

## Vitamin D and Females Infertility: A Review Article

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### ABSTRACT

**Background:** Vitamin D can enhance semen quality and stimulate ovaries. Earlier research has linked fertility problems to a vitamin D insufficiency. However, because the field of study is very young, further research is required to establish the link between vitamin D and fertility.

Managing the levels of calcium and phosphorus in the blood and maintaining the health of the bones both depend on vitamin D. The main advantages of vitamin D are:- Increasing oral health, Supporting the immune system, Strengthening bones and muscles , Potentially lowering the incidence of cancer, managing hypertension, preventing diabetes, and promoting a healthy pregnancy.

**Methods:** matched the concept of "vitamin D" with a number of other concepts: " syndrome of polycystic ovary (PCOS) ", "ovarian reserve," "endometriosis," and "in vitro fertilization."

**Results:** There were conflicting findings on a state of vitamin D in polycystic ovary syndrome, in vitro fertilization and endometriosis. Anti-Müllerian hormone (AMH) levels in infertile females have not been found to significantly correlate with vitamin D concentrations in certain studies, however vitamin D deficiency may be related to a decreased ovarian reserve in females above the age of 40.

**Conclusion:** Both fertile and infertile females frequently suffer from vitamin D deficiencies. This deficit is linked to a number of unfavorable results in various infertility-related disorders. Vitamin D influences endometrial thickness, in spite of that there is many contradictory research on the link between vitamin D state and AMH , endometriosis and PCOS.

**Keywords:** infertility, vitamin D, polycystic ovary syndrome .

### فيتامين د والعقم عند النساء: مقالة مراجعة

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#### الخلاصة

**الخلفية:** تم التأكيد على أن فيتامين (د) قد يعزز تنشيط المبيض وتحسين جودة السائل المنوي. تم ربط نقص فيتامين (د) بالعقم في بحث سابق. ومع ذلك ، نظرًا لأن العلم لا يزال في مهده ، فإن الأمر يتطلب مزيدًا من الدراسة حول العلاقة بين فيتامين (د) والخصوبة. تحتاج أجسامنا إلى فيتامين د ، وهو أمر ضروري للتحكم في مستويات الكالسيوم والفوسفور في الدم والحفاظ على صحة العظام. المزايا الرئيسية لفيتامين (د) هي: - زيادة صحة الفم ، ودعم جهاز المناعة ، وتقوية العظام والعضلات ، وتقليل احتمالية الإصابة بالسرطان ، وإدارة ارتفاع ضغط الدم ، والوقاية من مرض السكري ، وتعزيز الحمل الصحي.

**الطرق:** مطابقة عبارة "فيتامين د" بالمصطلحات التالية: "متلازمة تكيس المبايض" ، "احتياطي المبيض" ، "الانتباز البطاني الرحمي" ، و"الإخصاب في المختبر".

**النتائج:** كانت هناك نتائج متضاربة حول مستويات فيتامين د في التلقيح الاصطناعي ومتلازمة تكيس المبايض ، وكذلك فيما يتعلق بوظيفة فيتامين د في سمك بطانة الرحم . على الرغم من أن بعض الدراسات لم تجد ارتباطًا مهمًا بين مستويات فيتامين (د) والهرمون المضاد للمولر لدى النساء المصابات بالعقم ، إلا أن نقص فيتامين (د) قد يكون مرتبطًا بانخفاض احتياطي المبيض لدى النساء فوق سن الأربعين.

**الخلاصة:** تعاني كل من النساء المصابات بالعقم وغير المصابات بالعقم من نقص فيتامين (د). يرتبط هذا النقص بعدد من النتائج غير المواتية في العديد من الاضطرابات المرتبطة بالعقم ، حيث يؤثر فيتامين د على سمك بطانة الرحم ، وهو أمر مهم لحقن الحيوانات المنوية داخل الهبيولى والتخصيب في المختبر ، على الرغم من وجود العديد من الأبحاث المتناقضة حول الارتباط بين فيتامين د. مستويات الهرمون المضاد للمولر ، متلازمة تكيس المبايض ، و سمك بطانة الرحم.

**الكلمات المفتاحية:** العقم ، فيتامين د ، متلازمة تكيس المبايض .

## INTRODUCTION

The skin produces 80 to 90 percent of the vitamin D we need when exposed to sunlight; the remaining 10 percent comes from dietary. It is widely recognized how vitamin D supports bone mineralization and calcium homeostasis<sup>1</sup>. However, mounting data indicates that vitamin D also has lots of non-skeletal advantages. Several chronic illnesses, involving the onset, progress, hormonal issues and cancer, are associated with low serum vitamin D levels, according to certain research<sup>2,3</sup>, as well as autoimmune diseases<sup>4,5</sup>. Because vitamin D is conveyed in reproductive tissues, the pituitary gland, and the hypothalamus, research on both humans and animals has shown that it also affects how men and women reproduce<sup>6-10</sup>. In the skin vitamin D3 is created from 7-dehydrocholesterol. Eating foods like fatty fish or egg yolks is a secondary way to obtain vitamin D3. Vitamin D2 is instead obtained from fungi, including yeast and mushrooms. As previously mentioned, only about 20% of our vitamin D comes from food; the majority is produced in our skin by exposure to sunlight. However, the ratios acquired from dietary sources and skin metabolism differ significantly between individuals<sup>11</sup>. Different 25-hydroxylase enzymes in the liver in humans are responsible for producing "25-hydroxyvitamin D". The blood's "25-hydroxyvitamin D" has a relatively brief half-life of two to three weeks, with ten to fifteen percent of it attached to albumin, 85 to 90 percent attached to vitamin D-binding protein, and less than 1% floating around free<sup>12</sup>. The only fraction that can breach a cell's membrane and have an impact on cells is the unbound fraction. To produce 1,25-dihydroxyvitamin D (calcitriol), "25-hydroxyvitamin D" must undergo a hydroxylation step. The receptor of vitamin D is most receptive to calcitriol. The activity of this kidney enzyme is regulated by elements impacting mineral metabolism, is aided by parathyroid hormone, and is hindered by fibroblast growth factor<sup>13</sup>. Rather, there is a strong substrate dependence in the formation of extra-renal "1,25 dihydroxyvitamin D". 1, 25 dihydroxyvitamin D's interaction with the receptor of vitamin D controls the downstream activation of several genes. Different biological effects are brought about by this binding. The breakdown of vitamin D begins with 24-hydroxylation. In pregnancy, vitamin D concentration was significantly increased and rapidly declines after birth. When compared to non-pregnant females, pregnant females have reduced PTH concentrations. The presence of immune cells like macrophages that synthesize vitamin D in the kidneys was suggested by some writers. The placenta also makes "1,25 dihydroxyvitamin D",

but it doesn't have a big impact on levels of the hormone in the blood<sup>11,12</sup>.

## METHODS

Vitamin D was searched for by matching it to the next phrases: " Syndrome of the polycystic ovary " ovarian reserve," "endometriosis," "in vitro fertilization".

## RESULTS

### Polycystic Ovary Syndrome (PCOS):

PCOS is expressed by polycystic ovarian morphology, prolonged anovulation with clinical or biochemical hyperandrogenism. Vitamin D has a crucial function in PCOS, as well as dyslipidemia, diabetes type 2, and heart disease, as well as disorders including obesity, infertility, and metabolic syndrome<sup>14</sup>.

Despite a fact that several research have been conducted, no observational study has been able to definitively link vitamin D deficiency to PCOS.

The authors of an Austrian study<sup>15</sup> discovered that testosterone levels were independently predicted by calcium ingestion and "25 hydroxyvitamin D", while androstenedione levels were independently predicted by calcium intake.

The body mass index (BMI) and "25-hydroxyvitamin D" insufficiency were significant predictive variables, according to Ott et al.'s analysis of 91 infertile females with PCOS. They discovered that "25 hydroxyvitamin D" levels below ten ng/ml, dramatically decreased the likelihood of developing follicles by 67 percent and gestation by 76 percent<sup>16</sup>.

Some researches claim that vitamin D may contribute to the emergence of resistant to insulin.<sup>17-20</sup> They demonstrated that "25-hydroxyvitamin D" is connected to increased levels of insulin receptor, improved sensitivity to insulin, increased insulin production and release, and a drop in pro inflammatory cytokines linked to insulin resistance. Furthermore, the hormone calcitriol has an indirect impact on insulin sensitivity because it regulates the amount of intracellular calcium needed for tissues like fat and muscle to use insulin to modulate cell signaling<sup>21,22</sup>.

In a part but not all observational studies, the fertility issues polycystic ovarian syndrome are linked to vitamin D insufficiency<sup>23</sup>.

In addition, vitamin D and BMI are independent indicators of the onset of the metabolic disorder in PCOS females, according to some studies. These discoveries were made in females with PCOS who were both fat and not obese. Several studies have also discovered a negative correlation between vitamin D levels and BMI.<sup>22,24-26</sup>

Based on the findings of the open-label and single-arm experiment by Pal et al. supplementing with vitamin D and calcium is linked to a significantly lower level of total testosterone and androstenedione. The researchers of this study also discovered that taking the supplement was linked to a considerable drop in blood pressure, however they found no effects on insulin and glucose balance<sup>27</sup>. In contrast to the control group, Jia et al. discovered that PCOS females's blood vitamin D values were lower<sup>28</sup>.

Muscogiuri et al.<sup>29</sup> concluded that overall body fat was related to "25 hydroxyvitamin D" values, this was supported by Tsakova et al.'s research<sup>30</sup>, which demonstrated that obese PCOS females had lesser 25 hydroxyvitamin D concentration than non-obese PCOS females. Instead, PCOS females exhibited higher levels of vitamin D than the controls, according to research by Mahmoudi et al.<sup>31</sup>

### Ovarian Reserve

Anti-Müllerian hormone (AMH) works by preventing the responsiveness of the primordial follicles to follicle stimulating hormone and inhibiting the first enrollment of follicles for growth. This preserves the ovarian reserve. Calcitriol, according to Merhi et al., encourages follicular maturation<sup>32</sup>.

Although vitamin D shortage and insufficiency are more prevalent in the infertile group, another study found that there was minimal probability of a relationship involving AMH and vitamin D.<sup>33</sup>

A favorable independent connection between "25 hydroxyvitamin D" levels and AMH was discovered in a research involving 388 premenopausal females with normal period. Therefore, vitamin D insufficiency may be linked to a reduced ovarian reserve in females who are past the prime of their reproductive years<sup>34</sup>.

Another short research by Dennis et al.<sup>35</sup> in 33 reproductive age group females revealed a correlation between the values of "25 hydroxyvitamin D" and AMH as well as seasonal change in both of these markers' levels. AMH decline can also be stopped by using vitamin D supplements.

It was demonstrated by Shapiro and colleagues that "25 hydroxyvitamin D" levels were insufficient determinants of AMH in an analysis of 457 infertile females within the age range of 21 and 50 years<sup>36</sup>.

### Endometriosis

About 10 percent of females in reproductive age have endometriosis. Its etiology is influenced by immune system malfunction and inflammatory responses<sup>37</sup>.

Vilarino et al. observed lack of connection between vitamin D receptor and endometriosis or infertility in a prevalence research of one hundred thirty three normal females, hundred thirty two females with endometriosis related infertility, and sixty two females with infertility that was idiopathic<sup>38</sup>.

According to research by Agic et al.<sup>39</sup>, they discovered that endometriosis affected females had greater levels of both vitamin D receptor and 1  $\alpha$ -hydroxylase expression than controls did. Additionally, they demonstrated no variation in "25 hydroxyvitamin D" levels among endometriosis affected females and the control group.

In contrast, Somigliana et al.<sup>40</sup>, reported that patients' "25 hydroxyvitamin D" levels were much greater than those of the control group in their study of 87 females with endometriosis and 53 healthy females, they also showed that elevated levels of "25 hydroxyvitamin D" are associated with the more severe stages of the illness.

regarding Ferrero et al. study, females with untreated endometriosis exhibited lower quantities of vitamin D bound protein in their fluid of the peritoneum than females who use contraceptive pills and the control group<sup>41</sup>.

According to a research by Faserl et al., vitamin D binding protein levels were considerably greater in ectopic endometrium than in normal tissues. Additionally, they discovered that all endometriosis-positive study participants had vitamin D binding protein levels that were three times higher than those of the control<sup>42</sup>.

### In Vitro Fertilization

The significance of vitamin D supplement on the success of in vitro fertilization is still up for debate, despite the fact that numerous studies have shown the crucial role that vitamin D plays in reproduction,<sup>43</sup>. In a prospective study, the "25 hydroxyvitamin D" levels were compared to the outcomes of IVF. The implanted rates were 17.3%, 15.3%, and 18.8%, respectively, while the fertilization rates were 43.2 percent in cases of vitamin D deficiency, 53.4% in cases of insufficiency, and 58.8 percent in cases of sufficiency in females. The likelihood of conception did not statistically significantly correlate with serum or follicular vitamin D levels. The tiny percent of females with appropriate vitamin D levels may be the cause of the lack of a statistically meaningful association (7.2 percent)<sup>44</sup>.

In 188 infertile females having in vitro fertilization in 2012, Rudick et al.<sup>45</sup> conducted a retrospective cohort study to examine the relationship between "25 hydroxyvitamin D" levels and clinical conception outcomes. In non-Hispanic whites, They noticed a gradual decline in pregnancy prevalence among non-Hispanic whites with

declining vitamin D levels, but Asian females had the opposite tendency. Based on the current research, non Hispanic white females who had appropriate level of vitamin D over 30 ng/ml had a 4-fold higher probability ratio of clinical pregnancy than those with low levels (20 ng/ml); this difference was statistical importance ( $P=0.01$ ). Intriguingly, neither ovarian stimulation parameters nor measures of embryo quality in this investigation showed a significant relationship with vitamin D status<sup>45</sup>.

Studies from 2014 found that serum or follicular fluid vitamin D measurements yield very similar findings. It was convenient to evaluate serum levels of vitamin D before beginning reproductive technology, and if required, vitamin D supplements may be given to females who demonstrated a shortfall<sup>42,45-48</sup>.

Vitamin D promotes endometrial growth within an intrauterine insemination cycle, according to studies by Asadi et al.<sup>49</sup>. In infertile females with PCOS, they examined how vitamin D affected the efficacy rates of intrauterine fertilization cycle.

Chu et al.<sup>50</sup> discovered in 2018 that females with adequate vitamin D reserves had a greater possibility of successfully conceiving following embryo transfer, they discovered a higher than average occurrence of vitamin D insufficiency in an analysis of seven trials. overall incidence of vitamin D deficits, insufficient, and repletion according to the meta-analysis was 34.6 percent, 45.3 percent, and 25.7 percent, respectively. In addition, they noted that females with appropriate vitamin D levels showed a better chance of having a live baby after ART than did females with vitamin D shortage or insufficiency.

In 153 infertile females who were receiving ovulation induction, the researchers examined the impact of vitamin D values on thickening of the endometrium and markers of follicle growth. They found a connection between the thickness of the endometrium, the number of antral follicles, and vitamin D. Furthermore they observed that there was no connection among BMI and vitamin D levels during this trial and that BMI had no bearing on how births turned out. The study's findings did not support a link between vitamin D and effective rates of inducing ovulation<sup>51</sup>.

A prospective study with two groups, group A: the recipients, and group B: the donors, was carried out in 2017. The people were then divided into subgroups based on levels of vitamin D to : A1 and B1 had insufficient vitamin D (less than twenty ng/mL), whereas A2 and B2 had inadequate vitamin D. The results of reproduction were shown to be affected by vitamin D deficiency, however the the variation wasn't of statistical significance.

It found that it had no negative effects on the success of IVF as a consequence<sup>52</sup>.

A 2019 study by Chu et al, patients receiving assisted reproductive technologies frequently have vitamin D shortage and inadequacy. They suggested that this may be an important consideration for women receiving these therapies<sup>53</sup>.

## CONCLUSION

Clinical research demonstrates that vitamin D insufficiency is quite prevalent in both fertile and infertile females. Infertile females who have this deficit are linked to a number of negative outcomes. In vitro fertilization benefit from vitamin D, which also appears to be connected with endometrial thickness. All In vitro fertilization patients who are determined to be vitamin D deficient or insufficient should take a vitamin D supplement. According to research, vitamin D values should be not less than 30 ng/ml.

Studies on PCOS and endometriosis have various discrepancies, which may be caused by an uneven population distribution. The majority of these investigations also revealed vitamin D inadequacy or insufficiency in the females with PCOS and endometriosis.

Expression levels of vitamin D receptor and 1-alpha-hydroxylase may be greater in endometriosis-affected females.

The determination of vitamin D should be made a standard procedure in the future for females who have PCOS, endometriosis, or are undergoing Intrauterine insemination . If a deficiency or insufficiency of vitamin D is discovered, it may be treated using vitamin D supplements, with the dosage dependent on the severity of the deficiency.

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