated with the longer menstrual cycle, short follicular phases or long luteal phases, and irregular cycles. Meanwhile, another study had shown that vitamin D status was not correlated with a woman's menstrual cycle.²⁰ Data extraction and methodological assessment score are summarized in Table 2.

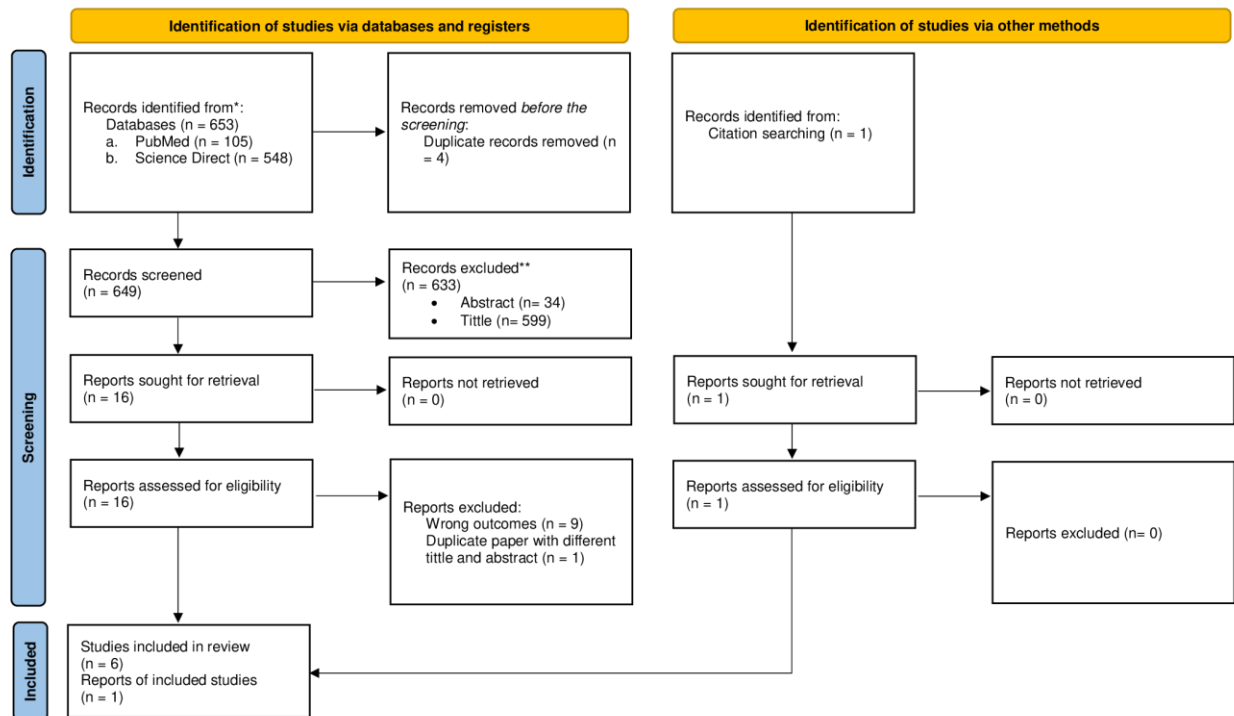


Figure 1. PRISMA flowchart showing the screening process and final articles included.

Table 1. PICO framework

Components of PICO	Definition
Population	Reproductive-age women
Intervention	Serum vitamin D levels
Comparison	None
Outcome	The regularity and length of the menstrual cycle

Outcome variables

Decreased 25(OH)D levels can cause menstrual cycle irregularities. This is related to a decrease in the hormone estradiol which affects the menstrual cycle. Furthermore, reduced levels of 25(OH)D result in prolonged menstrual periods.

Our findings are similar to those several studies^{17,27} who reported that inadequate vitamin D levels are linked to longer menstrual periods^{17,27} and cause oligomenorrhea or amenorrhea.²⁷ Women with sufficient 25(OH)D had around half the probability of having extended cycles as

women with insufficient status.²⁷ In the other study with 531 participants (29–44 years), Jukic et al²⁴ stated that lower 25(OH)D contributed to a longer menstrual cycle and follicular phase. 25(OH)D deficiency status has the strongest correlated with longer menstrual cycle. However, insufficiency status contributed with high risk of prolonged menstrual cycle.²⁴ Singh et al²⁸ found the vitamin D status on 166 women 18–40 years who have menstrual irregularities on a cross-sectional study and showed a decrease in 25(OH)D levels was correlated with a higher risk of irregular menstrual cycles.²⁸



PICO, Population, intervention, comparison, outcome

Table 2. Summary of included studies showing the effect of serum vitamin D levels on the menstrual cycle.

First Author (Year)	Study Design	Age (range in years)	Sample size	Serum 25(OH)D levels (ng/ml)	Outcomes	Results	JB1 score
Bahrami (2018) ¹⁴	Prospective study	12–18	897	<50: deficiency; 50–74.9: insufficiency; and 75: sufficiency	The supplementation of high dose vitamin D and menstrual cycle	<ul style="list-style-type: none"> Vitamin D supplementation was linked to a lengthy menstrual cycle Normal 25(OH)D levels were positively correlated with total subjects elevation which are normal menstrual cycle length ($p=0.015$) Increased normal cycle from 71,8% to 78% Decreased short length cycle from 23,6% to 18,0%, and long length cycle from 4,7% to 4,0% 	73%
Jukic (2018) ²⁴	A prospective cohort study	29–44	531	<20: deficiency; 20–<30: insufficiency	Serum 25(OH)D levels and follicular phase length.	<ul style="list-style-type: none"> 25(OH)D is linked with prolonged menstrual cycles, short follicular phases, and extended luteal phases Long menstrual cycles were three times more likely to occur in people with 25(OH)D deficiency. (OR(CI): 2.8 (1.0, 7.5)) 25(OH)D insufficiency was related to double the likelihood of prolonged menstrual cycles (OR(CI): 1.9 (1.1, 3.5). 	91%
Jukic (2016) ¹⁷	Prospective study	23–34	1,133	≤20: deficiency; >20: sufficiency	Vitamin D with menstrual cycle length and regularity	Serum vitamin D levels amelioration were linked to reduced odds and probability of long menstrual cycles.	91%
Al-Bayyari (2020) ²⁵	A prospective, randomized, double-blind, placebo-controlled clinical study	18–49	60	<20: deficiency	Serum 25(OH)D levels and regularity of the menstrual cycle	Vitamin D ₃ supplementation at 50,000 IU increased serum 25(OH)D levels and normalized menstrual cycles.	100%
Harmon (2020) ²⁰	A prospective cohort study	18–44	89	<20: deficiency	Three calciotropic hormones (25(OH)D, 1,25(OH)2D, iPTH) to evaluate LH and FSH cycle	<ul style="list-style-type: none"> No differences in the cyclic reproductive hormone pattern were compared with higher and lower 1,25(OH)2D. 25(OH)D <30ng/ml on FSH (95% CI: -0.2, 0.2) and LH (95% CI: -0.08, 0.4) 1,25(OH)2D <105pmol/L on FSH (95% CI: -0.5, 0.01) and LH (95% CI: -0.5, -0.02) 	82%
Jafari-Sfidvajani (2018) ²⁶	A double-blind, randomized, placebo-controlled trial	20–40	60	<20: deficiency	Vitamin D ₃ supplementation towards “Vitamin D” group and “Placebo” group to evaluate the menstrual cycle	<ul style="list-style-type: none"> Normalizing the vitamin D level serum increases the regularity of menstruation ($p=0.01$), and decreases amenorrhea and oligomenorrhea ($p=0.01$). Significantly increased the median vitamin D levels from 18.5 ng/ml to 42.69 ng/ml and improvement in the frequency of regular menstrual cycle 	100%
Lagowska (2018) ²⁷	Prospective cohort study	-	77	<30: deficiency; >30: sufficiency	Serum 25(OH)D levels and menstrual cycle	<p>25(OH)D deficiency (<30 ng/mL) were correlated with longer cycles (oligomenorrhea or amenorrhea) (OR(CI): 5.0 (1.047 to 23.871), $p = 0.04$)</p> <ul style="list-style-type: none"> A decreased 25(OH)D levels were associated with 13.3 times the odds of an irregular cycle (OR (95% CI): 13.30 (5.79-30.60), $p<0.001$) 	73%
Singh (2021) ²⁸	Cross-sectional study	18 ≥ 40	166	<20: deficiency; ≥20: sufficiency	25(OH)D and menstrual cycle characteristics (long and short cycle length and cycle irregularity)	<ul style="list-style-type: none"> There were a significant difference in mean 25(OH)D levels between individuals with irregular (14.56 ± 8.76) and regular (21.90 ± 6.15) menstrual cycles which were difference significant ($p<0.0001$) The mean 25(OH)D levels of females with infrequent and frequent cycles are not significantly different 	100%

25(OH)D, 25 Hydroxyvitamin D; CI, Confidence Interval; IU, International Unit; 1,25(OH)2D, 1,25-Dihydroxyvitamin D; 25(OH)D; 25-hydroxyvitamin D; FSH, Follicle-Stimulating Hormone; iPTH, Intact Para Thyroid Hormone; JBI, Joanna Briggs Institute; LH, Luteinizing Hormone

Vitamin D intake normalized the 25(OH)D levels of the participants (12–18 years) and normal menstrual length ($p=0.015$).¹⁴ This study implied that vitamin D 50,000 IU for nine weeks of supplementation helps to normalize 25(OH)D level serum and affects the normal

menstrual period.¹⁴ This study in line with a randomized placebo-controlled clinical trial conducted by Al-Bayyari et al²⁵, which found vitamin D intake 50,000 IU for 12 weeks ameliorated the menstrual length in 60 participants (18–49 years) ($p=0.001$).²⁵ A variety of

studies, although not all, have shown vitamin D fluctuations during the menstrual cycle, as well as differences in gonadal hormone levels during the luteal phase.²⁹⁻³¹ However, how vitamin D affects this phase mechanism remains unclear. This is assumed to be connected to vitamin D's action on AMH, a glycoprotein hormone generated by granulosa cells during the folliculogenesis process, which plays a role in ovulation and oocyte maturation.³² A randomized placebo-controlled clinical trial study conducted by Jafari-Sfidvajani et al.²⁶ showed that normalizing the vitamin D level serum increases the regularity of menstruation ($p=0.01$) and decreases amenorrhea and oligomenorrhea ($p=0.01$). Unlike the other two trials, this investigation integrated 50,000 IU vitamin D intake with a low-calorie diet for a week.²⁶

Vitamin D is categorized as corticosteroid³³ which modulates many beneficial reproductive processes, such as menstrual cycle regulation and sex hormone regulation.³⁴ It has several receptors in the nucleus of the body's organ tissue, one of which is in the hypothalamic-hypophysis-ovarium system; hence, it impacts the menstrual cycle.²⁰ Vitamin D is correlated with steroidogenesis and follicle development because its receptor is exist in ovarian cells.³⁵ Vitamin D influences sex steroid hormones forming process and human immune system regulation by interacting with progesterone through the induction of T cells and vitamin D receptors. It affects estradiol and estrogen biosynthesis which are correlated with aromatase gene expression and calcium metabolism.^{1,27} In addition, this vitamin affects folliculogenesis and the production of the hormone progesterone by affecting the sensitivity of follicle stimulating hormone (FSH).¹ AMH may be associated with 25(OH)D metabolism because it decreases primordial follicle recruitment, leading to a significant decrease in follicular development and further delaying atresia. In the AMH gene's promoter region is a domain for the vitamin D signaling pathway. Therefore, vitamin D are hypothesized as responsible for controlling AMH production.³⁶ This mechanism may explain how vitamin D has an essential role in menstrual regulation.

This study had several limitations. Several studies used a small population size. Some studies did not provide mean and standard deviation values of 25(OH)D. Therefore, we were unable to identify the general classification of the baseline population characteristics before intervention. The included studies were also undertaken mainly in high-income countries, limiting the generalizability of the study findings. Furthermore, only a few studies recorded menstrual phase testing previous to the intervention, which might lead to varied

25(OH)D levels interpretations among participants due to fluctuations across the menstrual phases.

CONCLUSION

The results of both observational studies and randomized controlled trials included in this review imply that serum vitamin D levels influence the length and the frequency of the menstrual cycle. This findings are due to the effect of serum vitamin D on female reproductive hormones that play a role on menstrual cycle regulation. Given the limitations of the current review, future studies, possibly with a randomized controlled design, are required to further confirm our findings.

DISCLOSURES

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None

Conflict of interest

There are no conflicts of interest in this study's content among all authors.

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Author contribution

AM, HS, and BS have contributed to all processes in this research, including preparation, data gathering, and analysis, drafting, and approval for publication of this manuscript.

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