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IMPLICATIONS OF SERUM VITAMIN D LEVELS IN FEMALE INFERTILITY: A REVIEW

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Abstract: Vitamin D is a fat-soluble vitamin with several physiological functions and has been related as a possible factor of influence on the reproductive process and, especially, on the female reproductive physiology. However, despite the increasing number of studies in the area, its influence on reproductive health has not been clarified, with conflicting results in responding if there is an association between low serum vitamin D levels and female infertility. The aim of this review is to elucidate the effect of vitamin D on female infertility, presenting current evidence of the association of serum levels of vitamin D in the face of several causes of infertility. A bibliographic search was performed in the MEDLINE (Pubmed), Google Academics, Scielo, Cochrane Central, Research Gate and Public Domain databases, using the word combinations: "vitamin D intertility", "vitamina D infertilidade", "vitamin d infertility polycystic ovary syndrome". The selected articles were from January 2018 to April 2019. Selected studies show that low vitamin D levels are associated with impaired fertility in women diagnosed with endometriosis and polycystic ovarian syndrome, as well as an association with successful *in vitro* fertilization. However, although there are suggestions and physiological evidence to support a relation of vitamin D deficiency and infertility, randomized controlled trials are still required in different populations to confirm that variations ins serum vitamin D concentrations compromises the health and fertility of women. Determination of serum vitamin D concentration in the reproductive period and the vitamin D supplementation would have important implications for the public health of different communities.
Keywords: Vitamin D, Infertility, Vitamin D deficiency.

INTRODUCTION

Infertility has a global rate of around 48.5 million (Voulgaris et al., 2017; Nandi, 2018). In the United States, it is estimated that 15.5% of women in reproductive age are affected by infertility (Chiu et al., 2018). In Brazil it is estimated that 8 million people are affected by infertility (Fertility Medical Group). The main causes of female infertility are anovulation, polycystic ovary syndrome (PCOS), tubal problems, endometriosis and unexplained cases (Vanni et al., 2014; Voulgaris et al., 2017; Chen et al., 2018).

Vitamin D deficiency has been increasingly recognized as a worldwide epidemic (Holick, 2007). Its deficiency in children may result in rickets incurring an increased risk of fracture and deformity and in adults it may result in osteomalacia with the same risk of fracture and deformity (Arefi et al., 2018). In addition, vitamin D deficiency appears to be involved in the pathogenesis of many chronic diseases, such as autoimmune diseases, infections, immune deficiency, cardiovascular disease, cancer, and neurocognitive disorders (Gröber et al., 2013).

There is a growing interest in the physiological role of vitamin D at various stages of reproductive function (Rudick et al., 2014), highlighting the expression of the vitamin D receptor (VDR) by the organs of the system (Johnson and Deluca, 2001; Avila et al., 2004; Parikh et al., 2010; Aleyasin et al., 2011; Arabian and Raoofi, 2018). The prevalence of vitamin D deficiency is high in women of reproductive age (Lerchbaum and Rabe, 2014) and its absence can provide a series of complications for both fertility and pregnancy (Arabian and Raoofi, 2018). Its deficiency in pregnant women has been associated with gestational diabetes mellitus and preeclampsia (Burris et al., 2012; Aghajafari et al., 2013; Barrett and Mcelduff, 2010), and its low concentration is related to infertility factors, such as: chronic

anovulation (PCOS), endometriosis, uterine myomatosis (fibroids), spontaneous abortion, preeclampsia, gestational diabetes, poor egg quality and implantation of the embryo by changing the results of *in vitro* fertilization (IVF) treatment (Chan et al., 2015).

Vitamin D is a secosteroid prohormone, mainly produced by the skin after exposure to sunlight or through diet and vitamin supplements (Holick and Chen, 2008; Holick, 2008; Voulgaris et al., 2017; Weinert and Silveiro, 2015). In the human body, vitamin D levels are measured through circulating levels of 25(OH)D because it is a longer half-life biomarker, and higher serum concentration compared to $1,25(OH)_2D$ (Holick, 2007; Weinert and Silveiro, 2015). Calcitriol acts in two ways: through its binding to the specific nuclear receptor, VDR, initiating multiple genomic effects (Voulgaris et al., 2017) or by binding to its receptor on the plasma membrane, mediating various non-genomic effects (Haussler et al., 2011).

Adequate plasma vitamin D levels and the recommended daily allowance is subject of debate, essentially because of the wide variety of health functions associated with it. According to the "Institute of Medicine" and the "Brazilian Society of Clinical Pathology/Laboratory Medicine", the cutoff value for diagnosis of vitamin D deficiency should be set at 20 ng/mL (50 nmol/L), but in the literature there is a range of 20 to 30 ng/mL (Holick, 2007; Holick et al., 2011; Muscogiuri et al., 2017). 20 to 52% of women of reproductive age are deficient in vitamin D (Lerchbaum and Rabe, 2014; Chu et al., 2018) and its absence can provide a number of complications for fertility and pregnancy (Arabian and Raoofi, 2018). During pregnancy, the role of vitamin D are still under evaluation, but the literature indicates that it is essential for fetal skeletal development and the health of pregnant women (Chan et al., 2015; Weinert and Silveiro, 2015).

The purpose of this review is to gather literature data on the effect of vitamin D on female infertility, specifying articles from the year 2018 and 2019, presenting as a cause of female infertility the polycystic ovary syndrome and endometriosis, as well as those presenting cohort data of women who underwent in vitro fertilization (IVF) (Chan et al., 2015).

MATERIALS AND METHODS

INCLUSION AND EXCLUSION CRITERIA

The studies of interest were original articles and reviews on the topic of vitamin D and infertility published between 2018 and 2019. Additional studies were considered when relevant data were cited by any reviewed article.

Animal model studies and those focusing on male infertility were excluded.

LITERATURE SEARCH

Data searches were performed through access to MEDLINE (Pubmed), Google Academics, Scielo, Cochrane Central, Research Gate and Public Domain. We selected articles in English and Portuguese. The keywords employed were: vitamin D intertility, "vitamina D infertilidade". Literature searches were conducted to identify studies published between January 2018 to May 2019.

The study research was performed by two authors (L.M.B and C.B.). Study selection, quality assessment via data collection sheets (designed according to the standards of the Cochrane Collaboration Book) and data extraction were performed dependently and blindly by two authors (L.M.B. and C.B.). Only studies with ethical approval were included in the systematic review.

For each study, the following information was extracted: first author's last name, year of publication, country of origin, number of subjects, design of the study, statistical analysis, outcomes assessed, confounding factors considered, results.

RESULTS

The PRISMA flow diagram of the review process is presented in **Figure 1**. There were 140 articles identified, 18 duplicates. Of the 122 articles, 70 were selected for reading and 55 were not considered relevant. 15 articles, dated 2018 and 2019, were analyzed.

STUDY CHARACTERISTICS

The characteristics of the 15 included studies are presented in **Table 1**. None of the included studies declared any conflicts of interest. The included studies were cross-sectional, randomized, observational, cohort and case control studies. Sample sizes varied from 40 to 1254 women. The selected studies analyzed vitamin D in different ways, as there were studies that analyzed serum 25(OH)D levels, studies that performed DNA extraction to analyze polymorphisms in the VDR gene, studies that analyzed the embryos ultrasound images, as well as mature oocyte counts and hormone levels to associate them with 25(OH)D. There were 6 studies with women with PCOS, 8 with infertile women, 1 with infertile women with PCOS, 1 with a cohort of women with endometriosis. One Study was performed with women with PCOS candidates for IVF and another with controlled ovarian stimulation. In 4 studies women had ovarian stimulation. 2 studies administered doses of vitamin D. In one study, serum vitamin D concentrations were analyzed in infertile women who had been assisted by different assisted reproduction technologies. In one study, besides ovarian stimulation, there was cytoplasmic injection and embryo transfer.

VITAMIN D DEFICIENCY

Literature data indicate that vitamin D metabolism may vary by race (Sohn et al., 2018). The prevalence of this vitamin deficiency in the general South Asian population is between 67-82%, in the Caucasian population is below 28.4% compared to 77% in Asians (Mogili et al., 2018). In addition, Chu et al. (2018) concluded by meta-analysis that clinical pregnancy is more likely in women with a high serum 25(OH)D concentration.

For Gaskins and Chavarro (2018), despite promising results in animal models, vitamin D does not appear to play an important role in human fertility, contradicting Chu et al. (2018), who concluded by meta-analysis that clinical pregnancy is more likely in women with high serum 25(OH)D concentrations.

POLYCYSTIC OVARY SYNDROME (PCOS)

There are a limited number of studies indicating the use of vitamin D supplementation to heal symptoms of PCOS such as menstrual cycle, follicular development, androgen levels and insulin resistance (Arslan and Akdevelioğlu, 2018). Vitamin D is believed to influence the development of PCOS through gene transcription, and this hormonal modulation influences insulin metabolism and fertility regulation (Thomson et al., 2012). However, Chen and colleagues (2018) found no correlation between vitamin D and PCOS, but they found a correlation between 25(OH) D levels and infertility due to tubal problems in Chinese women.

Bakeer et al. (2018) showed that serum 25(OH)D levels were significantly lower in the PCOS group compared to controls, corroborating previous studies (Hahn et al., 2006). In this study, the authors did not observe statistical correlation between antimullerian hormones (HAM) and 25(OH)

D levels, a result that was consistent with previous literature data (Cappy et al., 2016), despite the indication that HAM can be used as a PCOS biomarker. Other data show that vitamin D supplementation for eight weeks in patients with PCOS, candidates for IVF, was efficient under insulin and cholesterol metabolism (Dastorani et al., 2018), in addition to decreasing the levels of HAM.

In a 2019 cohort study, Butts et al. show that the association between vitamin D and ovarian stimulation treatment differ according to the patient's diagnosis of infertility. Data show that vitamin D deficiency in women with PCOS who underwent ovarian stimulation was significantly associated with low ovulation levels, low pregnancy rate, and a reduced chance of live birth. In contrast, the rate of live births in women with unexplained infertility who had ovarian stimulation did not decrease in association with vitamin D deficiency, which supports the hypothesis that vitamin D deficiency negatively affects specific pathways of PCOS.

Arefi et al. (2018) presented results that clearly demonstrate the correlation ($p < 0.001$) between vitamin D deficiency and a reduced ovarian reserve in the Iranian female population, while Shapiro et al. (2018) found no relationship between vitamin D levels and ovarian reserve markers in a female population in the United States. Among the reasons that may explain these inconsistencies in the data would be the experimental design, the sample size, which seems to play an important role in this type of analysis, and the population to be studied.

Several genetic polymorphisms have already been correlated with PCOS. The VDR gene has more than 25 described polymorphisms, with alterations associated with several diseases, but still inconsistent with PCOS. The association of three polymorphisms with PCOS, namely *BsmI*, *ApaI* and *TaqI*, confirming in the South Indian population data already found in other populations (Siddamalla et al., 2018). Reginatto et al. (2018) identified an association between VDR *TaqI* gene polymorphism and the reduced number of follicles in infertile women undergoing ovarian stimulation, suggesting that VDR signaling affects the ovarian response to stimulation via unknown mechanisms.

ENDOMETRIOSIS

Endometriosis is a benign estrogen-related inflammation characterized by the presence of endometrial tissue outside the cavity. It affects 5 to 10% of women in reproductive age (Voulgaris et al., 2017).

Buggio et al. (2019) found no differences in serum 25(OH)D levels in women with and without endometriosis, corroborating previous literature data (Agic et al., 2007), but also going against previous data (Somigliana et al., 2007).

Other studies have identified that women with endometriosis have more VDR receptors than control group (Arslan and Akdevelioğlu, 2018). In addition, immunomodulatory, antiinflammatory and antiproliferative properties of vitamin D indicate a possible role of this hormone in the pathogenesis of endometriosis (Buggio et al., 2019).

IN VITRO FERTILIZATION (IVF)

It is consistent in the literature that in cases of IVF, women with vitamin D deficiency have decreased their chance of conception compared with women where vitamin D levels are normal (Butts et al., 2019).

Ciepiela et al. (2018) observed that successfully fertilized oocytes contained significantly lower levels of 25(OH)D compared to those not fertilized; clinical pregnancy and live birth rate were obtained from oocyte-derived embryos with

significantly lower levels of 25(OH)D, but women's low serum vitamin D concentrations increase the abortion rate, as observed by Rafique et al. (2018). The reviews by Zhao et al. (2018) and Turan (2018) reinforce these data, where they point out that vitamin D deficiency has a negative effect on pregnancy after IVF, but because sample sizes and characteristics were different, cohort studies are necessary to observe the effect of vitamin D supplementation and to explore possible mechanisms.

Antunes et al. (2018) investigated whether 25(OH)D intrafollicular concentrations are related to the type of ovarian response in patients undergoing IVF, investigating the relationship between follicular fluid vitamin D concentrations and ovarian stimulation outcomes. They observed that follicular 25(OH)D concentrations remain unchanged through different common causes of infertility; Women with follicular fluid concentrations below vitamin D had a better response to ovarian stimulation, as demonstrated by higher production of larger follicles and higher serum estradiol concentration.

Yilmaz et al. (2018) found no relationship between lack of vitamin D and infertility. They did not find significant differences between pregnant and non-pregnant women who underwent ovulation induction with intrauterine insemination treatment in relation to serum 25(OH)D levels. In addition, no association was found between infertility and serum 25(OH)D levels. In this study conducted in Turkey, the authors highlight the fact that vitamin D deficiency is a public health problem in the country, with 200 of 207 patients, who also included women without fertility problems, who had vitamin D deficiency on initial examination. Similar results were found by Arabian and Raoofi (2018) in a cohort of 153 Iranian infertile women, where the authors indicate that vitamin D deficiency is not the main limitation for fertility.

DISCUSSION

Several functions of vitamin D have been studied in recent years, associating its deficiency with comorbidities. Despite the growing number of investigations about the physiological role of vitamin D in various stages of reproductive function, the results are still scarce and controversial. It is well known that this deficiency can negatively affect female fertility by disrupting ovarian physiology and deregulating follicular recruitment and selection (Heyden and Wimalawansa, 2018).

Results presented in the literature showed that 20 to 52% of women of reproductive age are vitamin D deficient (CHU et al., 2018). In a study of the Brazilian population, regardless of women's ethnicity, Lopes et al. (2017) reported a high proportion (81.1%) of Brazilian women with hypovitaminosis D, but found no difference between the control group and infertile women.

The association between vitamin D and PCOS manifestations is not well established. Although some studies have shown an inverse relationship between vitamin D and androgens, most studies have not confirmed a direct relationship between vitamin D and reproductive parameters (Nandi, 2018).

Systematic reviews and meta-analyzes (Vanni et al., 2014; Voulgaris et al., 2017) suggest the association of vitamin D with several metabolic and reproductive processes characteristic of PCOS and, therefore, vitamin D would be involved in the pathogenesis of the syndrome. Women with polycystic ovary syndrome have lower 25(OH)D levels compared to healthy women (Voulgaris et al., 2017); among the population of polycystic ovary syndrome, obese women had lower levels of 25(OH)D when compared to

overweight or thin women (Panidis et al., 2005; Ngo et al., 2011; Voulgaris et al., 2017). However, obesity leads to insulin resistance in these patients, but not necessarily to PCOS (Sur and Chakravorty, 2015).

Arslan and Akdevelioğlu (2018) point out that the results on the subject are conflicting because, while some suggest that vitamin D deficiency is more common among women with PCOS compared to healthy individuals, others find no differences between those with or without SOP. In addition, the limited number of intervention studies involving women with PCOS was not randomized and were conducted in a small cohort of patients, which makes it difficult to generalize the results.

There are studies examining the contribution of vitamin D receptor gene polymorphisms in metabolic and endocrine disorders of polycystic ovary syndrome (Mahmoudi, 2009; Mahmoudi et al., 2015; Jedrzejuk et al., 2015; Dasgupta et al., 2015; Nandi, 2018). *TaqI* polymorphism of the VDR gene, for example, is associated with increased risk of PCOS (El-Shal et al., 2013).

Data linking vitamin D and endometriosis emerge mainly from observational studies, but the results are still conflicting. Voulgaris et al. (2017) reviewed several studies and pointed out that there is no difference between serum 25(OH)D levels in endometriosis patients and healthy women. However, data from Harris et al. (2013) indicate an inverse relationship between vitamin D level and endometriosis, women with higher 25(OH) D levels had a 24% lower risk of developing endometriosis than women with lower levels. Somigliana et al. (2007) observed that endometriosis may be associated with higher serum vitamin D levels, but did not conclude whether such a high concentration of 25(OH) D would be the cause or consequence of the disease.

Correcting vitamin D deficiency in women with PCOS significantly improves the growth of ovarian follicles, the formation of dominant follicles and the regularity of menstrual cycles (Fang *et al*., 2017), which makes the recent evidence that the vitamin D may have a direct effect on folliculogenesis and oocyte maturation (Xu *et al.*, 2016). The results of Antunes et al. (2018) are in line with data already described in the literature, as in part those observed by Ozkan et al. (2010), who observed in their cohort that women with higher levels of vitamin D in serum and fluid follicular are more likely to develop a pregnancy after IVF; pregnancy rates after IVF are higher in women who have elevated 25(OH)D levels than in those who are vitamin D deficient.

In a meta-analysis study, Lv et al. (2016) concluded that a lower serum vitamin D level is not associated with a lower clinical pregnancy rate, but is related to a lower live birth rate. In a study in India, Banker et al. (2017) found no statistical difference in reproductive outcomes in the oocyte recipient and oocyte donor groups, although the study suggests that recipients and donors with an insufficient level of vitamin D have a better reproductive outcome compared to the group with vitamin D deficiency.

In a systematic review, Skowrońska et al. (2016) conclude that concentrations of several forms of vitamin D may be associated with endometriosis, but their possible dependence on environmental factors, such as time of year and skin type, should also be taken into account.

CONCLUSION

Due to the heterogeneity of the findings, there are few conclusions drawn from the results of the relationship between vitamin D and female fertility. Studies in the literature indicate that there is a correlation between

hypovitaminosis D and reproductive problems, but the true role of vitamin D in the reproductive system has not yet been determined (Franasiak et al., 2017).

It is not known whether the effects of vitamin D are direct on genes generated in reproduction or whether vitamin D acts through secondary messengers, such as calcium, estradiol signaling, insulin pathway or immune modulation (Nandi, 2018; Gaskins and Chavarro, 2018). While vitamin D deficiency may possibly be detrimental to fertility, it is unclear whether higher vitamin D levels confer additional benefit once sufficiency has been achieved. Being a very new topic of scientific focus, data linking vitamin D with female infertility still contradict each other. Therefore, it is important to constantly review the literature so that it is possible to identify the results that are really relevant and clarify the causes of such contradiction.

REFERENCES

AGHAJAFARI, F. *et al*. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. **BMJ**, v. 26, p. 346-f1169, 2013.

AGIC, A. *et al*. Relative expression of 1,25-dihydroxyvitamin D3 receptor, vitamin D 1 alpha-hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers. **Reprod Sci**, v. 14, n. 5, p. 486-497, 2007.

ALEYASIN, A. *et al*. Predictive value of the level of vitamin D in follicular fluid on the outcome of assisted reproductive technology. **Eur J Obstet Gynecol Reprod Biol**, v. 159, n. 1, p. 132–137, 2011.

ANTUNES, R.A. *et al*. Lower follicular fluid vitamin D concentration is related to a higher number of large ovarian follicles. **Reprod Biomed Online**, v. 36, n. 3, p. 277-284, 2018.

ARABIAN, S.; RAOOFI, Z. Effect of serum vitamin D level on endometrial thickness and parameters of follicle growth in infertile women undergoing induction of ovulation. **J Obstet Gynaecol**, v. 38, n. 6, p. 833-835, 2018.

AREFI, S. *et al*. Is the ovarian reserve influenced by vitamin D deficiency and the dress code in an infertile Iranian population? **J Ovarian Res**, v. 11, n. 1, p. 62, 2018.

ARSLAN, S.; AKDEVELIOĞLU, Y. The relationship between female reproductive functions and vitamin D. **J Am Coll Nutr**, v. 37, n. 6, p. 546-551, 2018.

AVILA, E. *et al*. Regulation of 25-hydroxyvitamin D3 1alpha-hydroxylase, 1,25-dihydroxyvitamin D3 24-hydroxylase and vitamin D receptor gene expression by 8-bromo cyclic AMP in cultured human syncytiotrophoblast cells. **J Steroid Biochem Mol Biol**, v. 89-90,n. 1-5, p. 115-119, 2004.

BAKEER, E. *et al*. Anti-Müllerian hormone as a diagnostic marker in egyptian infertile polycystic ovary syndrome females: correlations with vitamin D, total testosterone, dyslipidemia and anthropometric parameters. **J Med Biochem**, v. 37, n. 4, p. 448-455, 2018.

BANKER, M. *et al*. Vitamin D deficiency does not influence reproductive outcomes of IVF-ICSI: a study of oocyte donors and recipients. **J Hum Reprod Sci**, v. 10, n. 2, p. 79-85, 2017.

BARRETT, H.; MCELDUFF, A. Vitamin D and pregnancy: an old problem revisited. **Best Pract Res Clin Endocrinol Metab**, v. 24, n. 4, p. 527-539, 2010.

BUGGIO, L. *et al*. 25-hydroxyvitamin D serum levels and endometriosis results of case-control study. **Reprod Sci**, v. 26, n. 2, p. 172-177, 2019.

BURRIS, H. H. *et al*. Vitamin D deficiency in pregnancy and gestational diabetes mellitus. **Am J Obstet Gynecol**, v. 207, n. 3, p. 182 e1–182 e8, 2012.

BUTTS, S.F. *et al*. Vitamin D deficiency is associated with poor ovarian stimulation outcome in PCOS but not unexplained infertility. **J Clin Endocrinol Metab**, v. 104, n. 2, p. 369-378, 2019.

CAPPY, H. *et al*. Low vitamin D3 and high anti-Müllerian hormone serum levels in the polycystic ovary syndrome (PCOS): is there a link? **Ann Endocrinol (Paris)**, v. 77, n. 5, p. 593–5999, 2016.

CHAN, S.Y. *et al*. Vitamin D promotes human extravillous trophoblast invasion in vitro. **Placenta**, v. 36, n. 4, p. 403-409, 2015.

CHEN, W. *et al*. Vitamin D deficiency and high serum IL-6 concentration as risk factors for tubal factor infertility in Chinese women. **Nutrition**, v. 49, p. 24-31, 2018.

CHIU, Y.H. *et al*. Diet and female fertility: doctor, what should I eat? **Fertil Steril**, v. 110, n. 4, p. 560-569, 2018.

CHU, J. *et al*. Vitamin D and assisted reproductive treatment outcome: a systematic review and meta-analysis. **Hum Reprod**, v. 33, n. 1, p. 65-80, 2018.

CIEPIELA, P. *et al*. Vitamin D as a follicular marker of human oocyte quality and a serum marker of *in vitro* fertilization outcome. **J Assist Reprod Genet**, v. 35, n. 7, p. 1265-1276, 2018.

DASGUPTA, S. *et al*. Association of vitamin D receptor gene polymorphisms with polycystic ovary syndrome among Indian women. **Indian J Med Res**, v. 142, n. 3, p. 276-285, 2015.

DASTORANI, M. *et al*. The effects of vitamin D supplementation on metabolic profiles and gene expression of insulin and lipid metabolism in infertile polycystic ovary syndrome candidates for in vitro fertilization. **Reprod Biol Endocrinol**, v. 16, n. 1, p. 94, 2018.

EL-SHAL, A.S. *et al*. Genetic variation in the vitamin D receptor gene and vitamin D serum levels in Egyptian women with polycystic ovary syndrome. **Mol Biol Rep**, v. 40, n. 11, p. 6063–6073, 2013.

FANG, F. *et al*. Effect of vitamin D supplementation on polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. **Complement Ther Clin Pract**, v. 26, p. 53–60, 2017.

FRANASIAK, J.M. *et al*. Vitamin D in human reproduction. **Curr Opin Obstet Gynecol**, v. 29, n. 4, p. 189-194, 2017.

GASKINS, A.J.; CHAVARRO, J.E. Diet and fertility: a review. **Am J Obstet Gynecol**, v. 218, n. 4, p. 379-389, 2018.

GRÖBER, U. *et al*. Vitamin D update 2013: from rickets prophylaxis to general preventive healthcare. **Dermatoendocrinol**, v. 5, n. 3, p. 331–347, 2013.

HAHN, S. *et al*. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. **Exp Clin Endocrinol Diabetes**, v. 114, n. 10, p. 577–583, 2006.

HARRIS, H.R. *et al*. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. **Am J Epidemiol**, v. 177, n. 5, p. 420-430, 2013.

HAUSSLER, M.R. *et al*. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)$_2$vitamin D$_3$: genomic and non-genomic mechanisms. **Best Pract Res Clin Endocrinol Metab**, v. 25, n. 4, p. 543-559, 2011.

HEYDEN, E.L.; WIMALAWANSA, S.J. Vitamin D: effects on human reproduction, pregnancy, and fetal well-being. **J Steroid Biochem Mol Biol**, v. 180, p. 41-50, 2018.

HOLICK, M.F.; CHEN, T.C. Vitamin D deficiency: a worldwide problem with health consequences. **Am J Clin Nutr**, v. 87, n. 4, p. 1080s-1086s, 2008.

HOLICK, M. F. *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. **J Clin Endocrinol Metab**, v. 96, n. 7, p. 1911–1930, 2011.

HOLICK, M.F. The vitamin D deficiency pandemic and consequences for nonskeletal health: mechanisms of action. **Mol Aspects Med**, v. 29, n. 6, p. 361-368, 2008.

HOLICK, M. F. Vitamin D deficiency. **N Engl J Med**, v. 357, n. 3, p. 266–281, 2007.

JAFARI-SFIDVAJANI, S. *et al*. The effect of vitamin D supplementation in combination with low-calorie diet on anthropometric indices and androgen hormones in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. **J Endocrinol Invest**, v. 41, n. 5, p. 597-607, 2018.

JOHNSON, L.E.; DELUCA, H.F. Vitamin D receptor null mutant mice fed high levels of calcium are fertile. **J Nutr**, v. 131, n. 6, p. 1787-1791, 2001.

LERCHBAUM, E; RABE, T. Vitamin D and female fertility. **Curr Opin Obstet Gynecol**, v. 26, n. 3, p. 145-150, 2014.

LOPES, V.M. *et al*. Highly prevalence of vitamin D deficiency among Brazilian women of reproductive age. **Arch Endocrinol Metab**, v. 61, n. 1, p. 21-27, 2017.

LV, S.S. *et al*. Serum vitamin D status and *in vitro* fertilization outcomes: a systematic review and meta-analysis. **Arch Gynecol Obstet**, v. 293, n. 6, p. 1339-1345, 2016.

MAHMOUDI, T. *et al*. Association of vitamin D receptor gene variants with polycystic ovary syndrome: a case control study. **Int J Reprod Biomed (Yazd)**, v. 13, n. 12, p. 793-800, 2015.

MAHMOUDI, T. Genetic variation in the vitamin D receptor and polycystic ovary syndrome risk. **Fertil Steril**, v. 92, n. 4, p. 1381-1383, 2009.

MOGILI, K.D. *et al*. Prevalence of vitamin D deficiency in infertile women with polycystic ovarian syndrome and its association with metabolic syndrome - a prospective observational study. **Eur J Obstet Gynecol Reprod Biol**, v. 229, p. 15-19, 2018.

MUSCOGIURI, G. *et al*. Shedding new light on female fertility: the role of vitamin D. **Rev Endocr Metab Disord**, v. 18, n. 3, p. 273-283, 2017.

NANDI, A. Vitamin D in male and female reproduction. In: Liao E. (eds) Extraskeletal effects of vitamin D. **Contemporary Endocrinology**. Humana Press, Cham, 2018.

NGO, D.T. *et al*. Determinants of insulin responsiveness in young women: Impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. **Nitric oxide**, v. 25, n. 3, p. 326-330, 2011.

OZKAN, S. *et al*. Replete vitamin D stores predict reproductive success following in vitro fertilization. **Fertil Steril**, v. 94, n. 4, p. 1314–1319, 2010.

PARIKH, G. *et al*. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. **Horm Metab Res**, v. 42, n. 10, p. 754-757, 2010.

PANIDIS, D. *et al*. Serum parathyroid hormone concentrations are increased in women with polycystic ovary syndrome. **Clin Chem**, v. 51, n. 9, p. 1691-1697, 2005.

RAFIQUE, M. *et al*. Role of vitamin D deficiency in female infertility and ART outcomes. **J Soc Obstet Gynaecol Pak**, v. 8, n. 1, p. 29-35, 2018.

REGINATTO, M.W. *et al*. Vitamin D receptor *Taq* polymorphism is associated with reduced follicle number in women utilizing assisted reproductive technologies. **Front Endocrinol (Lausanne)**, v. 9, p. 252, 2018.

RUDICK, B.J. *et al*. The role of vitamin D levels on IVF outcomes in donor-recipient cycles. **Fertil Steril**, v. 101, n. 2, p. 447-52, 2014.

SHAPIRO, A.J. *et al*. Vitamin D levels are not associated with ovarian reserve in a group of infertile women with a high prevalance of diminished ovarian reserve. **Fertil Steril**, v. 110, n. 4, p. 761-766, 2018.

SIDDAMALLA, S. *et al*. Vitamin D receptor gene polymorphisms and risk of polycystic ovary syndrome in South Indian women. **Gynecol Endocrinol**, v. 34, n. 2, p. 161-165, 2018.

SKOWROŃSKA, P. *et al*. The role of vitamin D in reproductive dysfunction in women – a systematic review. **Ann Agric Environ Med**, v. 23, n. 4, p. 671-676, 2016.

SOHN, J.O. *et al*. Does vitamin D deficiency affect the IVF-ET outcomes in infertile Korean women? **RBM online**, Abstracts – alpha poster, 2018.

SOMIGLIANA, E. *et al*. Vitamin D reserve is higher in women with endometriosis. **Hum Reprod**, v. 22, n. 8, p. 2273–2278, 2007.

SUR, D.; CHAKRAVORTY, R. The relationship between vitamin D, insulin resistance and infertility in PCOS women. **Gynecol Obstet (Sunnyvale)**, v.5, p. 5, 2015.

THOMSON, R.L *et al*. Vitamin D in the aetiology and management of polycystic ovary syndrome. **Clin Endocrinol (Oxf)**, v.77, n. 3, p. 343-350, 2012.

VANNI, V. S. *et al*. Vitamin D and assisted reproduction technologies: current concepts. **Reprod Biol Endocrinol**, v. 31, p. 12-47, 2014.

VOULGARIS, N. *et al*. Vitamin D and aspects of female fertility. **Hormones (Athens)**, v. 16, n. 1, p. 5-21, 2017.

WEINERT, L.S.; SILVEIRO, S.P. Maternal-fetal impact of vitamin D deficiency: a critical review. **Matern Child Health** J, v. 19, n. 1, p. 94-101, 2015.

XU, J. *et al*. Direct vitamin D3 actions on rhesus macaque follicles in three-dimensional culture: assessment of follicle survival, growth, steroid, and antimüllerian hormone production. **Fertil Steril**, v. 106, n. 7, p. 1815-1820, 2016.

YILMAZ, N. *et al*. Do serum vitamin D levels have any effect on intrauterine insemination success? **Int J Fertil Steril**, v. 12, n. 2, p. 164-168, 2018.

ZHAO, J. *et al*. Whether vitamin D was associated with clinical outcome after IVF/ICSI: a systematic review and meta-analysis. **Reprod Biol Endocrinol**, v. 16, n. 1, p. 13, 2018.

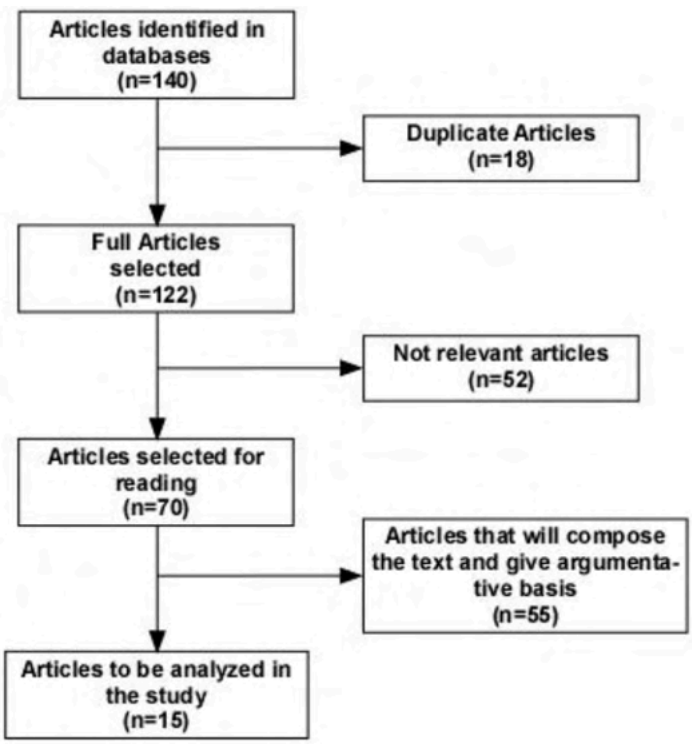

Figure 1: PRISMA flow diagram for selecting articles.

Study	Time and type	Females	Intervention	Analysis	Results	Country and Financing fund
Antunes et al., 2018	Type: prospective study; Time: September 2013 to September 2015.	202 patients, with 2 excluded.	Women undergoing ovarian stimulation for IVF.	Follicular fluid 25(OH)D concentrations were assessed in the first follicle aspirate on oocyte retrieval day; oestradiol and progesterone concentrations were assessed on the trigger day.	Lower follicular 25(OH)D concentrations predicted a better response to ovarian stimulation shown by a greater production of larger follicles and higher serum oestradiol concentrations.	Country: Brazil; Fund: FAPERJ, CNPq, CAPES.
Arabian; Raoofi, 2018	Type: cross-sectional study; Time: from 2014 to 2016.	153 infertile women undergoing induction of ovulation.	Induction of ovulation.	Serum vitamin D level was measured and the rate of clinical pregnancy and patient and cycle parameters were determined.	There was no correlation between the serum level of vitamin D and pregnancy rate.	Country: Iran; Fund: Uninformed.
Bakeer et al., 2018	Type: cross-sectional study; Time: uninformed.	53 PCOS females aged from 17 to 39; 17 control group females, aged from 19 to 35.	Without intervation.	Serum AMH and 25(OH)D were measured.	AMH were significantly higher in PCOS females in comparison to control group.	Country: Egypt; Fund: Uninformed.
Buggio et al., 2019	Type: case–control study; Time: October 2014 to January 2017.	217 endometriosis women.	Without intervation.	25(OH)D serum levels in women with and without endometriosis.	The results do not support an association between serum vitamin D levels and different phenotypes of endometriosis.	Country: Italy; Fund: Italian fiscal contribution 2012.
Butts et al., 2019	Type: retrospective cohort study; Time: uninformed.	607 participants from the Pregnancy in Polycystic Ovary Syndrome II RCT; 647 participants from the Assessment of Multiple Intrauterine Gestations from Ovarian Stimulation RCT of unexplained infertility.	Serum 25(OH)D levels measured.	Primary: live birth; secondary: ovulation (PPCOS II), pregnancy, and early pregnancy loss.	The association between vitamin D deficiency and diminished live birth relied on carrying the diagnosis of PCOS and was not observed in unexplained infertility.	Country: USA; Fund: National Institutes of Health.

Chen et al., 2018	Type: case–control; Time: from 2013 to 2015.	377 women who were diagnosed with infertility.	Without intervation.	Serum concentrations of 25(OH)D, IL-6, IL-1 β, and interferon-α were measured.	There was an interaction between IL-6 and 25(OH)D for the risk for tubal factor infertility.	Country: China; Fund: Uninformed.
Ciepiela et al., 2018	Type: perspective cohort study; Time: February 2014 to October 2015.	198 infertile women.	Intracytoplasmic sperm injection and a single embryo transfer provided serum samples and follicular fluid specimens.	Serum sample from infertile women scheduled for intracytoplasmic sperm injection and a single embryo transfer and 322 follicular fluid specimens, each from a single follicle on the day of oocyte retrieval.	The level of 25(OH)D in follicular fluid correlates negatively with the oocytes' ability to undergo fertilization and subsequent preimplantation embryo development. Oocytes matured in follicular fluid with low 25(OH)D concentration are more likely to produce top quality embryos and are associated with higher pregnancy and delivery rates. Low serum vitamin D concentration is associated with higher miscarriage rates.	Country: Poland; Fund: National Science Centre of Poland.
Dastorani et al., 2018	Type: randomized, double-blinded, placebo-controlled trial; Time: from December 2017 through March 2018.	40 infertile women, aged 18 to 40 years old, with PCOS, who were candidate for *in vitro* fertilization.	2 intervention groups for receiving either 50,000 IU vitamin D or placebo (n = 20 each group) every other week for 8 weeks.	Gene expression for insulin and lipid metabolism was conducted using peripheral blood mononuclear cells (PBMCs) of women with PCOS, via RT-PCR method.	50,000 IU vitamin D supplementation every other week for 8 weeks had beneficial effects on insulin metabolism, and lipid profile of infertile women with PCOS who are candidate for IVF.	Country: Iran; Fund: Vice-chancellor for Research, Kashan University of Medical Sciences, Kashan, Iran.

Jafari-Sfidvajani et al., 2018	Type: randomized controlled clinical trial; Time: March 2016 to February 2017.	60 PCOS women with vitamin D insufficiency.	Participants randomly recruited to a 12-week intervention arm consisting of 50,000 IU/week of vitamin D3 pearl + low-calorie diet (n = 30) or to a control arm of a weekly placebo pearl + low-calorie diet (n = 30).	At the beginning and end of the study, the anthropometric indices, body composition, 25-hydroxyvitamin D, total testosterone, dehydroepiandrosterone sulfate, sex hormone-binding globulin and free androgen index were measured and regularity of menses was compared among the two groups.	In women with PCOS, androgen profile did not change with vitamin D supplementation when combined with low-calorie diet, but menstrual frequency significantly improved.	Country: Iran; Fund: Faculty of Health, ShahidSadoughi University of Medical Sciences, Yazd, Iran.
Mogili et al., 2018	Type: observational study; Time: from March 2016 to March 2017.	256 infertile women with PCOS, in the age group of 20–40 years.	Without intervation.	The primary outcome was estimation of the prevalence of vitamin D deficiency in infertile PCOS women. Secondary outcomes were to study the association of hypovitaminosis D with metabolic syndrome, obesity and hypercholesterolemia in PCOS patients.	Vitamin D deficiency is highly prevalent in infertile PCOS women and there seems to be no association between hypovitaminosis D and the metabolic syndrome in the same population.	Country: India; Fund: No funding.
Rafique et al., 2018	Type: retrospective cohort study; Time: January 2012 to January 2016	192 infertile women.	Analysis of the outcome after the intervention done in the form of different assisted reproduction treatment options.	Association between vitamin D deficient (less than 50nmol/l) and insufficient group (50-75nmol/l) through the application of chi-square test for evaluate to see the 25(OH)D and major outcome measure (successful pregnancy).	Vitamin D deficiency, as well as insufficiency, adversely affect the outcome of assisted reproduction treatment contributing to lower pregnancy rates among Arabian women in the reproductive age group.	Country: Saudi Arabia; Fund: Research center at KFMC.

Reginatto et al., 2018	Type: case–control study; Time: uninformed.	121 control group; 70 women undergoing controlled ovarian stimulation.	Controlled ovarian stimulation.	Evaluate the association between the *TaqI*, *BsmI*, and *FokI VDR* polymorphisms and ovarian responses in women undergoing controlled ovarian stimulation.	Association between the *VDR TaqI* polymorphism and reduced follicle number in women undergoing controlled ovarian stimulation.	Country: Brazil; Fund: FAPERJ, CNPq, CAPES.
Shapiro et al., 2018	Type: retrospective cohort study; Time: September of 2014 to November of 2017.	457 infertile women 21–50 years of age.	Controlled ovarian stimulation	Hormone measurements.	Vitamin D levels were not associated with ovarian reserve in a large group of infertile women with a high prevalence of diminished ovarian reserve.	Country: USA; Fund: Uninformed.
Sohn et al., 2018	Type: cross-sectional study; Time: uninformed.	233 infertile women without any supplementation of vitamin D.	Serum samples were obtained on oocytes retrieval day and tested vitamin D level and divided women into two groups according to their vitamin D levels.	The group analyzed their relation with antimullerian hormones, number of total oocytes, mature oocytes, pregnancies, as well as implantations.	Infertile Korean women who were not vitamin D insufficient/replete did not have a decreased ovarian reserve; antimullerian hormones levels did not present any significance; vitamin D deficiency have no effect on in vitro fertilization.	Country: South Korea; Fund: Uninformed.
Yilmaz et al., 2018	Type: cross-sectional study; Time: March 2014 to June 2014.	104 infertile women; 103 fertile women.	Clinical assessment; infertile patients were evaluated for clomiphene citrate or gonadotropins and intrauterine insemination use.	Individual characteristics and 25(OH)D levels were compared between the groups.	There is no association between female infertility and serum vitamin D levels.	Country: Turkey; Fund: Uninformed.

Table 1: Characteristics of articles included in the Systematic Review.