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Participation of vitamin D endocrine system in human fertility.

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ABSTRACT

Interest is growing in the knowledge of the mechanisms of action of vitamin D in very different areas of pathology. In recent years, very different actions of vitamin D have been discovered. Far from being a simple vitamin, it is a hormonal complex that acts in very different parts of the body equipped with hormonal receptors for vitamin D. It controls more than 900 different genes making it. It represents up to 3% of the total human genome. There is a deficit in levels of 25 (OH)D in populations around the world, including young couples affected by fertility problems. In the field of infertility, it has shown beneficial actions on the evolution of polycystic ovary syndrome. It is capable of decreasing the growth of uterine fibroids and correlates well with anti-Mullerian hormone. It has also been shown to improve oocyte quality and the embryo implantation rate in assisted reproduction: Its adequate levels in pregnancy reduce the risk of gestational diabetes and improve perinatal outcomes: The objective of this manuscript is to review the most important aspects that relate to the endocrine system. of vitamin D with fertility and pregnancy.

KEYWORDS: Vitamin D. Fertility. Infertility. Cholecalciferol. Calcifediol.

INTRODUCTION

In recent times, we have been witnessing a true bibliographic boom of publications on vitamin D (VD) that exceeded 100,000 indexed according to new data[1]. Since 2021 alone, 447 meta-analyses have been published on various topics in relation to VD. Differentiating the two basic drug forms of VD endocrine system (VDES), cholecalciferol and calcifediol, since 1945 the investigations and the data do not stop growing as shown in **Table 1**.

Product								
	1945-2020	2010.20	2020-23	10 years	5 years	1 year	5 years	1 year
Cholecalciferol	27.378	7.559	2.688	1.351	685	55	74	22
Calcifediol	4.040	1.641	694	226	104	18	29	13

Table 1. Constant increase in the number of VDES publications, differentiating cholecalciferol and calcifediol, barely marketed since 1943* (own elaboration from citation[1]).

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The presence of VD receptor (VDR) in many different tissues related to fertility (breast, epididymis, hair follicle, embryonic muscle, ovary, placenta, prostate, testis, uterus, yolk sac..., among others)[23] justifies that researchers have devoted special interest to the relationships between VDES and the different disorders that cause infertility. It seems evident today that VDES has different actions in different age groups, and in young women and men it can have influence on fertility and reproductive performance[4].

It is amply justified to affirm that it really is a hormone[2,5], considering the classical criteria of the hormone concept and its mechanisms of action[3] with an extraordinarily complex secretion and metabolism that involves the skin, the liver and the kidney until obtaining the metabolically active product[4], so we will no longer insist on its name as VDES.

The objective of this manuscript is to review the relationship between different levels of 1,25(OH)2D as the best determinant of its actions[6] and the main causes that negatively influence the fertility; In the same way and secondarily, we will briefly review whether there is justification for certain therapeutic regimens of Vitamin D in the different fertility diagnoses and in pregnancies, based on the results of gestational complications and perinatal results.

INFLUENCE OF VDES ON FERTILITY

1.- Hypovitaminosis D in infertility patients.

The specialized literature generally agrees that 25(OH)D levels are low in different regions of the world[7], and this would even include healthy young people from subtropical regions of southern Europe (presumably aware of the importance of maintaining these levels due to their condition as medical students), as demonstrated in a study carried out in the Canary Islands[8]. It is therefore not strange to think of the possibility that the same finding could be observed among patients with fertility problems in relation to 25(OH)D levels.

A high rate of hypovitaminosis D has been observed in women of childbearing age. The current results of a well-designed study show that circulating 25(OH)D levels fluctuate seasonally in a cohort of women who seek medical help for partner fertility despite residing in the northern part of Italy, in a sunny region like southern Europe. Similarly, vitamin D (25(OH)D) status is associated with specific causes of infertility and the physical characteristics of everyone. The authors of the study that showed these findings conclude that the use of supplementation continues to be a problem in this population and reproductive physicians should consider this aspect in their clinical practice[9].

2.- VDES and polycystic ovary syndrome (PCOS).

It is known that about 67 to 85% of women diagnosed with PCOS are deficient in 25(OH)D or calcifediol[10]. It is also known that VDES is involved in the pathogenic mechanisms of metabolic imbalances, the true pathophysiological motor of PCOS[11].

It has been argued that the metabolic syndrome that accompanies PCOS is at the crossroads of the metabolic disturbance that leads to anovulation; this being the case, maintaining adequate levels of 25(OH)D would be the basis for improving results with this type of patient. A meta-analysis has recently been published that reviews whether vitamin D supplementation in this group of patients would be justified[12]. Well, the authors evaluated a total of 11 studies (among the more than 446 previously selected) that were methodologically well designed for the stated objective. They conclude that the evidence from the randomized clinical trials (RCTs) reviewed suggests that supplementation of PCOS patients with continuous low doses of vitamin D (<4000 IU/day) or supplementation with vitamin D as a co-supplement may improve sensitivity to insulin in terms of fasting glucose concentration (vitamin D supplementation in combination with other micronutrients) and significantly improve the HOMA-IR index (Homeostasis Model Assessment and Insulin resistance) or homeostatic model to assess insulin resistance[12], a one of the most clinically proven tools to assess insulin resistance and pancreatic beta cell function, a true workhorse of the future for women affected by PCOS[13].

3.- Relations between VDES and uterine myomatosis (UM).

It is difficult to define an association between infertility and UM due to the heterogeneity of fibroids in terms of location, size, and number, as well as the different prevalence rates observed among different patient populations[14]. Notwithstanding this, VDES suppresses cell proliferation and cell growth, causing a reduction in MU[15]; furthermore, it acts as a suppressor of transforming growth factor-beta (TGF-β), which is involved in the development and progression of MU16. In fact, sufficient serum 25(OH)D levels were associated with a 32% reduced risk of UM compared with those with insufficient 25(OH)D [OR = 0.68, CI (0.48–0. 96)], regardless of the ethnicity studied[17,18].

From a therapeutic point of view, vitamin D supplementation after 12 months restored serum 25(OH)D levels in women with hypovitaminosis D and reduced MU growth, suggesting that it is an effective therapeutic strategy to prevent vitamin D deficiency. surgical intervention in small fibroids (<5 cm in diameter)[19]. Even with only 10 weeks of vitamin D

supplementation (50,000 IU), serum 25(OH)D levels were significantly higher in patients with 25(OH)D deficiency (36.08 ng/mL vs 16.25 ng/ml) p < 0.001) and the MUs decreased significantly in size[20].

The scientific evidence is not entirely conclusive. No statistically significant decrease in fibroid volume was observed in the experimental group [mean difference (MD): -0.71, 95% confidence interval (CI): -0.1 to 1.53, p = 0.085], in a recent RCT, but its additional growth was prevented[21]. To overcome the major limitations of previously published studies, which included only a small number of subjects, an ongoing open-label RCT involving more than 2,000 Chinese individuals is currently evaluating the efficacy of vitamin D supplementation in reducing the incidence of UM in women of reproductive age[22]; no results have been reported to date[23].

Despite the lack of a clear consensus, the treatment with calcifediol or cholecalciferol could be a potentially economical treatment for the prevention of further growth of UM and the treatment of uterine fibroids[24,25].

4.- Status of anti-Mullerian hormone (AMH) and calcifediol.

AMH is a member of the transforming growth factor beta (TGF-β) superfamily. It is a homodimer disulfide-linked glycoprotein with a molecular weight of 140 kDa, whose gene is located on the short arm of chromosome 19 in humans, band 19p 13.3[26]. A significant advantage of serum AMH is its low intracycle and intercycle variability, since it is produced from small antral follicles, which are independent of gonadotropins. Its strong correlation with the number of follicles and its high negative predictive value for premature ovarian failure (POI) make it an attractive tool in the study of infertility. It also helps in the individualization of assisted reproductive techniques (ART) protocols, thus minimizing iatrogenic effects and the total cost of the procedure.

In this context, women with 25(OH)D <30 ng/mL in follicular fluid have increased mRNA expression of AMH receptor type II in granulosa cells of small follicles, suggesting an important role for 25(OH)D in the expression and signaling of the AMH gene[27]. Interestingly, after controlling for seasonal fluctuations, a negative linear correlation was found between AMH levels and 25(OH)D levels only up to ca. 30ng/ml (p= 0.06). Beyond this value, there was no statistically significant relationship (p = 0.50)[28].

In another similar study, the authors found a positive correlation between serum 25(OH)D levels and AMH levels in late reproductive age (>40 years) (regression slope = +0.011; p= 0.028). However, in women <35 years of age, and after adjustment for covariates, an insignificant correlation was observed between 25(OH)D and AMH (r 2 = −0.0086; p = 0.054)[29]. However, again, the evidence is not always consistent; in women trying to conceive spontaneously, 25(OH)D levels did not correlate with AMH, but there was a tendency to associate insufficient 25(OH)D levels <30 ng/ml with low AMH (<0.7 ng/ ml) [OR 1.8, CI (0.9–4)][30]. Similarly, another cross-sectional study that included infertile women with a high prevalence of decreased ovarian reserve confirmed the lack of association between serum 25(OH)D levels (<20 ng/mL vs. ≥20 ng/mL) and AMH. (0.8 ± 3.0 ng/mL vs. 0.5 ± 1.6 ng/mL, p = 0.1761, respectively) after adjusting for age, BMI, and seasonal fluctuations[31]. Finally, in the same sense and in a mainly caucasian population without 25(OH)D deficiency (69.3% ≥20 ng/ml), no correlation was found between vit D and AMH[32].

5.- VDES and assisted reproductive techniques (ART).

In this specific area of knowledge, the agreement seems more unanimous whenever the evidence is uniform. In fact, in a systematic review that correlated 25(OH)D levels and ART results[33], most of the studies reviewed reported a decrease in ART results in patients with vitamin D deficiency. Specifically, in 34 studies reviewed, only one showed unrelated results, two showed to be indifferent, and the remaining thirty two showed positive correlations[33]. Cost-benefit analysis suggested that vitamin D screening and supplementation prior to ART might be profitable, but, as usual, more evidence is needed. Given the absence of level I evidence regarding vitamin D status and ART outcomes, it is premature to fully support 25(OH)D screening and supplementation prior to ART, but because the low complexity of the measure and the indicated results we think the suggestion valid[33].

Another study compared prospectively the results of in vitro fertilization (IVF) in a group of 173 patients, of which only 78 had sufficient levels of 25(OH)D[34]. The two groups were epidemiologically homogeneous (sufficient vs. insufficient or deficient), pregnancy rates per cycle started were 52.5% vs 34.75 (p<0-001) and 54.7% vs 37.9% (p<001) per embryo transferred, respectively. These findings, the authors report, suggest that women with sufficient levels of vitamin D are significantly more likely to achieve a clinical pregnancy after IVF. Vitamin D supplementation, they argue, could provide an easy and cost-effective way to improve pregnancy rates, this warrants further investigation. Therefore, it may be beneficial to determine vitamin D status as part of routine infertility evaluation and before artificial reproductive treatment, especially in women with a higher BMI. This study was registered before its development and had international controls[35].

In recent years, the general trend behind the innumerable improvements in embryo culture techniques is the trend towards single embryo transfer. In this context, 25(OH)D levels have also been evaluated in IVF[36] cycles, confirming that vitamin D deficiency affects pregnancy rates in women who undergo a single blastocyst transfer. In this case, the group was much larger (239 patients against 129 but only discriminated by having the first <20ng/ml of 25(OH)D in plasma vs >20 in the other group). The clinical pregnancy rates from the same study (beyond the biochemicals) of 52% vs 67% in both groups were equally significant ($p<0.015$); but beyond that, the rates of "baby at home", the true objective of ART, were still equally different ($p<0.015$), (35% vs 48%, respectively).

We still do not know the precise mechanism by which VDES exerts these positive effects, which have been demonstrated in practically all the studies reviewed in this regard, regardless of whether they were retrospective or prospective, as the first author of this paper demonstrated in a previous review[25]. In this regard, the results of a study carried out more than a decade ago that correlated embryo quality with 25(OH)D levels measured in the follicular fluid obtained on the day of IVF oocyte retrieval can help us[37]. The authors started from the division of the patients between pregnant women after IVF (n=26) versus non-pregnant women (n=58); well, in addition to differing significantly by consuming fewer doses of gonadotropins in the stimulations in the former ($p<0.001$), the latter consumed fewer days of stimulation ($p<0.002$), all of which is perfectly logical when dealing with patients with better performance in IVF. The most important thing, in the same order of things, is that pregnant patients showed significantly higher intra-follicular 25(OH)D levels than non-pregnant patients (34.42 ng/ml vs 25.62, $p<0.013$) also receiving significantly higher number of embryos (2.56 vs 1.98, $p<0.011$). The differences were even greater for patients who were in the highest fertile of intra-follicular 25(OH)D with embryo implantation rates greater than 35% and pregnancy rates greater than 50% per attempt. The authors conclude that the findings that women with a higher level of 25(OH)D in their serum and follicular fluid are significantly more likely to achieve a clinical pregnancy after IVF and embryo transfer are novel.

In relation to the mechanisms that support the effect, they suggest a potential benefit of vitamin D supplementation in the success of treatment in infertile patients undergoing IVF and deserves further investigation, and deserves further investigation, as the first author of this paper concluded in his recent review on the topic[25], which would at least suggest generalizing the determination of 25(OH)D as part of the fertility study even before deciding whether the patient is a candidate for IVF or a different ART in order to achieve the desired pregnancy in the fewest number of attempts possible.

INFLUENCE OF VDES IN PREGNANCY

1.- Vitamin D and gestational evolution.

To the extent that SEVD is responsible, among other effects, for intestinal calcium (Ca++) absorption, the adaptive processes of calcium homeostasis in human pregnancy and lactation, compared to normal[38], are well known. and situations of loss of bone mass during pregnancy with diagnoses of established osteoporosis have even been described among especially predisposed patients who have suffered low-impact fractures due to high calcium consumption during this period.

In a similar way to what we have pointed out among infertility patients, the geographical location of the residence and the number of hours of sunlight exposure in the area do not in any case guarantee adequate levels of 25(OH)D in a group of pregnant women analyzed. Pérez López et al.[39] detected up to 63% of deficient or insufficient pregnant women in a group of pregnant women in Almería (an area with more than 3,500 hours of sunshine per year), making it irrelevant whether the women analyzed were Spanish or of foreign nationality, mostly North Africans in that region[39]. Moreover, the situation was not significantly different in the different seasons, so they concluded that living on the Mediterranean coast of Spain does not guarantee good 25(OH)D levels during pregnancy or in summer. The logistic regression analysis on the factors related to the low state of 25(OH)D < 20 ng/mL, were among others less striking, the BMI ≥25 (Odds ratio 0.48 IC 95% [0.28-0.84]) and being of Caucasian race (OR 0.18 95%CI [0.10-0.31])[39].

Almost twenty years ago, from experimental studies with KO mice genetically predisposed to developing diabetes mellitus (DM), the relationship between 25(OH)D levels and the possibility of developing DM throughout their lives[40] was known. In the same way in males as in females, those deficient in vitamin D at the beginning of life developed significantly more DM (66% vs 45% $p<0.01$ and 35% vs 15%, $p<0.005$, respectively for males and females), during its existence[40].

2.- VDES and gestational DM (GDM) development.

The extrapolation in humans of the findings observed in mice comes from the meta-analyses that try to correlate vitamin D and GDM. Some authors have described that RCT data remain limited, but are critical to understanding whether vitamin D supplementation,

beyond what is contained in routine prenatal vitamins, will prevent GDM or improve glucose tolerance in women with DMG[41].

Plasma markers of 25(OH)D status and insulin resistance (IR) during the 1st trimester and late pregnancy before and after daily oral supplementation of 200 IU, 2000 IU and 4000 IU demonstrated (with small groups of 35, 38 and 40 patients respectively for the three doses of cholecalciferol), which significantly improved not only the 25(OH)D levels before and after oral supplementation, but also the basal insulin levels, the HOMA-IR index, and glycemia. baseline and plasma Ca++ levels[42].

In the same sense, an observational cross-sectional study that included 160 pregnant women between 20-40 years of age, in the third trimester, demonstrated a statistically significant negative correlation (r = -0.245) between glycemic control and plasma 25(OH)D levels in the entire study population[43].

Up to 2014, two well-conducted meta-analyses reported evidence of an association between a low 25(OH)D level and increased odds of gestational diabetes mellitus (GDM). However, it is still unknown whether vitamin D deficiency contributes to the pathophysiology of GDM development. To our knowledge, none large randomized trial of multiple doses has been published. The only RCTs available were promising, but far from definitive, and RCTs were essential to prove a protective effect of optimal 25(OH)D status with respect to the development or management of GDM[41].

Later, in 2015, Chinese authors published a meta-analysis of observational studies, but with a good design and confirming two coincident findings[44]. Meta-analysis of 20 studies including 9,209 participants showed that women with 25(OH)D deficiency compared with control experienced an increased risk of developing GDM (OR = 1.53; 95% CI, 1.33, 1.75). But at the same time, they verified that the serum level of 25(OH)D was significantly lower in the participants with GDM than in the control (95% CI, -6.73, -3.14) p = 0.001. They conclude by stating that there is a consistent relationship between 25(OH)D deficiency and increased risk of GDM, and a significant decrease of 4.93 nmol/L (~12.5 ng/mL) in serum 25(OH)D in GDM participants. However, once again, well-designed RCTs with robust n are needed to determine the explicit effect of vitamin D supplementation in the prevention of GDM. Until then, one could consider screening women at risk of VD deficiency and supplementing them with vitamin D, as already noted in our consensus papers[6].

3.- VDES and perinatal results.

It is known that the interaction of VDES and pregnancy correlates with different VDR[2,3]. The 24,25(OH)2D3 (24,25 dihydroxy-cholecalciferol) synthesized by the placenta accumulates in bone and may be involved in the ossification of the fetal skeleton[45]. Through its much more complex non-genomic and genomic actions, vitamin D plays an important role in pregnancy, with emphasis on immune function and fetal ossification. It is known that there are main changes in the fetal-placental unit that condition the transfer of maternal calcium to the fetus[46]. All this conditions a whole series of changes in BMD (bone mineral density) of the ultradistal radius (measured by US - ultrasound), during pregnancy and postpartum[47], which cause loss of bone mass already in the 10th week of gestation that continues in the week 22nd and 34th when 92 pregnant women were compared to 75 non-pregnant women ($p<0.05$)[38], which would be at the base of the already mentioned possibility of even developing gestational osteoporosis[38, 46, 47].

A systematic review of 76 studies carried out a few years ago highlighted the unfortunate heterogeneity of the studies found and the need, once again, for adequate RCTs with a good design and sufficient n. The authors noted that at least at that time, the evidence base is insufficient to support definitive clinical recommendations regarding vitamin D supplementation in pregnancy. Although they found modest evidence to support a relationship between maternal 25(OH)D status and newborn weight (effect size 5.63 with 95% CI [1.11-10.16]), bone mass and serum calcium concentrations of the offspring, among the children of women treated with vitamin D during gestation (0.005 with CI 95% [0.02-0.07]), these findings were limited by their observational nature (in the data of birth weight and bone mass) or risk of bias and low quality (regarding calcium concentrations)[48].

The situation is probably universal; In tropical countries, vitamin D deficiencies have been repeatedly demonstrated among normal pregnant women49. Other evidence from well-designed studies suggests that vitamin D exposure during fetal development influences the newborn's immune system, which may contribute to protection against asthma-related outcomes, including infections, in the early years. of life[50]. This would be in perfect synchrony with the already known anti-inflammatory action of SEVD in terms of protection against infectious and viral diseases in particular[51,52]. Thinking that young or healthy people have sufficient levels of 25(OH)D just because they live in sunny areas, even with subtropical climates in southern Europe[8] or even tropical (almost 40% deficiency or insufficiency among women of reproductive age in Colombia)[53], it seems a profound error of presumption, based on the accumulated evidence.

GENERAL CONCLUSIONS

1. The presence of VDR in multiple tissues related to fertility and pregnancy allows to predict a determining role of VDES in human reproduction in general.

2. A situation of hypovitaminosis D has been repeatedly demonstrated among patients affected by infertility, even if their place of residence receives a sufficient level of solar radiation.

3. The finding of deficiency or insufficiency of 25(OH)D is common in patients with PCOS.

4. Likewise, 25(OH)D levels correlate inversely with the development of uterine fibroids and supplementation could be an adequate therapeutic alternative in selected cases.

5. Women with lower 25(OH)D levels tend to have lower AMH values in their fertility studies.

6. Patients undergoing IVF have better results in terms of pregnancy rates when their 25(OH)D levels are normal or supplemented before starting treatment.

7. While the exact mechanism is still unknown, VDES produces better results in embryo implantation rates when intra-follicular 25(OH)D levels are higher, even in cycles with single blastocyst transfer.

8. Extensive situations of hypovitaminosis D have been described among (young) pregnant women, including residents in the sunny south of Spain.

9. Pregnant women with lower levels of 25(OH)D have a higher risk of developing GDM and pregnant women with GDM have lower 25(OH)D levels than controls.

10. Adequate 25(OH)D levels allow predicting a better newborn weight and a better response from the immune system in general.

11. Although the accumulated evidence is limited and heterogeneous, it always points in the same direction of the improvement of fertility and pregnancy due to the action of VDES.

12. More RCTs with good design and large groups are needed to elucidate the mechanisms involved in these relationships, as well as confirm the limited scientific evidence to date.

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