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Systematic Review

The Effect of Calcium on Biomarkers of Ovarian Fertility in Premature Ovarian Failure: A Systematic Review

Sutrisno Sutrisno[1,2], Tri Aji Bangun Nuswantoro[1*]
[1] Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Brawijaya/ Saiful Anwar General Hospital, Malang, East Java, Indonesia
[2] Magister of Midwifery, Faculty of Medicine, Universitas Brawijaya, Malang, East Java, Indonesia

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CORRESPONDING AUTHOR
Tri Aji Bangun Nuswantoro
ajibangunnuswantoro@gmail.com
Department of Obstetrics and Gynaecology, Faculty of Medicine, Universitas Brawijaya/ Saiful Anwar General Hospital, Malang, East Java, Indonesia

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ABSTRACT

Introduction: *Premature ovarian failure* (POF) is a condition in which ovarian function decreases or follicles are depleted in women aged less than 40 years. Calcium, along with vitamin D, is a mineral with many benefits for the reproduction system. This review is written to observe the effect of calcium on ovarian fertility biomarkers in premature ovarian failure.

Methods: The literatures search was conducted utilizing numerous search engines, namely PubMed, Cochrane, Springer, Science Direct, Nature, and Google Scholar. Article publication year was restricted from 2016 to 2022. Article search keywords included "calcium", "vitamin D", "premature ovarian failure", "premature ovarian insufficiency", "amenorrhoea", "ovarian reserve biomarkers", "estradiol", "follicle stimulating hormone", and "luteinizing hormone". Article selection was performed using the preferred reporting items for systematic review and meta-analysis protocols guidelines (PRISMA-P). The first author's name, publication year, samples number, age range of subjects, duration of data collection, geographical setting, study design, and conclusions of research results were extracted from the selected paper.

Results: 8397 articles were obtained from the six search engines. 13 articles met the inclusion criteria. Research conducted by Iran reported a significant correlation between vitamin D levels and AMH levels ($p<0.001$). In comparison, the research in Bangladesh showed a significant positive correlation between vitamin D levels and AMH levels ($r=0.433$; $p=0.001$) and vitamin D levels and AFC values ($r=0.419$; $r=0.001$). However, 11 other researchers reported contradictory results.

Conclusion: The calcium and vitamin D effect on reproductive health related to POF occurrence is still inconsistent. Therefore, observational and experimental research is needed to analyze this topic.

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INTRODUCTION

Premature ovarian failure (POF), and known as premature ovarian insufficiency (POI), is a disorder in which a woman's follicle count decreases before 40 years or at reproductive age [1]. This condition is characterized by sudden amenorrhea or oligomenorrhea, infertility, and hypogonadal hypogonadotropic conditions [2]. Prevalence of POF in women younger than 40-year-old is 1%. However, 1 in 1000 women aged less than 30 years has POF. Several factors that may trigger POF include genetic mutations, autoimmune disorders, toxins such as chemotherapy drugs, and infections. The clinical manifestations of POF vary depending on the underlying condition of the POF. In addition to menstrual abnormalities and infertility, women with POF also experience menopausal symptoms, fatigue, and anxiety or depression. However, the associated manifestations are often subclinical.

Thus, POF often goes undetected, and the diagnosis of POF is delayed. This is dangerous because

POF can cause various health sequelae, such as premature bone loss, leading to fractures, decreased cognition and emotional disturbances, and cardiovascular complications [3].

Calcium is a mineral found in dairy products, particularly vegetables and fish. Based on numerous previous researches, calcium has many benefits on reproductive health. In pregnant women, calcium is essential for maintaining the bone health of the fetus and stimulating the maturity of fetal organs such as the liver and lungs. In studies with human or animal subjects, calcium, mediated by calcium-sensing receptors (CaSR), helps facilitate spermatogenesis, increases sperm motility, assists implantation of a fertilized ovum, stimulates placental maturation, maintains selected and mature follicles, triggers oocyte maturation [4].

In addition, calcium also helps activate signaling pathways related to reproductive function through its function as a secondary messenger. Calcium induces oocyte maturation, either luteinizing hormone (LH)-induced or spontaneous, and ovum development after fertilization. The purpose of this systematic review is to analyze the effect of calcium on reproductive health on POF incidence.

MATERIAL AND METHODS

Literature Search

The authors searched for articles published between 2016 and 2022, with keywords including "calcium", "vitamin D", "premature ovarian failure", "premature ovarian insufficiency", "amenorrhoea", "ovarian reserve biomarkers", "estradiol", "follicle-stimulating hormone", and "luteinizing hormone". Literatures search was conducted on several search engines such as PubMed, Cochrane, Springer, Science Direct, Nature, and Google Scholar. After the article search, the authors analyzed related articles to identify articles that did not meet the inclusion criteria of this systematic review before reviewing the abstract and the article as a whole. The selection of articles for inclusion in this systematic review is based on the preferred reporting items for systematic review and meta-analysis protocols guidelines (PRISMA-P).

Eligibility Criteria

The research selected to compile this systematic review are studies that meet the following criteria, as follow: (i) experimental, observational, or qualitative studies published in the period 2016 to 2022, (ii) measuring the parameters used to establish or support the diagnosis POF, (iii) comparing the correlation of vitamin D or calcium with ovarian fertility biomarkers, (iv) published in English.

Articles with poor abstract or article quality, systematic reviews, conference abstracts, case reports, only included expert opinion or news information and exclusively presented epidemiological data were excluded.

Definition

Premature ovarian failure or premature ovarian insufficiency is defined as amenorrhea or infrequent menstruation for at least four months with a hypogonadal hypogonadotropic condition detected on two examinations with an interval of 4 weeks. Hypergonadotropic conditions are defined as levels of FSH > 25 IU/l.

Data Extraction

Data from the research were extracted and recorded for inclusion in a Microsoft Excel application format. Before data collection, the authors selected research articles by analyzing the titles and abstracts of the literature sought. Studies that had titles and abstracts that match the appropriate topics were then retrieved for a full paper review related to the eligibility criteria for the study. Research data extracted by the authors included the first author's name, publication year, samples number, age range of subjects, duration of data collection, geographical setting, study design, and conclusions of research results.

RESULTS

8397 articles were obtained from the six search engines. After screening the title and eliminating duplication of articles, 647 articles were obtained. After screening the article abstracts, 610 articles were excluded, and 31 articles were obtained. The 31 articles were reviewed. 18 articles were then excluded. 13 articles met the inclusion criteria as depicted in Fig.1.

Research Characteristic

The number of study subjects included in this systematic review ranged from 62 to 457 women. The total number of subjects in the related research was 2786 subjects. The studies reviewed cover 4 continents, namely Asia, Europe, Africa, and North America. The details of the research countries were as follows: Pakistan 1, Iran 2, Bangladesh 1, South Korea 1, India 1, China 1, Turkey 2, United States 2, Belgium 1, and Nigeria 1. The age range of the subjects was from 18 years to 50 years. Subjects could be fertile or infertile women. The time of the research was from 2008 to October 2021 (Table 1).

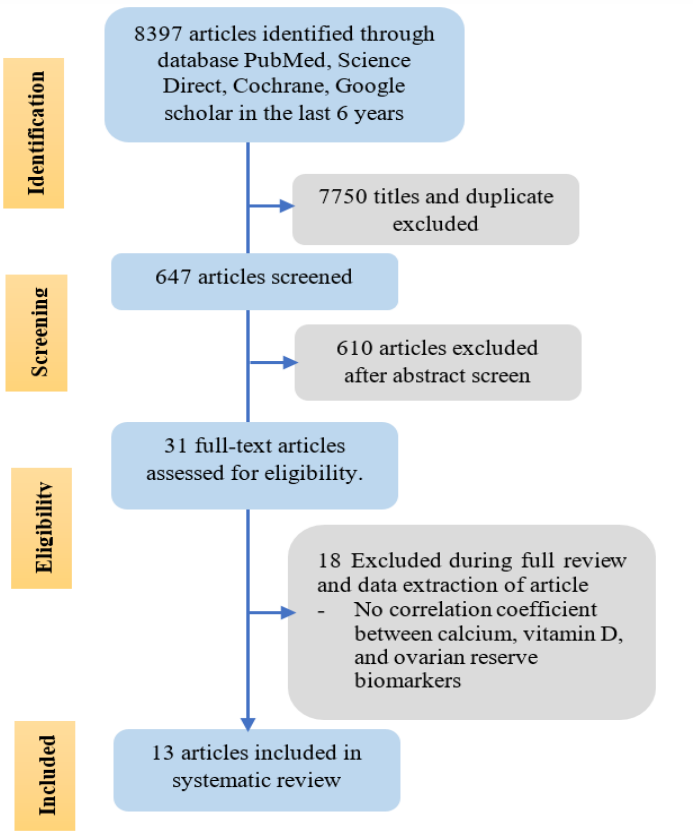


Fig.1. The Research Flow of Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)

The Relation between Calcium and Vitamin D with Ovarian Fertility Biomarkers

Two studies reported a significant correlation between vitamin D levels and antral follicle count (AFC) and anti-Müllerian hormone (AMH) [3,4]. Studies in Iran reported a significant correlation between vitamin D levels and AFC values ($p<0.001$) [3]. In comparison, the study in Bangladesh showed a significant positive correlation between vitamin D levels and AMH levels ($r=0.433$; $p=0.001$) as well as vitamin D levels and AFC values ($r=0.419$; $r=0.001$) [4]. Moreover, vitamin D levels in infertile women were significantly lower than in fertile women. A total of 11 other studies did not find a significant correlation between vitamin D levels and AMH levels, FSH levels, inhibin B levels, or AFC values [5,6,15,7–14].

DISCUSSION

Premature ovarian failure is a condition when the ovaries stop working, or the follicles are depleted long before the time of menopause in general [1,16]. Hence, POF occurs in women younger than 40 years. Moraes-Ruehsen first reported this condition in 1967 as non-physiologic amenorrhea [17]. The etiology of POF is generally idiopathic, but several chemotherapeutic agents are thought to trigger POF. Genetic disorders often trigger cases of POF, several genes involved include LHX8, SOHLH1, FOXO3A, NOBOX, FMR1, POLR3H, BMPR2, and AMH [18–21]. The main features of POF are the occurrence of amenorrhea and hypoestrogenism [22]. Menopausal symptoms of POF as a short-term consequence, such as hot flashes, night sweats, dry eyes, dyspareunia, and decreased sexual desire, reduce a woman's quality of life at reproductive age [23]. This condition becomes dangerous due to its long-term consequences, including infertility, osteoporosis, and cardiovascular and neurological complications [24]. These events potentially lead to the premature death of a woman.

Calcium is a mineral commonly found in the body, especially in bones, where its level is highest. Several recent research stated that calcium has a close relationship with reproductive function. In animal studies, low calcium levels can lead to delayed involution, risk of retained placenta, and uterine prolapse [25]. In humans, calcium has been shown to assist trigger oocyte maturation, either spontaneously or induced by LH. This is considered due to calcium modulation of intracytoplasmic cAMP concentrations [26]. Calcium is also involved in the activation of the ovum triggered by factors derived from sperm. Thus, the ovum can then develop into an embryo. In addition,

the surface healing of ovarian epithelial cells by proliferation also occurs in the presence of calcium. In follicles, the expression of CaSR in oocytes and granulosa cells. It is also observed at various stages of oocyte development, suggesting that calcium plays a role in the meiotic maturation of the oocyte [2]. Through CaSR function, calcium is considered to trigger gonadotropin-induced nuclear maturation of oocytes through the mitogen-activated protein kinase signaling pathway (MAPK) [27].

Vitamin D is a substance closely related to calcium. Because when an individual has a low level of vitamin D in the body, calcitriol, which is the active form of vitamin D, will be produced in small amounts. This further inhibits the absorption of calcium by the gastrointestinal system. As a result, the body will have to search for other sources of vitamin D from the bones. Therefore, vitamin D plays a role in maintaining serum calcium levels [28] When vitamin D levels in the body are adequate. The active metabolite of vitamin D, namely 1,25-dihydroxyvitamin D, will bind to the vitamin D receptor (VDR) in the intestine and stimulate calcium absorption from the intestinal lumen. When 1,25-dihydroxyvitamin D levels are low or < 20 nmol/L, active absorption of calcium from the intestinal lumen is reduced [29]. Moreover, calcium and vitamin D are often found in the same food source, where the collinearity of the two was high, indicated by a correlation coefficient of 0.86 ($p<0.001$) [30]. Thus, the relationship between calcium levels and reproductive health, represented by ovarian fertility biomarkers, can be studied indirectly through vitamin D levels.

In this systematic review, there are 2 contradictory findings regarding the correlation between vitamin D and ovarian fertility biomarkers. Ovarian fertility was evaluated using the amount of AFC, AMH levels, FSH levels, and inhibin B levels. Two research articles reported a significant correlation between vitamin D levels and AFC values, and AMH levels [3,4]. Dey, Dus, and Fatima also found significantly lower vitamin D levels in fertile women. This statement follows the finding of New Zealand research that vitamin D administration can stimulate AMH production in the ovaries [31]. Vitamin D also contributes by altering AMH sensitivity in humans. This decreases sensitivity, causes oocyte maturation, and triggers ovulation subsequently, thereby improving reproductive function [32]. Anti-Müllerian hormone is a hormone produced by large and small preantral follicles, able to represent the primordial follicle reserve. This finding is supported by the results of a study conducted by Purdue-Smith et al. (2017), who stated that women who experience a higher intake of vitamin D and calcium have a lower risk of experiencing early menopause or POF [30]. A lower risk of early menopause is associated with vitamin D and calcium from dairy products. Cow's milk is a rich source of the steroid hormone, progesterone. In addition, cow's milk also increases estradiol production and insulin-growth factor 1 (IGF-1).

Meanwhile, 11 other studies included in this systematic review reported contradictory results. Vitamin D levels do not have a significant correlation with ovarian fertility biomarkers [5,6,15,7–14]. This means that the level of vitamin D in an individual's body does not reflect a person's fertility. This can be caused by differences in the ethnicity of the included research subjects. Subjects in certain countries have certain habits that potentially act as confounding factors for related comparisons. Moreover, research by LeBlanc (2015) showed that administering calcium to postmenopausal women has no benefit in reducing menopause-related symptoms. There were no differences in sleep disturbances and emotional disorders in women receiving calcium compared to placebo [33].

The weakness of this systematic review is the lack of data regarding the direct effect of calcium administration on the occurrence of POF. Analysis of the correlation between calcium and a woman's fertility through vitamin D levels may lead to confusion due to other factors that might affect the role of vitamin D in assessing POF.

CONCLUSION

POF is still one of the crucial causes of infertility in women of reproductive age. This condition may pose a threat due to various associated long-term complications leading to premature death. Calcium is a mineral that has various benefits in the field of reproduction and may potentially prevent POF. However, recent findings show inconsistent results regarding the effect of calcium on reproductive health in terms of ovarian fertility biomarkers. Therefore, further observational or experimental research regarding the relationship of calcium to POF occurrence is necessary.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

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Table 1. Research Characteristic

Author	Publication Year	Number of samples	Subject Age (years)	Data Retrieval Duration	Geographical Background	Research Design	Conclusion
Ahmed *et al.* [12]	2019	139	18 - 45	August 2016 – July 2017	Pakistan	Retrospective cross-sectional	A poor correlation is found between vitamin D, AMH, and FSH.
Alavi *et al.* [11]	2019	287	18 - 45	July 2017 – December 2017	Iran	Prospective cross-sectional	There is no significant correlation between vitamin D and AMH and vitamin D and AFC.
Arefi *et al.* [5]	2018	189	21 - 43	N/A	Iran	Observational prospective	There is a significant negative correlation between age and vitamin D and age and AFC. There is a significant correlation between vitamin D and AFC.
Dey *et al.* [6]	2019	156	20 - 34	July 2018 – June 2019	Bangladesh	Case-control	Vitamin D deficiency has a significant positive correlation with AMH and AFC.
Drakopoulos *et al.* [17]	2016	283	18 - 42	12 months	Belgium	Prospective cross-sectional	There is no significant correlation between vitamin D and AMH or AFC.
Jukic *et al.* [10]	2018	562	30 - 44	2008 - 2016	United State	Prospective cohort	No significant correlation is found between vitamin D and AMH, FSH, or inhibin-B.
Kim *et al.* [14]	2020	63	<40	March 2018 – February 2019	South Korea	Prospective cohort	There is no significant correlation between vitamin D and AMH or AFC.
Makwe *et al.*[8]	2019	218	18 - 49	September 2016 – December 2016	Nigeria	Prospective cross-sectional	There is no correlation between vitamin D and AMH.
Shapiro *et al.* [15]	2018	457	21 - 50	September 2014 – November 2017	United State	Retrospective cohort	There is no difference in AMH and FSH levels between patients with or without vitamin D deficiency.
Xu *et al.* [16]	2019	105	18 - 40	September 2015 – April 2016	China	Case control	There is a negative correlation between vitamin D and FSH and a positive correlation between vitamin D and AMH, but not significant.
Altuntas *et al.* [13]	2022	195	18 - 45	October 2020 – October 2021	Turkey	Retrospective cohort	There is no significant correlation between vitamin D and AMH or AFC.
Bacaknagil *et al.* [9]	2022	62	18 - 41	June 2019 – September 2019	Turkey	Prospective, non-randomized, cross-sectional	There is no significant correlation between vitamin D and AFC, AMH, and FSH before and after vitamin D supplementation.
Lata *et al.* [7]	2017	70	18 - 40	April 2014 – April 2016	India	Prospective cross-sectional	There are significant differences in vitamin D and AMH levels between fertile and non-fertile patients. However, there was no significant correlation between vitamin D and AMH levels.