Section A-Research paper

Overview about Vitamin D and Reproduction

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Abstract

Background: The expression of the vitamin D receptor (VDR) and enzymes involved in the metabolism of vitamin D in female reproductive tissues, suggests that vitamin D is involved in the physiologic reproduction process. VDR is expressed in granulose cells (GCs) and cumulus oophorus cells of human ovarian tissue, in decidua and placenta, in endometrium and fallopian epithelial cells and in the pituitary gland. Further, the human cultured syncytiotrophoblasts express VDR, which stimulates the expression and the secretion of human chorionic gonadotropin (hCG). The human placenta, the endometrium and the ovary express also 1α-hydroxylase (encoded by CYP27B1), indicating that these tissues are able to synthesize locally the 1,25 dihydroxyvitamin D3 [1,25(OH)2D3, or calcitriol], which is the active form of vitamin D. Vitamin D deficiency is hypothesized to contribute to the pathophysiology of a spectrum of gynecological disorders, of which polycystic ovary syndrome (PCOS) appears to be most well studied. An overexpression of VDR and vitamin D metabolizing enzymes is also described in the peritoneal lesions and in endometrial tissue of women with endometriosis compared with healthy controls. Serum 25 hydroxyvitamin D levels are reported to predict ovarian response in women undergoing ovulation induction with clomiphene citrate (CC). Low levels of 2m 25 hydroxyvitamin D levels and vitamin D deficiency (25 nmol/l or 10 ng/ml) were found to be associated with lower rates of follicle development and pregnancy after ovarian stimulation with 50 mg CC; of note, the threshold taken to define vitamin D insufficiency in this latter study is consistent with a state of severe vitamin D deficiency.

Keywords: Vitamin D, Reproduction

Introduction

Vitamin D nowadays is discovered to have different un-ordinary functions. It is viewed to be a pro-hormone not a true vitamin ***(Bearden et al., 2020).***

There are 2 different types of vitamin D (calciferol):

Vitamin D2 is a synthetic product , while vitamin D3 is a pro-hormone synthetized under the skin by the effect of Ultraviolet beam illumination on a cholesterol precursor (7-dehydrocholesterol). The two kinds haven't the same structure. Where in D2 there is a methyl bunch at C24 and two-fold bond at C22 and C23 as seen in figure (2) which not present in D3. This explains the difference in metabolism between both. However, both are turned to 25 Hydroxy vitamin D and 1, 25 hydroxy vitamin D ***(Goldsmith, 2016).***

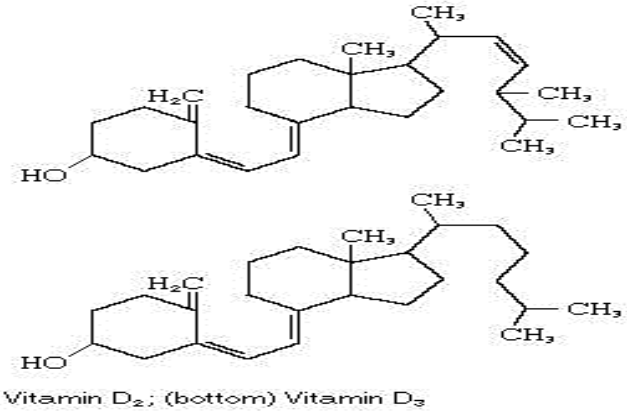

Figure (1): Chemistry of vitamin D ***(Volmer et al., 2015)***

Sources:

Vitamin D is a fat-dissolvable vitamin that is one of steroid compounds. The main source of vitamin D in adults is synthesis from sun rays. Thirty minutes of daylight produces 50,000 iu of vitamin D with white-complexioned skin. Dietary intake of vitamin D makes little percentage of whole vitamin D status as there is little vitamin D normally in the food supply like fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. Melanin absorbs ultraviolet B (UVB) from sunlight and brings down cholecalciferol creation by about 90%. Dietary vitamin D is retained from the digestive tract and found in plasma bound to its binding proteins ***(Rejinold et al., 2019).***

Vitamin D3 is three folds more compelling than vitamin D2 in increasing vitamin D concentrations and keeping up those levels for delayed time ***(Pludowski et al., 2018).***

Various components, for example duration of sun exposure, season, period of day, skin pigmentation, utilization of sunscreen, behavioral patterns and diet, influence vitamin D production through the skin ***(Neville et al., 2021).***

Metabolism:

In humans, the predominant source of vitamin D is endogenous cutaneous synthesis, whereas dietary sources contribute to, 20% of the circulating levels of vitamin D ***(Moulas and Vaiou, 2018)***

Endogenous synthesis of vitamin D (cholecalciferol or D3) occurs after photolytic conversion of 7-dehydrocholesterol, located in the dermal fibroblasts and epidermal keratinocytes, by the ultraviolet B component of sunlight (wavelength between 290 nm and 315 nm ***(Pelczyńska et al., 2016).***

Nutritional forms of vitamin D consist of D3 (cholecalciferol), which is found in foods such as fatty fish (i.e. sardine, salmon and mackerel), eggs and calf liver, and D2 (ergocalciferol) which is manufactured through the ultraviolet irradiation of ergosterol from yeast and fungi ***(de la Guía-Galipienso et al., 2021).***

Both forms of dietary vitamin D are inactive and are efficiently absorbed by the gut. The dietary vitamin D (D3 and D2) is nearly identical to the skin derived form of this secosteroid ***(Bivona et al., 2019).***

Renal 1-α hydroxylase (CYP27B1) is recognized as the principal determinant and the rate-limiting enzyme in the generation of the active1,25(OH)2D metabolite. Recently, the expression of CYP27B1 has been described in a variety of non-renal tissues, suggesting the existence of local mechanisms by which vitamin D is generated ***(Bikle et al., 2017).***

The activity of CYP27B1 is directly regulated by the parathyroid hormone PTH. More recently, the activity of CYP27B1 has been shown to be inhibited by fibroblast growth factor 23 (FGF-23), a component of the previously unrecognized hormonal bone–parathyroid–kidney axis that is itself modulated by PTH, 1,25(OH)2D and serum phosphorus levels ***(Jacquillet and Unwin, 2019).***

Serum vitamin D level

As regarding the available scientific data, serum vitamin D concentration is better reflected by 25(OH)D, due to its long life and stability. Levels that defining vitamin D deficiency are debatable. Vitamin D deficiency is defined as a serum 25(OH)D level of less than 20 ng/ml, whereas vitamin D insufficiency is a serum level of 25(OH)D from 21 to 29 ng/ml ***(Jorde and Grimnes, 2018)***

Vitamin D is considered sufficient at 30 ng/ml**.** At this level the optimal calcium absorption occurs. As the preferred value is being ranged from 40 to 60 ng/ml ***(Pludowski et al., 2018).***

Mechanism of action:

Vitamin D belongs to the family of steroid hormones. The cellular effects of vitamin D and its metabolites are mediated primarily through the cognate intranuclear vitamin D receptor (VDR), a ligand-activated transcription factor that belongs to the nuclear hormone receptor super-family ***(Petta et al., 2016)***

The interaction of 1,25 hydroxy vit D with nuclear vitamin D receptors influences gene transcription. Nuclear receptors for 1,25 hydroxy vit D are present in a range of tissues including bone, intestine, kidney, lung, muscle and skin. Similar to steroid hormones, 1,25 hydroxy vit D acts via signal transduction pathways linked to vitamin D receptors on cell membranes ***(Bikle and Christakos, 2020)***

Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Its biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle ***(DiMeglio and Imel, 2019)***

The biological effects of 1,25 hydroxy vit D are diverse. It inhibits PTH secretion and adaptive immunity, while promoting insulin secretion and innate immunity. It also inhibits cell proliferation and stimulates their differentiation. Signaling via the VDR has additionally been linked to CYP19 (aromatase) gene expression, functionally linking vitamin D with the family of reproductive steroid hormones ***(Khammissa et al., 2018).***

Vitamin D – role in pathophysiology of infertility

Vitamin D has important role in the inflammatory pathways. It regulates immunological, circulatory and neurological processes. In adults (also in the perinatal period) vitamin D regulates the immune system and is an anti-inflammatory agent that lower the expression of pro-inflammatory cytokines and chemokines as tumor necrotic factor α (TNF-α), interferon γ (INF-γ), and interleukin6 (IL-6) ***(Kim et al., 2018)***

Steroid hormones (e.g., estrogens and progesterone) and human chorionic gonadotropin (HCG) are also connected with vitamin D pathways as regarding several available studies. Vitamin D active metabolites have broad and diverse biological functions. As regarding older and recent reports, vitamin D deficiency is associated with a lot of different conditions (as, type 1 diabetes mellitus, malignant neoplasms, cardiovascular diseases, etc.). Other conditions -not less important- are chronic kidney disease gastro-intestinal diseases, and liver failure ***(Jeon et al., 2016)***

Vitamin D role in uncomplicated pregnancy

Vitamin D plays an important role in human reproduction. The effect of vitamin D on pregnancy is a topic of major interest in the current medicine. Vitamin D influences folliculogenesis, modulates endometrial receptivity, and regulates embryogenesis ***(Galesanu and Veronica, 2015).***

It has an important role in trophoblast invasion. Many studies have proved its effects on placental implantation, angiogenesis and endothelial function, immune function, inflammatory response during pregnancy, oxidative stress, and glucose homeostasis ***(Musson and Collin, 2015).***

Vitamin D plays an important role in the embryo and fetal skeletal development. The most important role of vitamin D during pregnancy is to elevate placental calcium transport ***(Nageshu et al., 2016).***

Vitamin D status during pregnancy relies mostly on the maternal stores. During pregnancy, mobilization of maternal calcium increases to ensure adequate fetal bone mineralization. ***(Nageshu et al., 2016).***

25 hydroxy vit D is a metabolite that crosses the placental barrier and is the main form of vitamin D used by the fetus**.** Appropriate 25(OH)D serum concentrations are important to sustain the increased levels of 1,25 (OH)2D during pregnancy. 1,25(OH)2D serum levels increase in early pregnancy and continue to grow until delivery ***(Rajput et al., 2019).***

Vitamin D and pregnancy

There is growing interest in the effect of maternal vitamin D concentrations on pregnancy outcomes. Maternal vitamin D status is proved to be associated with various obstetrical outcomes, such as early miscarriages, but also in the pathophysiology of other important obstetric complications ***(Christoph et al., 2020)***

The studies on vitamin D intake and its role in protection against adverse pregnancy outcomes differ, but there are still no large randomized control trials (RCTs) or clear guidelines regarding this problem ***(Nageshu et al., 2016).***

There are still many contradictory opinions. There are studies that suggest the increase of vitamin D deficiency in pregnant women and its connection with adverse pregnancy outcomes (maternal, fetal and in mgkchild) such as preeclampsia, gestational diabetes mellitus (GDM), preterm birth, low birth weight, impaired neurodevelopment, asthma development or future problems with body composition ***(Palacios et al., 2016)***

Newer data proves the safety and efficacy of 4000 IU vitamin D, administered daily over 6 months of pregnancy**.** Recent study demonstrated a significant decrease in complications of pregnancy, and comorbidities of pregnancy ***(Sulaiman et al., 2022)***

Etiology of vitamin D deficiency of infertile female it can be caused by various medical disorders, as:

1- **Kidney and liver diseases.** They bring down the amount of an enzyme needed to convert vitamin D to its active form. Absence of this enzyme results in vitamin D deficiency ***(Bikle and Christakos, 2020)***

2- **Cystic fibrosis, Crohn's disease, and celiac disease**. These conditions prevent the intestine from absorbing sufficient vitamin D ***(Mărginean et al., 2022)***

3- **Gastric bypass surgery**. This weight-reduction medical procedure eliminates part of stomach and/or the intestine. Decreasing the size of these organs, diminish the amount of absorbed vitamin D-containing nutrients ***(Omar et al., 2021)***

4- **Obesity.** Body mass index over 30 is combined with decreased vitamin D concentrations. It is believed that fat bind to the vitamin D, preventing its release into the bloodstream ***(Pankiv and Pankiv, 2018)***

Other factors that can lead to vitamin D deficiency: *(Galesanu and Veronica, 2015).*

1) ***Age.*** The skin's capacity to build up vitamin D lowers with age.
2) ***Mobility.*** Individuals that are home bound or are rarely gets out (e.g., in nursing homes and different facilities) can't utilize sun exposure to produce vitamin D.
3) ***Skin color.*** Dark-colored skin is less capable of vitamin D synthesis than fair-colored ones.

Vitamin D levels can be diminished by special drugs. These like: laxatives, steroids (e.g., prednisone), cholesterol-lowering drugs (e.g., cholestyramine and colestipol), anti-epileptic drugs (e.g., phenobarbital and phenytoin), a tuberculosis drug (rifampin), and a weight-reducing drug (orlistat) ***(Galesanu and Veronica, 2015).***

Vitamin D and Reproduction

Vitamin D and female reproductive physiology:

The expression of the vitamin D receptor (VDR) and enzymes involved in the metabolism of vitamin D in female reproductive tissues, suggests that vitamin D is involved in the physiologic reproduction process. VDR is expressed in granulose cells (GCs) and cumulus oophorus cells of human ovarian tissue, in decidua and placenta, in endometrium and fallopian epithelial cells and in the pituitary gland. Further, the human cultured syncytiotrophoblasts express VDR, which stimulates the expression and the secretion of human chorionic gonadotropin (hCG). The human placenta, the endometrium and the ovary express also 1α-hydroxylase (encoded by CYP27B1), indicating that these tissues are able to synthesize locally the 1,25 dihydroxyvitamin D3 [1,25(OH)2D3, or calcitriol], which is the active form of vitamin D ***(Muscogiuri et al., 2017).***

Vitamin D deficiency is hypothesized to contribute to the pathophysiology of a spectrum of gynecological disorders, of which polycystic ovary syndrome (PCOS) appears to be most well studied. An overexpression of VDR and vitamin D metabolizing enzymes is also described in the peritoneal lesions and in endometrial tissue of women with endometriosis compared with healthy controls ***(Malky et al., 2018).***

Serum 25 hydroxyvitamin D levels are reported to predict ovarian response in women undergoing ovulation induction with clomiphene citrate (CC). Low levels of 2m 25 hydroxyvitamin D levels and

vitamin D deficiency (25 nmol/l or 10 ng/ml) were found to be associated with lower rates of follicle development and pregnancy after ovarian stimulation with 50 mg CC; of note, the threshold taken to define vitamin D insufficiency in this latter study is consistent with a state of severe vitamin D deficiency ***(Yilmaz et al., 2018)***

Additionally another group of investigators reported adverse impact of higher 25 hydroxyvitamin D levels on embryo quality. Additional studies are needed to explore these associations better and to study the direct effects of vitamin D and its metabolites on the endometrium and implantation. Serum and follicular fluid levels of 25 hydroxyvitamin D levels ***(Gaksch et al., 2017).***

Vitamin D defeciancy and PCO:

Women with PCOS presented a relative high prevalence of vitamin D deficiency in comparison with the general population and vitamin D deficiency correlates with comorbidities associated to PCOS.

Vitamin D pathway might have a regulatory role in several PCOS associated symptoms, including ovulatory dysfunction, endocrine alterations, and insulin resistance. VDR expression was demonstrated in ovarian follicles, and predominantly localizes in the nuclei of GCs of largest follicles ***(Muscogiuri et al., 2017).***

Vitamin D deficiency has been demonstrated to play an important role in the development of insulin resistance. Calcitriol has been shown to increase the expression of the insulin receptor, insulin synthesis and secretion, insulin sensitivity and to decrease the production of pro-inflammatory cytokines involved in insulin resistance.In in vitro experiments calcitriol was shown to up-regulate insulin receptor in a dose dependent manner at both mRNA and protein level; moreover calcitriol treatment enhanced insulin responsiveness in terms of glucose transport ***(Muscogiuri et al., 2017).***

Overall, PCOS is the most common cause of an ovulatory infertility in women. There is some evidence suggesting that vitamin D deficiency might be involved in the pathogenesis of insulin resistance and the metabolic syndrome in PCOS. Whether vitamin D is also related to endocrine parameters and fertility in PCOS is less clear ***(Morgante et al., 2022).***

Vitamin D supplementation in PCOS women did not significantly improve metabolic parameters of insulin resistance, except for fasting insulin and triglycerides. Therefore, vitamin D supplementation had no effect on androgen levels and clinical features of hyperandrogenism ***(Muscogiuri et al., 2017).***

*** Vitamin D and ovarian reserve markers:**

Evidence suggests a correlation between vitamin D and ovarian reserve markers and, in particular, with anti-Mullerian hormone (AMH) at both genetic and serum levels. In humans, a cross-sectional study including 388 premenopausal women aged ≥40 years and with regularmenstrual cycles, demonstrated that serum 25 hydroxyvitamin D levels levels correlate with serum AMH levels, suggesting that vitamin D deficiency may be associated with lower ovarian reserve in late-reproductive-aged women. A more recent study of a large cohort of premenopausal women, aged 30- to 49-years, demonstrated that Vitamin D is inversely related to urinary FSH and that for every increase of 10 ng/mL of 25 hydroxyvitamin D levels serum levels, urinary FSH decreased by 14% (95% CI, −23 to −5; P = 0.003). This result is consistent with the previous cited literature which relate low 25 hydroxyvitamin D levels to lower AMH levels, and suggests that vitamin D may have a role in the regulation of ovarian reserve. However, prospective and randomized controlled clinical trials are necessary to better elucidate this aspect ***(Muscogiuri et al., 2017).***

Vitamin D and IVF:

Higher vitamin D (25-OHD) levels are associated with better pregnancy outcomes after ICSI. This association was as a result of effect of vitamin D in improvement of endometrial thickness ***(Abdullah et al., 2017).***

IVF Studies investigating the association of vitamin D status with IVF outcome revealed inconsistent results. In a study among 84 infertile women undergoing IVF, women with higher levels of 25 hydroxyvitamin D levels in serum and follicular fluid were significantly more likely to achieve clinical pregnancy following IVF, and high vitamin D levels were significantly associated with improved parameters of controlled ovarian hyperstimulation ***(Banker et al., 2017)***

It was that reported 41% increased rate of pregnancy and 28% live births in IVF patients (egg recipient) with optimal levels of vitamin D. They elaborated that vitamin D imparts its action primarily by effecting endometrium locally via VDR. VDR binds to calcitriol and expresses genes which are involved in regulation of factors that enhances implantation ***(Abdullah et al., 2017).***

In contrast, it was found no significant associations of 25 hydroxyvitamin D levels in serum and follicular fluid with IVF outcomes in a study including 82 infertile women undergoing assisted reproductive technology ***(Muyayalo et al., 2022)***

Vitamin D and Implantation:

Vitamin D deficiency impairs fertility in animal models, but the role of vitamin D in human fertility or treatment of infertility is less clear, Although vitamin D may be associated with higher fertilization rates, but this apparent benefit does not translate into higher probability of pregnancy or live birth ***(Abadia et al., 2016).***

Vitamin D has potent effects on immune responses and influences both the innate and adaptive arms of the immune system. Immune adaptations are vital for successful pregnancy outcome and vitamin D likely acts to promote implantation due to its role in inflammatory pathways and immune function. Thus, administration of 1,25(OH)2D3 in rats promotes decidualization, and vitamin D likely has a key role to play in the immune function of the decidua, given its important immunomodulatory effects on trophoblasts. Indeed, vitamin D metabolites enhance extravillous trophoblast invasion in vitro and act in a paracrine manner to suppress cytokine secretion in uterine natural killer cells and villous trophoblast ***(Yates et al., 2017).***

Highest implantation rates were observed in women with a follicular fluid level of 25 hydroxyvitamin D levels in the highest tertile (43.01+10.65 ng/ml) compared with those with follicular fluid 25 hydroxyvitamin D levels in the lower tertiles. While these data relate vitamin D status with reproductive success in otherwise healthy, women undergoing IVF others fail to confirm these associations ***(Pal and Taylor, 2018)***

Vitamin D and pregnancy:

Maternal vitamin D deficiency has become a significant problem in modern day obstetrics; the rates of vitamin D deficiency have increased in recent decades, and it is estimated that between 18% and 84% of pregnant women worldwide are vitamin D deficient ***(Triunfo et al., 2017)***

Although vitamin D has traditionally been associated with bone health through its regulation of calcium and phosphate absorption, it also plays central roles in cellular proliferation and differentiation, vascular function and immune regulation ***(Ji et al., 2017)***

As a consequence of these pleiotropic functions, vitamin D metabolism is important for a range of key developmental events, including decidualization, modulation of maternal immune function and fetal bone formation ***(Cyprian et al., 2019)***

Accordingly, maternal vitamin D deficiency has been linked to pregnancy complications such as preeclampsia, bacterial vaginosis, preterm birth and gestational diabetes mellitus. Moreover, gestational vitamin D deficiency is associated with intrauterine growth restriction in infants and adverse postnatal health outcomes in offspring, including increased rates of asthma, hypertension and impaired neurodevelopment ***(Yates et al., 2017).***

Maternal calcium metabolism undergoes dramatic modulation so as to maintain the skeletal mineralization needs of the developing fetus. The gravid woman's physiology adapts to the escalating fetal requirements with advancing gestation; increasing gastrointestinal calcium absorption is evident early in pregnancy, and maximized in the last trimester ***(Stenhouse et al., 2022)***

Several pregnancy-related disorders that have been hypothesized to relate to maternal vitamin D deficiency include pre-eclampsia, gestational diabetes mellitus (GDM) and a risk for delivery by Cesarean section ***(von Websky et al., 2018)***

Pre-eclampsia is one of the most common obstetric complications, and a significant contributor to maternal and fetal morbidity and mortality. While the etiology is not entirely clear, abnormal placentation, poor

placental perfusions, endothelial dysfunction and oxidative stress are recognized mechanisms underlying pre-eclampsia ***(Phipps et al., 2019)***

The presence of vitamin D and its receptors in the placenta as well as the ability of vitamin D to modulate immune, inflammatory and vascular responses has suggested a causative role of maternal vitamin D deficiency in the pathogenesis of pre-eclampsia ***(Purswani et al., 2017)***

Higher maternal vitamin D levels are associated with a lower incidence of pre-eclampsia and with lower blood pressure reading. Others have explored the relationship between maternal D levels earlier in pregnancy with the likelihood of developing preeclampsia during the course of pregnancy ***(Song et al., 2017)***

Although a relationship between vitamin D deficiency and risk for type 2 diabetes mellitus is well described in non-pregnant populations the association of vitamin D with GDM, however, has shown mixed results maternal rickets and concomitant pelvic deformities are a recognized contributor to inefficient labor and difficulties with parturition ***(von Websky et al., 2018)***

The increased risk of Cesarean section (emergent or elective) was attributed to negative effects of low vitamin D levels on uterine musculature and contractibility. However, the relationship between vitamin D and the route of delivery is not consistent. Moreover, others researchers fail to observe any effect of maternal vitamin D status (assessed early or mid-pregnancy or at the time of delivery) on the route of delivery ***(Gernand et al., 2015)***

Future research that focuses on the critical period(s) leading up to conception and during pregnancy to correct deficiency or maintain optimal vitamin D status remains to be studied. In addition, what effects vitamin D has on genetic signatures that minimize the risk to the mother and her developing fetus have not been elucidated. Clearly, while there is much more research that needs to be performed, our understanding of vitamin D requirements during pregnancy has advanced significantly during the last few decades ***(Hollis and Wagner, 2017).***

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