Chapter 12

Vitamin D and Human Reproduction

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Additional information is available at the end of the chapter

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Abstract

Vitamin D is one of the steroid hormones. The precursor of vitamin D, 7-dehydrocholesterol, which is an intermediary for cholesterol pathway, is available in the skin. Ultraviolet B (UVB) radiation makes the transformation of 7-dehydrocholesterol to provitamin D3, which automatically isomerizes to cholecalciferol (vitamin D3). Vitamin D3 is secreted into blood circulation and carried by the vitamin D–binding protein (VDBP). Around 80–90% of vitamin D is from sunlight-derived production in the skin. A little amount of vitamin D is also extracted from foods and/or additional supplementation. Vitamin D has been well known for its function in maintaining calcium and phosphorus homeostasis and promoting bone mineralization. Accumulating evidence from animal and human studies suggests that vitamin D also modulates reproductive processes in women and men and is involved in many functions of the reproductive system. Vitamin D receptor (VDR) and vitamin D–metabolizing enzymes are found in reproductive tissues of women and men. This chapter presents an up-to-date review for describing the function of vitamin D in female reproduction throughout reproductive ages from menarche to menopause, during pregnancy and lactation, and some disorders affecting women and also the role of vitamin D applied to male fertility.

Keywords: vitamin D, vitamin D receptor, metabolism, female reproduction, male reproduction

1. Introduction

1.1. Overview of vitamin D: production, metabolism and action

Vitamin D (VD) is one of the fat-soluble vitamins from steroid hormones family. While there are various forms of vitamin D, two main forms are necessary for human body: (i) D2 (ergocalciferol) and (ii) D3 (cholecalciferol) [1]. In the presence of ultraviolet radiation, vitamin D2 is derived primarily in plants, yeast, and fungi, and also vitamin D3 is synthesized predominantly by the conversion of 7-dehydrocholesterol, a VD precursor present in the skin, under ultraviolet B radiation with only a small amount of this vitamin with around <10–20% obtained through diet supplements [2]. VD precursor isomerizes into cholecalciferol. Cholecalciferol is bound to serum vitamin D-binding protein (DBP). To become biologically active, two-step enzymatic pathways are necessary; involving 25-hydroxylase of the liver and 1a-hydroxylase (CYP27B1) of the kidney and extra-renal tissues, it is converted to the biologically active hormone calcitriol (1α,25(OH)2D3) [3, 4].

Vitamin D secretion is set out in the renal 1α-hydroxylase phase. Parathyroid hormone (PTH) upregulates the expression of this enzyme and also 1,25(OH)2D3 could suppress itself [5].

Finally, in the kidneys, both 25(OH) D and 1,25(OH) 2D3 convert into an inactive compound of calcitroic acid by 24-hydroxylase, which is water soluble and excreted in bile. Whereas 1α-hydroxylase is predominantly found in the kidneys, it can also be expressed in different extra-renal tissues including bones, colon, breasts, prostate, and placenta. In this respect, it is suggested that macrophages could locally produce 1,25(OH)2D3 [6].

Biological roles of vitamin D are mediated by the VD receptor (VDR), a ligand-dependent transcription factor mainly localized in the target cell nuclei that mediate the genomic action of 1,25(OH)2D3, which influences on the transcription of more than 900 genes [7]. It is widely distributed in over 38 tissues and organs including skeleton, parathyroid glands, and the reproductive tissues indicating its potential role in the regulation of numerous metabolic processes [8].

The regulation of VDR expression is one of the main mechanisms through which target cells respond to vitamin D so that polymorphisms of this receptor can change the usual mode of functioning [9, 10]. After the linking of vitamin D, vitamin D receptors transform to a heterodimer with retinoid x-receptor (RXR) after which this complex binds to specific DNA sequences named vitamin D–response elements (VDREs) in the promoter zone of vitamin D–responsive genes. So, this trimeric complex of VDR-RXRVDRE acts as a molecular switch in nuclear 1,25(OH)2D3 signaling [11].

The genomic response lasts for longer times from a few hours to 1 day for the changes that occur in the transcription of gene. However, the nongenomic response is faster, taking only seconds to a few minutes due to the interaction that occurs with a cell surface receptor and the second messenger [10].

Catabolism of 1,25(OH)2D and 25-OHD to biologically inactive calcitroic acid is mediated by 24-hydroxylase, in the kidney and liver [4]. It is generally accepted that the serum levels of 25(OH)D are considered the best indicator of vitamin D status because of its easy measurement and long half-life in circulation (~2–3 weeks) [12, 13].

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The three main steps in vitamin D metabolism, 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation, are all performed by cytochrome P450 mixed-function oxidases (CYPs) (**Figure 1**).

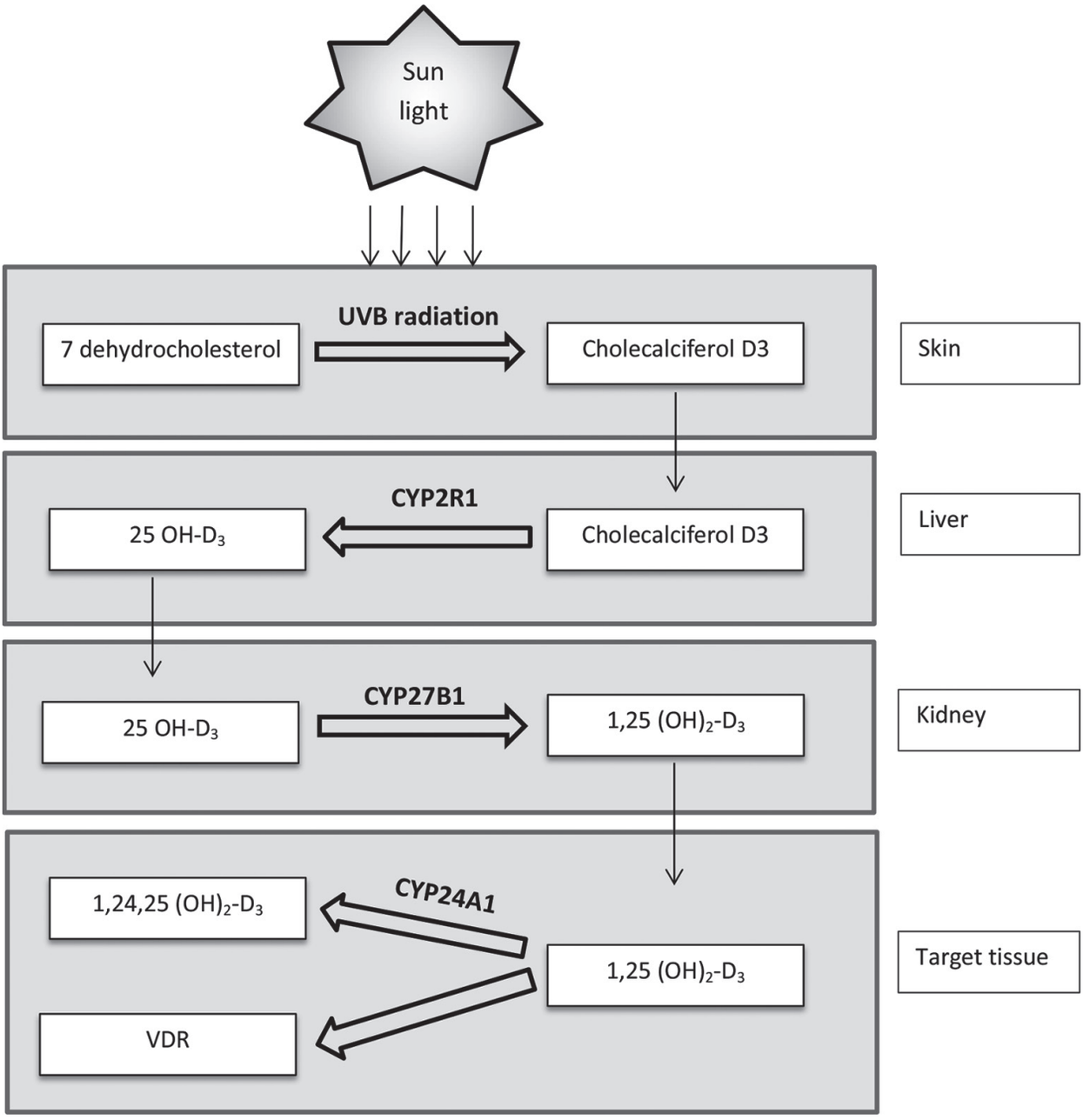

Figure 1. The main steps in vitamin D metabolism.

These enzymes are located either in the endoplasmic reticulum (ER) (e.g., CYP2R1) or in the mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1). The electron donor for the ER enzymes is the reduced nicotinamide adenine dinucleotide phosphate (NADPH)-dependent P450 reductase. The electron donor chain for the mitochondrial enzymes is composed of ferredoxin and ferredoxin reductase. These are not specific for a given CYP—specificity lies within

the CYP. Although the CYPs involved in vitamin D metabolism, only CYP2R1 and CYP24A1, have been crystallized, it is likely that these enzymes contain a number of common structural features. These include 12 helices (A–L) and loops and a common prosthetic group, namely the iron-containing protoporphyrin IX (heme) linked to the thiolate of cysteine. The I helix runs through the center of the enzyme above the heme where a thr(ser) and asp(glu) pair is essential for catalytic activity [14]. CYP2R1, like other microsomal CYPs, contains two extra helices that appear to form a substrate channel in the bilayer of the ER [14]. The B′ helix serves as a gate, closing on substrate binding. Whether a similar substrate channel exists for the mitochondrial CYPs is not clear.

1.2. Physiologic functions of vitamin D

As previously mentioned, once VD is produced in the skin received from the diet, it travels to blood circulation and is bound to vitamin D–binding protein. In the liver, it converts to 25(OH) D as the main circulating form of vitamin D that is measured to determine an individual's vitamin D deficiency. In biological perspectives, 25(OH) D is in an inactive form. However, it converts to [1,25(OH)2D] in the kidney as a free form and travels to the target tissues and participates in the regulation of calcium and phosphorus metabolism. In the intestine, 1,25(OH)2D is bound to vitamin D receptor to increase the expression of an epithelial calcium channel due to increasing the transportation of calcium from the intestinal lumen into the absorptive cell [15]. In this respect, 1,25(OH)2D could enhance the expression of a calcium-binding protein (calbindin9k) to help the transportation of calcium to the intestinal absorptive cell to deposit it into the blood circulation [16]. In addition, 1,25(OH)2D could transport to the skeleton which interacts with VDR in the osteoblast to enhance the expression of RANKL (receptor activator of NFκB ligand).

Monocytic preosteoclasts express the RANK receptor that interacts with RANKL making signal transduction resulting in the formation of multinucleated osteoclasts which are capable of secretion of HCl to save the bone mineral and collagenases to demolish the matrix releasing calcium into the blood circulation.1,25(OH)2D could also directly enhance the calcium tubular reabsorption on the kidneys. As such, 1,25(OH)2D and its receptors reversely regulate the secretion of parathyroid hormone. In addition, among intestine 1,25(OH)2D induces phosphorus absorption. Thus, the main biological functions of vitamin D are to maintain serum calcium and phosphorus in physiological border to support metabolic functions of them and to save the mineralization of the skeleton [17]. The main factors that control the renal secretion of 1,25(OH)2D include PTH, hypocalcemia, and hypophosphatemia that increase its secretion. In this respect, fibroblast growth factor 23 (FGF 23) is secreted by osteocytes and osteoblasts and decreases the renal secretion of 1,25(OH)2D [18].

The dominant physiologic function of vitamin D is the increase of plasma concentration of calcium and phosphate. Both of them are essential for the mineralization of skeleton. Furthermore, the increase in the plasma level of calcium to regulate it in normal levels is also necessary for the functioning of the neuromuscular junction vasodilatation, nerve transmission, as well as hormonal production. Plasma levels of calcium are remained at a very

constant level, in supersaturated bone mineral situation. If its plasma concentration becomes lower than saturated level, then mineralization fails, which leads to rickets among children and osteomalacia among adults [17].

The vitamin D could increase the serum level of calcium from three separate pathways:

(i) It could induce the proteins related to active intestinal calcium absorption throughout the entire length of the intestine, although its greatest activity is in the duodenum and jejunum which does not require parathyroid hormone. It is clear that vitamin D directly stimulates intestinal calcium and, independently, phosphate absorption, although it could stimulate active intestinal absorption of phosphate too.

(ii) In no-calcium diet, vitamin D plays an essential role in the mobilization of calcium from bone, a process requiring parathyroid hormone. Vitamin D induces osteoblasts to secretion receptor activator nuclear factor-κ B ligand. RANKL then induces osteoclastogenesis and activates resting osteoclasts for bone resorption [19]. So, vitamin D appears to be implicated in allowing persons to remove calcium from bone when it is not sufficient in the diet [20].

(iii) The distal renal tubule is responsible for reabsorption of the last 1% of the filtered load of calcium, and the two hormones interact to stimulate the reabsorption of this last 1% of the filtered load. Because 7 g of calcium is filtered every day among humans, this represents a major contribution to the calcium pool. Both parathyroid hormone and the vitamin D hormone are required. Calcium physiologic processes are such that a single low concentration of the vitamin D hormone stimulates enterocytes to absorb calcium and phosphate. If the plasma calcium concentration fails to respond, then the parathyroid glands continue to secrete parathyroid hormone, which increases the production of the vitamin D hormone to mobilize bone calcium (acting with parathyroid hormone). Under normal circumstances, environmental calcium is used first; if environmental calcium is absent, then internal stores are used.

Therefore, in general, vitamin D functions on the intestine, bone, and kidney to increase the serum concentration of calcium. If the serum calcium concentrations increase, the parathyroid hormone secretion decreases. In this respect, if serum concentration of calcium elevates too high, the parafollicular cells ("C" cells) of the thyroid produce the calcitonin hormone that could block calcium resorption from bone and lead to maintain serum level of calcium within the normal range. Vitamin D, through its receptor, suppresses parathyroid gene expression and parathyroid cell proliferation, providing important feedback loops that strengthen the direct mechanism of elevated serum concentration of calcium.

Also, it is shown that a deficiency of phosphate stimulates CYP27B1 to produce more vitamin D, which in turn stimulates phosphate absorption in the small intestine, and vitamin D can also induce the secretion of fibroblast-like growth factor-23 (FGF23) by osteocytes in bone, which results in phosphate excretion in the kidney, as well as feedback on vitamin D metabolism [21].

1.3. Vitamin D deficiency

High prevalence of vitamin D deficiency is present in all races, even in temperate areas. It is now recognized that vitamin D deficiency and insufficiency are the most common nutritional deficiency/medical condition in the world, with 20–90% of reproductive-age women being deficient [22]. The recently revised guidelines of the Endocrine Society of North America defined vitamin D deficiency as 25OH-D levels of <20 ng/mL and insufficiency as levels of 20–30 ng/mL [23]. These definitions are based in part on provocative testing in healthy adults. Intestinal calcium absorption is dramatically decreased when vitamin D deficiency occurred. This results in a transient reduction in ionized calcium concentration in the blood that is immediately sensed by the calcium sensor in the parathyroid glands leading to the enhanced secretion of PTH into the blood. As such, PTH enhances the renal tubular reabsorption of calcium and modulates the osteoblasts to increase the expression of RANKL which in turn improves the production of osteoclasts to remove calcium stores from the skeleton. It also increases the kidney secretion of 1,25(OH)2D which in turn transports to the bone and intestine to modulate calcium metabolism. The elevated level of PTH also causes internalization of the sodium-phosphorus cotransporter leading to the loss of phosphorus into the urine [15, 24].

Vitamin D deficiency among children during childhood leads to poor mineralization of the skeletal matrix and contributes to a wide range of skeletal deformities related to rickets such as bowed or knocked knees, rachitic rosary, widened epiphyseal plates at the end of the long bones, and frontal bossing. In older children, it prevents the attainment of the maximum amount of calcium that can be deposited into their skeletons based on their genetic makeup. In addition, vitamin D insufficiency among children leads to osteomalacia. Opposite to osteoporosis, which is an asymptomatic disease, osteomalacia has symptoms including bone pain and muscle weakness that is often misdiagnosed as fibromyalgia, chronic fatigue syndrome, or depression. The mineralization defect is due to the phosphaturic influence of PTH. It decreases the serum phosphorus level to be in the low normal or low range as a result of inadequate calcium-phosphorus secretion for sufficient bone mineralization [25, 26]. In adults, vitamin D deficiency and secondary hyperparathyroidism increase the loss of mineral and matrix which can cause osteopenia, osteoporosis, and an increased risk of fracture. In addition, vitamin D has a wide range of actions that include cell differentiation, apoptosis, antiproliferation, immunosuppression, and anti-inflammation [18, 27].

Mounting evidence suggests that hypovitaminosis D is linked to an increased risk for autoimmune diseases, diabetes, and cardiovascular diseases [28], indicating the importance of sufficient vitamin D levels. In addition, vitamin D deficiency has been linked to an increased risk for several types of cancer including prostate, colon, ovarian, and breast cancer [29]. However, the daily intake of vitamin D for the prevention of those adverse effects is recommended.

However, in this chapter, we focus on the role of vitamin D in three important phases of reproductive women's life span including menarche and adolescence, reproductive period, and menopause. Then, we discuss the role of vitamin D in male fertility.

2. Vitamin D status in adolescent

There is mounting evidence that adolescents are at risk for poor vitamin D status. Since vitamin D is critical for optimal bone mineral accrual in the developing skeleton, poor vitamin D status in adolescence is a matter of concern. In vitamin D deficiency status, calcium homeostasis due to parathyroid and renal regulation at the expense of bone is maintained. In a growing child or adolescent, the lack of calcium accumulation in the skeleton can have negative impact for the attainment of peak bone density [30, 31]. Despite evidence indicating the crucial role of vitamin D in many physiological functions, maintaining adequate vitamin D status in adolescents is challenging in today's food and living environment. It is reported that only 50% of girls (aged 9–13 years) and 32% of girls (aged 14–18 years) are meeting the Dietary Reference Intake (DRI) recommendation for vitamin D (200 IU/d or 5 mg/d) [32]. In adolescents, vitamin D deficiency leads to decreased dietary calcium absorption, altered formation of the growth plate, and defective mineralization of the skeleton, resulting in rickets. Also, it has been determined that subclinical vitamin D deficiency may also result in secondary hyperparathyroidism, lower serum calcium, increased serum alkaline phosphatase, and increased risk of bone abnormalities [33]. A positive correlation between bone mineral density (BMD) and 25(OH)D levels in previous studies supports the important role of vitamin D in protecting adolescent bone [34]. In addition, obesity is a major health problem among children and adolescents. Interestingly, a number of studies have supported the potential role of vitamin D in the modulation of obesity, energy metabolism, and insulin resistance in adolescent and children [35].

Also, vitamin D receptor is expressed in calcium-regulated tissues, including the ovary, and it appears to be necessary for full ovarian functions which indicate that vitamin D plays a key role in estrogen biosynthesis potentially via the maintenance of extracellular calcium concentrations and by direct regulation of aromatase gene expression. This point is discussed later on.

One needs to be aware of the high prevalence of calcium and vitamin D insufficiency in the adolescent age group, and make assessment and management of vitamin D deficiency as the component of routine adolescent health care.

2.1. Vitamin D and puberty (the potential role of vitamin D in hypothalamic hypophyseal ovarian axis)

Puberty is a time of dramatic developmental changes during which a child's body progresses through a sequential set of stages to reach mature adult reproductive function. Although genetic factors play an important role in the timing of puberty, it is well documented that environmental factor may have an effect to the current change in pubertal progression [36]. In this respect, a geographic north-south-gradient effect on age at menarche [37] was proven; young women who live at higher latitudes seem to experience an earlier onset of menses than adolescents who live near to the equator [37]. Although, the time of menarche are influenced by temperature, sun light and socioeconomic situation, but this time also related to the geographic gradient with the especial sun exposure, coincided with vitamin D status [38].

Recent studies reported that vitamin D status was associated with the timing of menarche. Mechanistic explanations of an effect of vitamin D deficiency on early menarche are speculative. However, it is suggested that vitamin D deficiency is associated with the development of adiposity in children [39], and childhood obesity could be a risk factor for early puberty [38]. Thus, vitamin D status could indirectly affect the timing of menarche through its effect on obesity. Biochemical pathways might involve adipose-derived hormones. Some studies indicated that the serum level of leptin increases at early puberty; however, vitamin D is negatively associated with leptin concentrations, but it is unclear whether the leptin or other adipokines derived from adipose tissue could alter in response to vitamin D supplementation [40–42].

Meanwhile, there is possible mechanism involved in the correlation of VD insufficiency with early onset of menarche which is not related to obesity. Insulin-like growth factor-1 (IGF-I) is one of the growth factors which may regulate the timing of puberty and puberty regression by inducing the gonadotropin-releasing hormone (GnRH) pulse, gonadotropin, and sex hormone [43]. It is showed that IGF-I increased the expression of gonadotropin-releasing hormone *in vitro* [43–45].

However, vitamin D receptors have been shown in different parts of the brain including the hypothalamus [46]. Therefore, it is possible that vitamin D plays other unknown roles in the neuroendocrine regulation of the gonadotropic axis [47].

In conclusion, vitamin D status was positively related to age at menarche, and vitamin D insufficiency was associated with earlier menarche. In regard to the serious problems associated with early menarche, the simple inexpensive medication such as vitamin D supplementation may be essential, which is needed to be studied in a randomized trial.

3. Vitamin D and female reproductive system: health implications of vitamin D deficiency in female reproduction

The secosteroid hormone of vitamin D regulates the expression of a large number of genes in reproductive tissues implicating a role for vitamin D in female reproduction. Human and animal data suggest that vitamin D plays an important role in female reproduction. It is demonstrated that VDR is located in several tissues including the immune system, the endocrine system, and the reproductive system [5]. As such, VDR is distributed among nuclei and cytoplasm of granulosa cells of human ovaries which shows that vitamin D is involved in the physiologic functions of ovarian follicles [48]. Also, it is well documented that VDR mRNA is expressed in the ovarian cell and in a purified granulosa cell culture [49]. The expression of VDR in female reproductive organ indicates that vitamin D is involved in female reproductive function.

In this respect, vitamin D deficiency is related to subfertility, endometriosis and polycystic ovary syndrome (PCOS), preeclampsia, preterm delivery, gestational diabetes, and bacterial vaginosis. However, the definition of optimal vitamin D levels in the reproductive period

and the determination of the best dose of vitamin D supplementation need to achieve those levels for several actions of vitamin D through a woman's life are important public health implications.

Current research on the role of vitamin D in earlier age at menarche, fertility impairments, polycystic ovary syndrome, uterine fibroids, endometriosis, maternal, and neonatal adverse outcome even improper semen parameters in the case of *in vitro* treatments suggests that vitamin D deficiency plays an important role in human reproduction processes. Here, in this section, we summarize the recent evidence that vitamin D status influences female reproductive system.

3.1. Vitamin D and ovaries

The physiological role of vitamin D in human reproduction and ovarian steroidogenesis is not well understood. There are several animal studies suggesting the importance of vitamin D in reproduction. It seems that vitamin D induces secretion of progesterone, estrone, and estradiol secretion in ovarian cells independently and, in the case of estradiol, synergistically with insulin. Vitamin D also enhances IGFBP-1 secretion. It is described subsequently.

3.1.1. Vitamin D and follicular development

Recently, it has been shown that vitamin D plays an important role in human follicular development. Vitamin D could downregulate anti-Müllerian hormone (AMH) gene (as the best markers for ovarian reserve) and upregulated FSHR gene expression. An explanation of these findings is as follows: During a women's follicular phase, the follicle that contains the most number of FSH receptors, therefore that is most sensitive to FSH, emerges as dominant at the time of inter-cycle FSH rise during the follicular phase. By inhibiting AMH expression, vitamin D may counteract the repressive effects of AMH on granulosa cell differentiation, thereby allowing follicles to reach terminal maturation and ovulation. A reason for the conflicting results seen between prostate cancer cell line studies (where vitamin D was found to downregulate AMH gene) and granulosa cell studies could be explained by differences in sex and species. In human luteinized granulosa cells, vitamin D decreased AMHR-II and FSH-receptor (FSHR) gene expression. Following follicular selection in a women's late follicular phase, the follicle becomes less dependent on FSH and more dependent on LH, followed by terminal maturation and ovulation. Similar to AMHR-II, FSHR expression in granulosa cells has been found to be the highest in small immature follicles and gradually diminishes during folliculogenesis. FSHR expression decreases along with the progression of maturation of oocytes after human chorionic gonadotropin (hCG) administration. It is not clear if the mechanistic effect of vitamin D on FSHR is happening via AMH signaling. It is well documented that there is an interaction and strong positive correlation between AMHR-II and FSHR gene expression in humans. It could be that vitamin D alters common intracellular mechanistic pathways involved in the regulation of both AMHR-II and FSHR. Clearly, a complicated interrelationship exists between these parameters. These findings suggest that vitamin D might promote the differentiation and development of human granulosa cells [50–54].

Of importance is the fact that there is a seasonal variation in serum AMH (being 18% lower in the winter than in the summer) that correlated with changes in seasonal serum 25OH-D. Also, 25-dihydroxyvitamin D3 supplements were sufficient to block the seasonal changes in both 25OH-D and AMH levels [55].

3.1.2. Vitamin D and steroidogenesis

All sex hormones are derived from cholesterol as the common precursor, which can be obtained through dietary sources or synthesized *de novo* from acetyl CoA. Sex hormone production is controlled by multiple enzymes. There are growing literature body suggesting that vitamin D affects the expression and activity of some of these enzymes. For example, it is reported that the treatment of human granulosa cells with 1,25-dihydroxy vitamin D3 *in vitro* increased progesterone production in the presence of the precursor substrate pregnenolone [54]. Also, it has been shown that vitamin D increased progesterone, estrogen, estrone, and insulin-like growth factor-binding protein 1 production in human ovarian cells. Moreover, 1,25-dihydroxyvitamin D3 stimulated estrogen and progesterone production in human placenta [56].

However, two of these steroids are explained particularly as follows:

- *17β-hydroxy steroid dehydrogenase (17β-HSD):* the biological active form of androgens and estrogens are biologically active in their 17β-hydroxy configuration. As well, 17-oxo derivatives are not capable to bind to their receptors. The ribozymes is the convertor enzyme which is one of the 17β-hydroxy steroid dehydrogenase (17β-HSD) families. These isozymes modulate intracellular level of steroid hormones in target tissues [57]. However, vitamin D application *in vitro* increased 3β-HSD mRNA levels and progesterone production. These suggest that vitamin D may play a role in enhancing certain key steroidogenic enzymes such as 3b-HSD. During the normal menstrual cycle, luteinized human granulosa cells usually form the corpus luteum which produces large amounts of progesterone (and some estrogens) and induces endometrial changes such as decidualization to support a pregnancy. Literature suggests that 1,25-dihydroxyvitamin D3 may potentiate granulosa cell luteinization as reflected by increased progesterone production, thus providing a better endometrial environment. Whether this is clinically relevant still needs to be determined *in vivo* [50].
- *Aromatase:* Aromatase is an estrogen synthetize, which catalyzes estrogen biosynthesis from androgen precursors. Aromatase is found in several tissues including the ovaries, liver, breasts, brain, and adipose tissue [58–60].

3.1.3. Vitamin D and ovarian reserve

According to recent evidences, in the serum the positive correlation exists between circulating vitamin D and ovarian reserve markers, particularly anti-Müllerian hormone as the best predictor of ovarian reserve.

Gonadal-specific glycoprotein of AMH is a kind of transforming growth factor (TGF) superfamily. In men, sertoli cells produce the AMH during male fetal sex differentiation which stimulates the regression of the Müllerian ducts [61]. In women, AMH is secreted by

granulosa cells in growing primary and prenatal follicles but does not produce until near birth. Slight variations in AMH concentration during the menstrual cycle and its unique secretion by growing ovarian follicles make it a suitable predictive indicator for assisted reproductive technology (ART). However, some studies have been reported that environmental factors including vitamin D deficiency may change its expression and serum concentration [54, 62, 63]. The fact that vitamin D supplementation prevented the seasonal changes in serum AMH strongly indicates that AMH production in adults may be regulated by vitamin D. Thus, the assessment of vitamin D status, theoretically, might be considered as part of the routine workup in infertile women. Additionally, appropriate supplementation of patients with vitamin D deficiency might translate to better ovarian reserve markers and better ovarian follicular dynamics. However, most of the studies to date used markers of ovarian reserve/function rather than pregnancy as an outcome, which limits the translational significance of the findings [50].

3.2. Vitamin D and fertility

A seasonal distribution in human natural conception and birth rates has been consistently demonstrated, showing a peak conception rate during summer in northern countries with strong seasonal contrast in luminosity [64].

Some studies have demonstrated that the low level of vitamin D leads to a 75% decrease in fertility of female rats which is associated with 50% reduction in fecundation and enhancement of the probability of complications during pregnancy [65]. Also, vitamin D deficiency may lead to uterine hypoplasia and impaired folliculogenesis [66]. In this respect, vitamin D modulates estrogen biosynthesis through the maintenance of calcium homeostasis [65, 67]. It is shown that infertility was a secondary consequence of the low level of calcium rather than a direct result of the non-functional VDR [67, 68]. The indirect consequence of vitamin D deficiency on fertility through the regulation of calcium level in reproductive organ was also shown by literature in diet-stimulated vitamin D–deficient animals, in which both vitamin D and a diet supplemented with high levels of calcium repaired fertility. As such, some studies have been reported that the low level of vitamin D itself and not hypocalcemia is responsible for subfertility in vitamin D–deficient rats, exposed to different levels of serum calcium and phosphorus [68, 69]. Different studies have examined the role of vitamin D in a spectrum of female reproductive system disorders, such as adverse effect on pregnancy, endometriosis, and subfertility treated by IVF and PCOS.

3.3. Vitamin D and pregnancy: adaptations and metabolism during gestation

During pregnancy and lactation, there is an increase in the rate of synthesis and plasma levels of active form of vitamin D, which presumably functions to increase the intestinal absorption of calcium and the mobilization of maternal bone. The human embryos consume 30 g of calcium. More than 99% of this calcium is contained within the skeleton. Nearly 150 mg/kg/day of this calcium is transferred by placenta during the last trimester [70]. Serum protein-bound and complexed fraction calcium levels decrease during pregnancy due to the decrease in serum albumin. This physiological decrease is not an evidence of

real hypocalcemia. The physiologically active form of calcium, ionized calcium, does not change during pregnancy. Parathyroid hormone decreases to the lower limit of the normal range and can become undetectable. Serum levels of other hormones potentially regulate the calcium including estradiol, prolactin, human placental lactogen (hPL), and parathyroid hormone-related protein (PTHrP), and they increase during pregnancy [70]. Doubling the amount of intestinal calcium absorption starting early in pregnancy seems to meet the fetal requirement for calcium. Skeletal resorption can also provide mineral to the blood, but evidence is controversial on whether the maternal skeleton contributes considerable amounts of calcium to the fetus. In this respect, bone resorption indicators are enhanced during pregnancy. The maternal kidneys do not reclaim calcium avidly during pregnancy; instead, urinary calcium excretion increases in parallel with the increase in intestinal calcium absorption [70]. Ionized calcium levels are stable until third trimester of pregnancy. PTH is decreased early in pregnancy but can increase in the third trimester of pregnancy. Skeletal mineral enhances in early pregnancy. It is well known that vitamin D deficiency is prevalent among pregnant women. Decrease of plasma vitamin D could contribute to the reduction in plasma calcium level during pregnancy and may result from increased maternal metabolism or enhanced utilization of vitamin D by the fetus [71]. Moreover, maternal low level of vitamin D might be independently correlated with an increased risk for gestational diabetes mellitus (GDM), preeclampsia, and small-for-gestational age (SGS) births [72–74] as well as with offspring rickets [75]. 25-hydroxyvitamin D [25(OH)D], the storage form of vitamin D, easily could pass from placentas in rats [76] and probably crosses the hemochorial human placenta easily. As well, the cord blood 25(OH)D levels are similar to or up to 20% lower than maternal level [77]. Thus, neonates with an adult level of normal 25(OH)D, their mothers have the sufficient level of vitamin D. Maternal transient of 25(OH)D to fetus could decrease maternal levels, especially if the mother has normal and adequate vitamin D concentration, whereas some studies have been demonstrated that either no change or a modest decrease in maternal 25(OH)D levels during pregnancy. The low fetal level of 1,25(OH)2D shows the low fetal PTH and high phosphorus level, which suppress renal 1α-hydroxylase. Although PTHrP is increased in the fetal blood circulation, it seems to be less able to induce the renal 1α-hydroxylase than PTH [78, 79].

The total serum level of 1,25(OH)2D doubled or tripled in the maternal circulation starting in the first trimester of pregnancy, but studies have only shown increased free concentrations during the last trimester. This elevation is due to maternal synthesis by the renal 1α-hydroxylase.

In addition, intestinal calcium absorption doubles in humans and rodents early in pregnancy, well before free 1,25(OH)2D concentrations increase late in pregnancy [80].

3.4. Vitamin D and maternal outcomes in pregnancy

It is shown that during pregnancy, vitamin D deficiency has been related to increased risks of adverse pregnancy outcome including gestational diabetes, recurrent pregnancy loss (RPL), preeclampsia, and small-for-gestational-age babies (**Figure 2**).

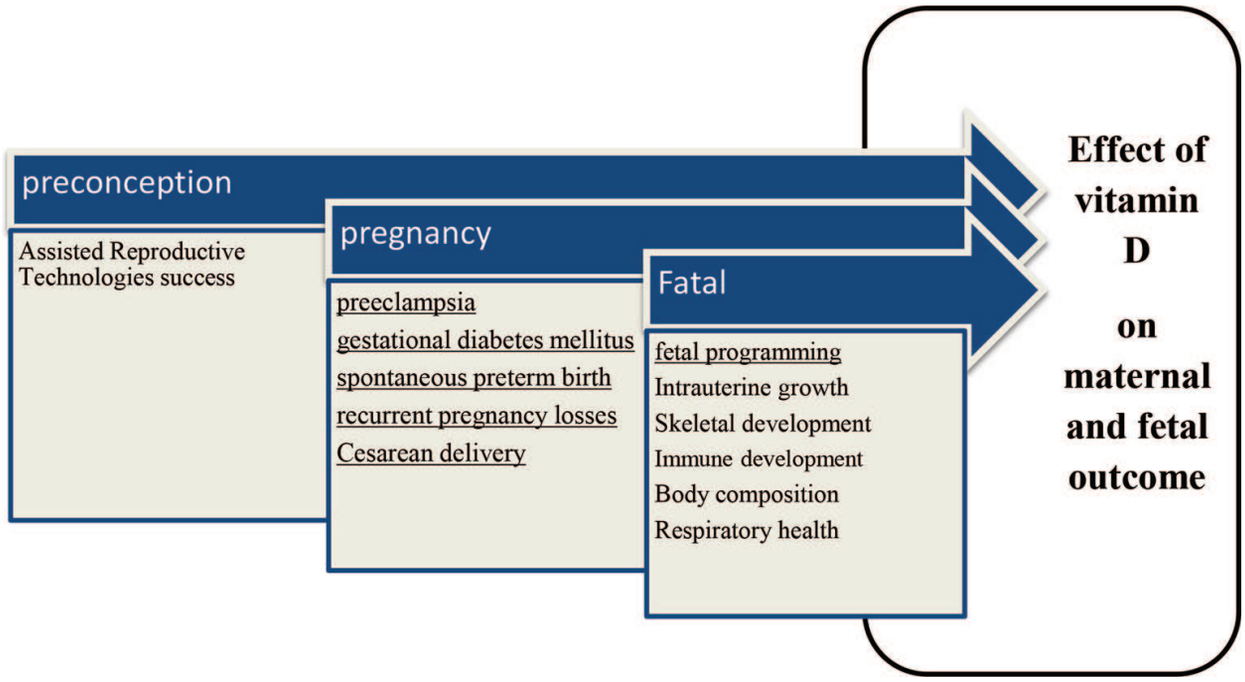

Figure 2. Serum level of vitamin D and pregnancy outcome.

3.4.1. Maternal plasma vitamin D levels and preeclampsia

Preeclampsia is a pregnancy-induced multi-systemic problem characterized by *de novo*-onset hypertension and proteinuria after 20 weeks of gestation which is prevalent in 2–8% of all pregnancies. It is one of the major acute and long-term health risks for maternal and perinatal mortality and morbidities [81, 82]. The underlying etiologies of preeclampsia are not completely understood. It has been hypothesized that abnormal trophoblastic invasion, oxidative stress, inflammatory responses, and endothelial dysfunction are possible contributing factors [83]. Maternal low level of vitamin D is so prevalent during pregnancy and is a kind of worldwide public health problem [84, 85]. As we state before, vitamin D effects on placental function and inflammatory response [86]. Recently, epidemiological studies have demonstrated an association between low maternal vitamin D status during pregnancy and the incidence of preeclampsia and suggest that vitamin deficiency may be an independent risk factor for preeclampsia [74, 87].

However, the underlying mechanisms remain unknown. Vitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction. Proinflammatory cytokines such as tumor necrosis factor-a, interleukin-6, and interferon-c have been reported to be increased in pregnancies with vitamin D deficiency. The molecular mechanisms involving hypovitaminosis D in endothelial dysfunction might be regulated, in part, by proinflammatory transcription factor nuclear factor-κB (NF-κB), as a major proinflammatory nuclear transcription factor, and interleukin-6, low VDR, 1α-hydroxylase, and hypocalcemia [88]. The endothelial cell expression of NF-κB and interleukin-6 and downregulation of NF-κB were more in the low level of vitamin D. Interleukin-6 expression in endothelial cells was strong negatively associated with 25(OH)D [89].

The levels of other circulating proinflammatory cytokines, including tumor necrosis factor-a33and C-reactive protein (CRP), are inversely associated with serum level of 25(OH)D [90]. Oxidative stress is elevated in vitamin D deficiency. Vitamin D supplementation could reverse this effect. High levels of thiobarbituric-acid-reactive substances, which indicate lipid peroxidation, have been shown in women with low level of vitamin D [91]. Endothelial cell damage or dysfunction appears to be a basic pathophysiological event of the maternal vascular system in women with preeclampsia [89, 92]. Maternal low level of vitamin D may influence a proinflammatory response, enhancement of oxidative stress, and lead to endothelial dysfunction and finally preeclampsia [93]. As such, some evidence demonstrates that vitamin D affects the genes responsible for trophoblast invasion and angiogenesis critical for implantation that appears to be implicated in the pathophysiology of preeclampsia [87]. Although calcium and vitamin D supplementation in pregnancy was associated with a significant reduction in blood pressure, the effect of intervention on the incidence of preeclampsia is controversial. In this respect, more research is needed.

3.4.2. Vitamin D and small-for-gestational age

Fetal growth restriction, most often estimated by the incidence of a birth weight that is small-for-gestational age, is a major public health issue across the globe. Infants suffering from SGA have a higher risk for serious neonatal morbidities and mortalities among infancy into adulthood. Growth restriction is related to a wide range of maternal factors including nutritional status, obesity, age, smoking, and infection, although there are insufficient effective interventions for prevention [94]. Several observational studies have linked maternal 25(OH)D concentrations and the risk of SGA in general obstetric populations [95]. It has been shown that maternal second trimester vitamin D status was inversely associated with the risk of SGA in singleton pregnancies.

The biologic mechanism that may connect maternal vitamin D status to fetal growth remains elusive. A plausible mechanism for the impact of maternal vitamin D on fetal growth is placental vascularization, which has received considerable attention in its association with fetal growth [96, 97]. Vitamin D has several biologically possible roles in fetal growth. In this respect, the vitamin D–activating enzyme CYP27B1 and VDR are expressed in human placenta [98]. The active form of vitamin D, 1,25-dihydroxyvitamin D, which acts through the VDR and the cAMP/protein kinase A (PKA)-signaling pathway, modulates human chorionic gonadotropin production in human syncytiotrophoblast and enhances placental sex steroid secretion. Vitamin D is also essential in glucose and insulin metabolism in glucose availability for transplacental transport and fetal use. As a regulator of calcium homeostasis and transport, calcitriol also can effect on fetal growth directly due to impacts on skeletal muscle and bone growth and development [56, 99].

In addition, several observational studies have connected poor vitamin D status with a higher risk of preeclampsia, which, like fetal growth restriction, has placental origins related to angiogenesis and uterine blood flow [97]. Vitamin D deficiency makes labyrinth of placental vessels narrower, indicating dysregulated vascularization [100].

Also, it is suggested that fetal VDR gene may play a role in the regulation of fetal growth. It is observed that sequence variation in the VDR gene modified the effect of maternal vitamin D deficiency on infant size at birth. Low 25(OH)D concentrations were associated with lower-birth-weight infants only among infants that were either homozygous for the *Fok*I major allele or heterozygotes [95].

More basic science research is needed in this area as well as studies with multiple measurements of fetal growth and placental vascularization.

3.4.3. Vitamin D and gestational diabetes mellitus

Gestational diabetes mellitus is one of the most prevalent disorders which have long-term consequence for the health of mothers and their children. It can increase the risk of developing type 2 diabetes, while their children may be at risk of obesity and diabetes later in life [101].

Polymorphisms of vitamin D have been related to insulin release and glucose tolerance [102]. A genetic influence of CYP27B1 polymorphisms may modulate 25(OH)D3 concentration in gestational diabetes patients [103]. Recent evidence from meta-analysis indicated a significant inverse relation of serum 25OHD and the incidence of GDM [104]. It is reported that 25(OH) D3 levels of <50 nmol/l at 16 weeks of gestation before the onset of GDM were associated with a 2.7-fold increased risk for the development of GDM later in pregnancy independent of measured confounders [72]. There are several mechanisms that explain the association between vitamin D deficiency and gestational diabetes risk: (i) vitamin D could directly or indirectly regulate pancreatic β-cell function and production by binding its circulating active form, 1,25-(OH)D, to β-cell vitamin D receptor and controlling the balance between the extracellular and intracellular β-cell calcium pools [105, 106]. (ii) Vitamin D can stimulate insulin sensitivity by inducing the expression of insulin receptors and increasing insulin responsiveness for glucose transportation. It also controls extracellular calcium to ensure normal calcium entry through cell membranes and a sufficient intracellular cytosolic calcium pool, which is crucial for insulin-mediated intracellular processes in insulin-responsive organs [72]. Finally, (iii) it is probable that the negative association of 25-[OH] D concentration with GDM risk shows the impact of other components of major endogenous and exogenous sources of vitamin D on glucose homeostasis due to other mechanisms. For instance, endogenous secretion of vitamin D in the skin with the sun exposure is a main source of plasma vitamin D. Sun exposure could be positively associated with outside home physical activity, a protective factor for insulin resistance, impaired glucose tolerance, and GDM [107].

However, randomized controlled trials (RCTs) of vitamin D supplementation, initiated early in pregnancy, are now required to demonstrate whether vitamin D supplementation might reduce the incidence or severity of GDM.

3.4.4. Vitamin D and spontaneous preterm birth

Spontaneous preterm birth (SPB) happens before 37 weeks of gestation. Intrauterine infection and inflammation is one of the main factors underlying this disorder. One important

factor is bacterial vaginosis, which could disturb the normal balance of vaginal flora with enhanced growth of anaerobic bacteria responsible for the secretion of inflammatory cytokines, prostaglandins, and phospholipase A2 [108]. In this respect, studies have shown a linear inverse association between maternal vitamin D status and the prevalence of bacterial vaginosis among pregnant women [109–111]. Vitamin D has immunomodulatory and anti-inflammatory effects, including the control of the secretion and function of cytokines and neutrophil degranulation products that is important and relevant to prevent microbial invasion which may have a protective effect on SPB risk [27, 112]. Several cells of the immune system express VDRs and are regulated by vitamin D [113]. Although vitamin D function adjusts the activation of the acquired immune system in response to autoimmunity, it has key role to increase the innate immune system. It is involved in cell-mediated immunity by decreasing the secretion of inflammatory cytokines including IL-1, 6 and TNF-α that are involved in SPB [114, 115].

Human decidual cells are capable to synthesize the active form of vitamin D. Therefore, some studies demonstrated that vitamin D is involved in the modulation of acquired and innate immune responses at the fetal-maternal interface across gestation [116]. Vitamin D might decrease the risk of SPB also by helping to maintain myometrial quiescence. Myometrial contractility is related to calcium within the muscle cell and this process is manipulated by vitamin D [117]. The prevalence of SPB was lowest among women who conceived in summer and fall and was highest among winter and spring conceptions [118] and vitamin D supplementation in early pregnancy may protect against preterm birth [119]. More large studies are awaited to validate these important findings that might represent vitamin D supplementation as a simple and inexpensive method to reduce the risk of this adverse pregnancy outcome.

3.4.5. Vitamin D and recurrent pregnancy losses

Recurrent pregnancy loss is a devastating reproductive problem affecting approximately 5% of couples trying to conceive [120, 121]. RPL is typically defined as two or three or more consecutive pregnancy losses. Genetic, hormonal, metabolic, uterine anatomical, infectious, environmental, occupational and personal habits, thrombophilia, or immune disorders were reported as possible etiologies [121]. Despite the many etiologies, a majority of women with recurrent miscarriage have no discernible cause. It has been postulated that immunologic aberrations may be the cause in many of such cases.

Tissue responses to vitamin D include the regulation of hormone secretion, the modulation of immune responses, and a control of cellular proliferation and differentiation [122]. Vitamin D could inhibit the proliferation of T helper 1 (Th1) cells and limit the secretion of cytokines, such as interferon gamma (IFN-g), interleukin-2 (IL-2), and tumor necrosis factor-alpha (TNF-a). Also, vitamin D stimulates T helper 2 (Th2) cytokines, such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 [123]. Furthermore, in many studies vitamin D has been presented as a modifiable environmental factor for Th1-mediated autoimmune disease and appears to be important for susceptibility to and severity of the disease. Vitamin D also regulates B-cell immunity. It downregulates the proliferation and differentiation of B lymphocytes and inhibits IgG production [123].

With these immune-regulatory effects of vitamin D, it has been hypothesized that vitamin D could regulate immune response during implantation. In early pregnancy, trophoblasts secrete and respond to vitamin D, which influences local anti-inflammatory responses and stimulates decidualization for successful pregnancy [124]. A dominant Th2 immune response is important to maintain maternal-fetal relationship for successful pregnancy. By contrast, autoimmunity and dysregulated cellular immune reactions may be responsible for immunological alterations leading to recurrent pregnancy losses (RPL). High proportion of women with RPL has vitamin D deficiency, which is associated with increased cellular and autoimmunity. Women with RPL have increased prevalence of various autoantibodies, such as APA, ANA, and TPO antibody [124]. Vitamin D was shown to prevent autoimmune thyroiditis by inhibiting lymphocyte proliferation and secretion of inflammatory cytokines [125].

Low vitamin D appears to be important for autoimmune disease susceptibility and severity and vitamin D deficiency was associated with an increased presence of autoantibodies [126] via B-cell hyperactivation and autoantibody production [127]. It can be inferred that vitamin D plays a role in regulating B-cell proliferation and function during successful pregnancy.

Several studies have reported a link between RPL and altered cytotoxicity and level of peripheral natural killer (NK) cells [128]. Preconception evaluation of NK cell activity in women with RPL has been reported to predict pregnancy outcome of the subsequent pregnancy [128]. Furthermore, elevated peripheral NK cells in pregnant women predict spontaneous abortions with normal karyotype in index pregnancy. Recently, increasing evidence supports a novel immune-regulatory role of vitamin D [129]. Vitamin D and NK cytotoxicity seem to have a direct inverse relationship, which might associate with RPL. Vitamin D may be regulating the NK cell population and cytotoxicity. Elevation of NK cell and/or cytotoxicity is risk factor for abortion.

Briefly, the high prevalence of hypovitaminosis D was detected among women with RPL. Vitamin D deficiency has immunological function in RPL. Vitamin D is related to B- and NK-cell immunity and Th1/Th2 balance, and vitamin D deficiency leads to a tendency to develop APA and other autoantibodies, which are associated with autoimmune disease and adverse reproductive outcome. Therefore, the assessment of vitamin D status is very important in women with RPL and autoimmune or cellular immune abnormalities. As such, vitamin D–deficient women have significantly increased risk for autoimmune abnormalities that is a risk factor for RPL and infertility. NK-cell cytotoxicity and Th1 polarization were significantly decreased *in vitro* by vitamin D, and vitamin D decreased perforin production and polarization in NK cells. Also, vitamin D suppressed type 1 cytokine secretion and increased type 2 and growth factors from NK cells. So, these results raise the likelihood that vitamin D could be available as a new therapeutic choice for RPL and infertility [124]. Further study is required to elucidate immune-regulatory function of vitamin D.

3.4.6. Vitamin D and mode of delivery

Serum calcium status, which is regulated by vitamin D, plays a role in smooth muscle function in early labor [130]. It was speculated that the higher serum calcium levels played a role in the mechanism of the initiation of labor [130].

An inverse association with having a primary cesarean section and vitamin D deficiency is shown. Severe vitamin D–deficient women with levels of 25(OH)D3 of <37.5 nmol/l delivered nearly four times as often by cesarean section than those with 37.5 nmol/l or greater (odds ratio (OR): 3.84) [131]. Because vitamin D is essential for the maintenance of calcium homeostasis, it is possible that the low level of vitamin D, which leads to modest lowering of the serum calcium, is associated with both skeletal muscle and smooth muscle strength and may have a role in the initiation of early labor. Poor maternal vitamin D status might reduce the strength of the pelvic musculature and the mother's ability to push and deliver vaginally [132]. Also, vitamin D status is associated with preeclampsia [123] and gestational diabetes [133], which may increase the odds of cesarean [134]. It is also suggested that the low level of vitamin D is associated with cesareans due to cephalopelvic disproportion or failure to progress, although there is some controversy.

However, it should be noted that intravenous hydration would have diluted the blood and artificially imitate the lower level of 25(OH) D. However, the volume of intravenous fluids associated with blood loss is essentially the same.

However, vitamin D status and the mode of delivery should be examined and therefore the issue needs further investigation.

3.4.7. Vitamin D and fetal programming

Vitamin D stimulates more than 3000 genes. Several of them play a role in fetal growth and development [135]. It might be possible that vitamin D may be specifically relevant to the fetal programming indicating that vitamin D as an environmental factor may influence the genomic programming of fetal and neonatal development and following disease risk in childhood and adult life [136]. In this respect, in later life, mother and child who suffered from vitamin D deficiency during pregnancy suffer more often from chronic diseases such as wheezing and asthma [137, 138], schizophrenia [139], multiple sclerosis [140], type 1 diabetes mellitus, and insulin resistance [141, 142]. Mechanisms underlying this long-term effect of the intrauterine environment are not known [143–145] yet, but epigenetic mechanisms that lead to persistent changes in structure and function in endocrine systems are hypothesized [101].

3.4.8. Vitamin D and infertility

Infertility is a complex disorder with significant medical, psychosocial, and economic aspects, which affects about 15% of couples [146]. In accordance with preview findings, vitamin D deficiency has emerged as a factor that influences female infertility. The role of vitamin D in reproduction processes and its significance in infertility therapy covering topics of polycystic ovary syndrome, endometriosis infertility, myoma infertility, male infertility, premature ovary failure, and *in vitro* fertilization (IVF) techniques will be discussed.

3.4.9. Vitamin D and polycystic ovary syndrome

PCOS is one of the most common female endocrinopathies in reproductive-aged women [147, 148] which is characterized by elevated ovarian and adrenal androgen production,

hyperandrogenic symptoms such as hirsutism, acne and/or alopecia, irregular menstruation, and polycystic ovaries morphology [149]. Women with PCOS typically produce an increased number of oocytes, often of poor quality, resulting in lower fertilization and implantation and higher miscarriage rate. In addition, insulin resistance is common in PCOS women who are therefore at an increased risk of type 2 diabetes [150, 151]. PCOS is the most common cause of anovulatory infertility in women [152].

There might be a relationship between vitamin D deficiency and PCOS phenotype. In this respect, several studies have demonstrated that vitamin D deficiency is more common in women with PCOS compared with control women [153, 154]. Also, vitamin D deficiency might be a contributing factor to insulin resistance, obesity, and metabolic syndrome, all of which are commonly observed in PCOS and associated with ovulatory dysfunction [151]. Interestingly, vitamin D supplementation might improve menstrual irregularity, follicular development, and pregnancy rate in women with PCOS [155, 156]. The mechanisms underlying the association of low 25(OH)D levels with PCOS are not fully understood. It is briefly discussed in the subsequent text:

- *Vitamin D and insulin resistance and obesity*: There is some evidence suggesting that vitamin D deficiency might be involved in the pathogenesis of insulin resistance and the metabolic syndrome in PCOS [157]. Several studies have shown that there is an inverse correlation between 25OH-D and IR, obesity, and free androgen index [154, 158]. Additionally, several studies have shown that vitamin D supplementation might improve IR and reduce serum androgens [159]. The mechanisms underlying the association of low 25(OH)D levels and insulin resistance are unclear. As obesity is related to insulin resistance in PCOS [160], it may contribute to low circulating vitamin D levels by trapping vitamin D in fat tissues. There are some mechanisms explaining the correlation between low level of vitamin D and insulin resistance. Vitamin D may have a positive influence on insulin action by inducing the expression of insulin receptors and so increasing insulin responsiveness for glucose transport [161]. In addition, vitamin D modulate extracellular and intracellular calcium which is necessary for insulin-mediated intracellular processes in insulin-responsive organ including skeletal muscle and adipose tissue. Moreover, changes in calcium flux can have negative effects on insulin production, which is a calcium-dependent process.
- *Vitamin D and sRAGE*: Advanced glycation end products (AGEs) have been shown to be involved in the pathogenesis of PCOS, and their serum levels are elevated in women with PCOS. AGEs accumulate in ovarian theca and granulosa layers of women with PCOS. This accumulation may be implicated in worsening ovarian follicular growth [162, 163]. However, significant increase in serum 25OH-D following replacement was associated with a significant increase in receptor for advanced glycation end product (sRAGE) levels, and a significant decrease in the abnormally elevated serum AMH levels that are usually observed in PCOS. The increase in sRAGE is usually beneficial because it binds circulating AGEs and inhibits their inflammatory deleterious effects. Lower serum AMH level in PCOS might potentially improve the ovulatory process because it decreases intrafollicular androgens and increases follicular sensitivity to FSH [164, 165].

- *Vitamin D receptor polymorphism and PCOS*: Vitamin D receptors modulate more than 3% of the human genome, including genes that are fundamental for glucose metabolism. In this atmosphere, it has been reported that VDR-related polymorphisms (Cdx2, Bsm-I, Fok-I, Apa-I, and Taq-I) are associated with vitamin D metabolism and might participate to PCOS susceptibility [166, 167]. It seems possible that variants in the VDR through their effect on luteinizing hormone, sex hormone-binding globulin (SHBG) levels, and testosterone are involved in the pathogenesis of PCOS.
- *Vitamin D and gene product of PCOS*: Phosphoprotein enriched in diabetes gene product (PED/PEA-15), an antiapoptotic protein, has been shown to be overexpressed in insulin resistance, DM type 2, and PCOS. Recent data suggested that the low level of vitamin D may elevate the serum levels of this antiapoptotic protein, contributing to the impairment of the ovarian apoptotic mechanism. In addition, the low level of adiponectin that is present in PCOS has been related to vitamin D concentrations, due to body mass index (BMI)-dependent mechanisms. Further genes involved in vitamin D synthesis, hydroxylation, and transport, and their role in PCOS are currently under investigation [168–170].

3.5. Vitamin D and uterine leiomyoma

Leiomyoma (fibroids) are benign tumors that develop in the uterine muscle of premenopausal women. The most common symptoms are pain and bleeding with associated anemia [171]. Although fibroids are hormonally dependent, factors that stimulate development are largely unknown. Vitamin D status has recently been related to the development of uterine leiomyomas, with observations showing that lower 25(OH)D levels correlate with a higher risk and a greater volume of uterine [171, 172]. Recent studies showed that both myometrial and leiomyoma cells are highly sensitive to the regulatory effect of 1,25-dihydroxyvitamin D3 [173]. The signaling of 1,25(OH)2D3 is mediated via its ubiquitously expressed nuclear receptor, the vitamin D receptor, which is expressed in both the myometrium and endometrium of the human uterus throughout the menstrual cycle [174].

The pathogenesis of fibroids has been hypothesized to involve a positive feedback loop between extracellular matrix production and cell proliferation, and vitamin D might act to block the positive feedback [175]. Vitamin D deficiency may stimulate cell proliferation [176]. The vitamin D [1,25(OH)2D3]-induced antiproliferative action is mediated predominantly through a G1/S phase block of the cell cycle. Because 1,25(OH)2D3 regulates many of the cell cycle–regulatory genes and reduces or increases the kinase activities of cyclin-dependent kinases (CDKs), this results in a decreased number of cells in the S phase and an accumulation of cells in the G0–G1 phase [177]. The cyclin-dependent kinase inhibitors p21 and/or p27 are genomic targets of the 1,25(OH)2D3-VDR complex in many cell types. Also, 1,25(OH)2D3 blocks mitogenic signaling, including that of estrogen, epidermal growth factor (EGF), and insulin-like growth factor 1, and upregulates growth inhibitors such as transforming growth factor β (TGF-β) [178]. In addition, 1,25(OH)2D3 activates VDR-mediated apoptosis [179].

Myometrial and leiomyoma cells are clearly target cells of 1,25(OH)2D3. The data are consistent with the observed expression of VDR protein in the myometrial and leiomyoma tissues

and cultivated cells and with our previous description of VDR mRNA expression in myometrial biopsies [180]. The punctuate pattern of expression within the nuclei of cultured cells has also been observed in other cell types and may display specific binding sites of VDR to target genes [181].

More research is needed to find out whether women with hypovitaminosis D also have more uterine leiomyomas than women with efficient vitamin D supplies.

3.6. Vitamin D and endometriosis

Endometriosis is one of the estrogen-dependent inflammatory problems characterized by the expression of endometrial tissue outside the uterine related to chronic pelvic pain and subfertility. The prevalence of this disorder is 10% of all women and 40% of infertile women. Although endometriosis is not a malignant disorder, disturbances in cellular proliferation, cellular migration, cellular invasion, and neoangiogenesis are common [182]. Endometriosis is dependent on a following complex interaction of immunologic, hormonal, genetic, and environmental factors; however, the etiology of endometriosis is not completely understood [182].

It is documented that the regulatory network of vitamin is involved in the pathogenesis of endometriosis [69]. The higher 25(OH)D levels in women with endometriosis are detected. The proposed associations of vitamin D status and endometriosis are as follows:

I: it has been shown that the VDR and 1a-hydroxylase are expressed in the endometrium [24], suggesting that endometrium is an extra renal site of vitamin D synthesis and vitamin D action which leads to overexpressing of them [183]. It has been shown that VDR and 1α-hydroxylase are expressed in both the orthotopic and ectopic endometria [183].

II: Genetic variation in the VDR could be involved as a potential link between the vitamin D–regulatory network and endometriosis pathogenesis. VDR polymorphism has been investigated as a potential link between vitamin D–regulatory network and endometriosis pathogenesis. It was indicated that VDR dysregulation compromises innate immune response, involving VDR in the pathogenesis of endometriosis. DNA methylation and transcriptional repression signaling have been suggested as the most affected pathways involving VDR dysregulation in women with endometriosis [69]. In this respect, the expressions were the highest in the endometria of women with endometriosis involving the epigenome of steroid hormone response in the pathogenesis of the disease, and also VDRmRNA expression has the upregulation of VDRmRNA expression in the ovarian tissue of patients with endometriosis [184]. DNA methylation and transcriptional repression signaling have been suggested as the most affected pathways involving VDR dysregulation in women with endometriosis, involving the epigenome of steroid hormone response in the pathogenesis of the disease.

III: Vitamin D is involved in the regulation of the immune system, which may be speculated about an influence of vitamin D in the local immune suppression and development of endometriosis. This finding may be explained by an influence of vitamin D on the local activity

of immune cells and cytokines maintaining endometriosis and an insufficiency to activate macrophage's phagocytotic function in those carrying the GC*2 polymorphism.

However, the hypothesis of a beneficial effect of vitamin D supplementation in the treatment of patients with endometriosis has not yet been clinically tested.

3.7. Vitamin D and assisted reproductive technologies

Vitamin D has also been shown to be involved in the pathophysiology of some disorders of women of childbearing age that are most commonly encountered among women undergoing *in vitro* fertilization procedures [185].

The issue of whether vitamin D levels are reliable predictors of ART outcomes is still controversial. In some studies, among infertile women undergoing IVF, women with higher serum concentration of vitamin D and follicular fluid were significantly more likely to achieve clinical pregnancy following IVF, and also high serum vitamin D concentration was significantly related to improved parameters of ovarian hyperstimulation [186].

The mechanism by which vitamin D affects fertility is unclear. However, vitamin D acts through the endometrium to influence IVF success and is supported by biological evidence. Postulated mechanisms include its effect on ovarian steroidogenesis and implantation [186, 187]. In addition, vitamin D signaling is involved in the cross-talk between the embryo and endometrium; in response to interleukin (IL)-1B secreted by the blastocyst, endometrial dendritic cells and macrophages produce 1-alpha hydroxylase and calcitriol (the active form of vitamin D) [188]. Calcitriol binds to the vitamin D receptor in the endometrium to regulate target genes such as calbindin, osteopontin, and HOX10A, genes critical for embryo implantation and placentation [189]. Endometrial HOX10A expression parallels that of the vitamin D–signaling pathway; both increase mid-cycle shortly before expected implantation, at the time of maximal endometrial differentiation [189]. Vitamin D also has immunomodulatory effects that may contribute to implantation [190]. Calcitriol attenuates decidual T-cell function. Decidual natural killer cells treated with calcitriol show decreased synthesis of cytokines CSF2, IL1, IL6, and TNF. Calcitriol has also been shown to interfere with the production of cytokines in whole endometrial cells isolated from women with a history of recurrent miscarriage, leading some investigators to hypothesize that vitamin D could play a role in the treatment for recurrent miscarriage [191]. VDR and 1-alpha hydroxylase expression continue to increase in the first and second trimesters. In cultured syncytiotrophoblasts, calcitriol regulates hCG expression and secretion, and it stimulates E2 and P secretion from trophoblasts in a dose-dependent manner [99]. Abnormal expression of 1-alpha hydroxylase has been observed in pregnancies complicated by preeclampsia, suggesting that calcitriol may regulate placental development. Thus, the impact of vitamin D deficiency may extend to the entire placental-decidual unit.

Further research is needed to elucidate the mechanism by which vitamin D acts to influence IVF success and to determine whether repleting one's vitamin D stores will improve pregnancy rates.

3.8. Vitamin D and fetal outcomes

Although research into fetal origins of disease in later life remains in its infancy, there is increasing suspicion that gestational nutritional sufficiency may be a determinant of health in later life. Vitamin D deficiency has been related to various adverse maternal, fetal, and postnatal outcomes.

Recent research has focused on the role of gestational vitamin D status in modulating intrauterine growth, body composition, skeletal development, immune development, and respiratory health of the offspring:

- *Intrauterine growth*

It is shown that low vitamin D levels during pregnancy may account for reduced fetal growth and for altered neonatal development [192]. Variation in the maternal VDR gene polymorphisms contributes to vitamin D–related disparities in fetal growth [193]. Maternal VDR genotype was significantly and independently associated with the risk of SGA, with implicated SNPs differing in white and black women. In this respect, single VDR SNP (rs7975232) has association with birth weight. rs7975232, an anonymous polymorphism, is part of a VDR gene haplotype associated with variation in mRNA stability. mRNA stability can directly affect the amount of protein produced, thus directly affecting vitamin D levels and calcium homeostasis [194]. In early pregnancy, more than 300 genes were differentially expressed in women indicating a role of vitamin D in the genetic regulation of processes contributed in fetal development [195]. Further research identifying the functionality of VDR gene polymorphisms in pregnant women will improve our understanding of the underlying mechanisms influencing birth weight.

- *Body composition*

Increasing evidence that vitamin D affects cell development and differentiation in tissues including bone, muscle, and fat suggests that the in utero vitamin D environment may influence body composition and cardiovascular disease risk factors in the offspring [196]. In this respect, greater adiposity was found for men and women born in winter-spring, possibly reflecting fetal exposure to low vitamin D during the second or third trimester of pregnancy [196]. Vitamin D deficiency is also emerging as a risk factor for the metabolic syndrome in adults. The evidence supports an inverse relationship between serum 25OHD and components of the metabolic syndrome, including blood glucose concentration, insulin resistance, dyslipidemia, raised blood pressure, and abdominal obesity [197]. The highly active form of vitamin D, 1,25(OH)2D3, exerts a coordinated control over lipogenesis and lypolysis [198]. Given current concerns about childhood obesity and the increasing prevalence of vitamin D deficiency with urbanization, it is important to explore the hypothesis that maternal vitamin D level may affect later body size and composition.

- *Skeletal development*

Advances in bone assessment technology have prompted research on gestational vitamin D status and offspring skeletal development. It is reported that maternal serum 25(OH)D was

inversely correlated with fetal femoral distal metaphyseal cross-sectional area and splaying index. Fetal femoral splaying is analogous to that seen in childhood rickets, suggesting that effects of vitamin D deficiency on bone development may initiate early in gestation [199]. Because bone size is related to bone strength, it is hypothesized that lasting differences in femoral distal metaphyseal cross-sectional area may have implications on future fracture risk [35].

- *Immune development*

The role of prenatal vitamin D status in fetal and neonatal immune development comprises a growing area of research. Cord blood gene expression of tolerogenic immunoglobulin-like transcripts 3 and 4 (ILT3 and ILT4) was significantly higher when mothers were supplemented with vitamin D during pregnancy [200]. Also, a researcher showed that there is a weak but significant positive correlation between cord plasma 25(OH)D and cord blood mononuclear cell release of IFN-ɣ, a cytokine that plays a key role in Th1 cell development, upon stimulation with lipopolysaccharide [200]. It suggests that prenatal vitamin D status could influence immune development and predisposition for allergy [201]. A recent body of work has begun to suggest that lower gestational vitamin D levels may also be associated with higher rates of pediatric atopic disease [202], food sensitivities [203], atopic dermatitis, eczema, asthma, impaired lung function, allergic disease, and other conditions frequently characterized by a hypersensitive immune state [204–206]. It appears that fetal vitamin D levels may play a modulating role in immune functions involved in atopic disorders. As hypersensitivity outcomes may also be seen in those children born to mothers contaminated with assorted xenobiotics in pregnancy [207, 208], however, it is not known whether the immune dysregulation and hypersensitivity may be the consequence of a primary gestational insufficiency of vitamin D, or whether various chemical toxicants might play a role by impairing vitamin D uptake, renal synthesis, and assimilation [209] while at the same time inducing immune compromise and hypersensitivity through other mechanisms [210].

- *Respiratory health*

Earlier findings of an inverse correlation between maternal intake of vitamin D during pregnancy and incidence of wheeze or asthma in the offspring [137] have raised interest in the role of vitamin D in childhood respiratory health. It is reported that maternal vitamin D deficiency increases the risk of both respiratory and general infections in the first 3 months of life, and also cord blood vitamin D status was inversely associated with wheeze during the first 5 years of life [211]. Similarly, infants born to mothers with a vitamin intake during pregnancy had significantly lower odds of developing wheeze or eczema [212]. It seems that vitamin D plays an essential role in myriad genes that encode for health and well-being in the offspring, it behooves the medical and public health community to endeavor to secure vitamin D adequacy in the gestational period.

3.9. Vitamin D and lactation

Near-exclusive breastfeeding for 6 months leads, on average, to maternal calcium loss four times higher than in pregnancy because lactation can require 150–300 mgCa/kg/day. Vitamin D goes across easily into breast milk, but 25(OH)D passes very poorly, and 1,25(OH)2D does not seem to pass at all [213]. 1,25(OH)2D level decreases quickly after pregnancy and are normal

during lactation [213]. 25(OH)D concentrations were decreased during lactation [214]. In lactating rats and mice, 1,25(OH)2D levels remain elevated until weaning [213].

Studies have generally shown that providing vitamin D to lactating mothers increases their 25(OH)D concentrations but has no significant effect on any other maternal outcome [215, 216]. Animal studies showed that skeletal resorption prepared most of the calcium required during lactation, irrespective of dietary calcium intake. The obligatory increase in PTHrP and decrease in estradiol program the lactational loss of skeletal calcium content, and vitamin D status does not affect this loss. Increasing calcium and vitamin D intake during lactation might simply increase urinary calcium and, thereby, increase the kidney stone risk [70].

4. Vitamin D and menopause

During menopause, the estrogen deprivation results in elevated bone turnover, reduction in bone mineral density, and increase in the risk of fracture. Musculoskeletal discomfort may impair health-related quality of life. Moreover, body composition changes including increased fat mass and decreased lean mass, which may be related to elevated risk of VD deficiency. However, we discuss the adverse health outcomes related to both menopause and VD deficiency and the possible interaction of both risk factors in these conditions.

4.1. Vitamin D and vasomotor climacteric symptoms

Hot flashes are the most common menopausal symptom. Although their exact pathophysiological mechanism is unclear, estrogen deprivation is suggested to cause stimulation in noradrenergic hyperactivity, which leads to a heat loss response and the sensation of warmth throughout the body followed by sweats [217]. There are several lines of evidence indicating shared complications of women affected by vasomotor climacteric symptoms and vitamin D deficiency such as accelerated bone turnover, increased loss of bone mass, hypertension, and depression. Also, it is suggested that decline in serotonin, as a neurotransmitter with known effects on thermoregulation, is an alternative underlying mechanism in vasomotor climacteric symptoms. In this respect, vitamin D can protect against experimental serotonin depletion; one proposed mechanism for symptom alleviation is the prevention of serotonin decline in menopause [218]. RCTs investigating the effect of VD supplementation using adequate doses in peri- or early postmenopausal women are warranted.

4.2. Vitamin D, obesity, and menopause

Some studies demonstrated that menopause is related to obesity and changed body fat distribution. Obesity occurs because fat-free mass was lost after menopause, due to lesser exercise and greater increases in fat mass [219]. This could increase the risk of cardiometabolic disease, cancer, and consecutive mortality [220]. It has been related to estrogen effects on lipolysis and lipogenesis in visceral adipocytes [221] and the SHBG-lowering effect of estrogen deficiency resulting in elevated free testosterone levels. Hyperandrogenemia is related to visceral fat accumulation [221]. Although the serum level of estrogens and androgen levels decrease during

menopause, but the more pronounced decrease in estrogen levels might result in increased visceral fat accumulation [219]. In addition, estrogen deprivation may also effect on energy balance, metabolic rate, fat oxidation, and total body weight [219]. It is well documented that obesity is associated with vitamin D deficiency. It is demonstrated that a higher degree of obesity leads to lower 25(OH)D, whereas any effects of lower 25(OH)D increasing BMI are likely to be small. Interestingly, vitamin D supplementation decreases body fat mass without any change in body weight or waist circumference [222]. Further, physical activity and thus sun exposure, which is essential for vitamin D production in the skin [223], decline during menopause [224].

4.3. Vitamin D, cardiovascular disease, and menopause

Cardiovascular diseases are not common among premenopausal women. Sex difference between cardiovascular outcomes in female and male may be associated with protective effects of endogenous estrogens. The estrogen deprivation during menopause may be related to the unfavorable changes of lipid and carbohydrate metabolism during menopause leading to the increased incidence of cardiovascular events [220]. There is large evidence from observational studies linking low vitamin D levels with cardiovascular risk factors as well as with cardiovascular events [225]. Vitamin D has been suggested to be involved in insulin resistance, type 2 diabetes, and the MetS in premenopausal as well as in postmenopausal women [225]. This association might in part be caused by the relation of hypovitaminosis D with obesity (**Figure 3**).

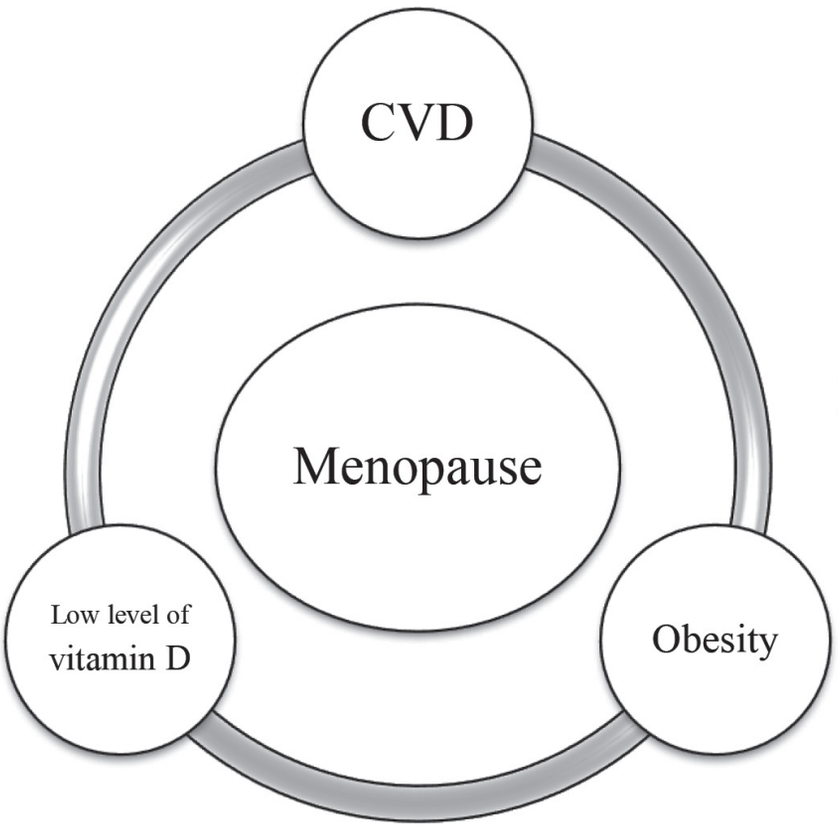

Figure 3. Menopause, low serum vitamin D, and cardiovascular diseases.

There are, however, mechanisms beyond obesity such as a beneficial VD effect on insulin action and VD-related genetic variants are associated with insulin resistance and insulin sensitivity [153]. Hypovitaminosis D has also been associated with hypercholesterolemia in several studies [226]. As low VD levels are associated with an unhealthy lifestyle such as few physical outdoor activities, a sedentary lifestyle, and obesity, it is difficult to interpret these findings.

4.4. Vitamin D, musculoskeletal disease, and menopause

Estrogen deprivation in menopause has been suggested as risk factor developing musculoskeletal symptoms such as aches and pain, joint pain, muscle stiffness, and skull and neck aching [227, 228]. Accelerated loss of bone mass occurs during the menopause as a result of naturally decreasing estrogen levels, putting women at risk of osteoporosis and fracture. Lifestyle advice including adequate calcium and VD intake, physical activity, encouraging nonsmoking, and only moderate alcohol consumption has been recommended for bone health in postmenopausal women [224]. It has been demonstrated that vitamin D has a dual effect on the musculoskeletal system: (i) on the bone mass, bone density, and bone quality and also (ii) on the muscle mass, muscle strength, and muscle function. In addition, adequate vitamin D status decreases the risk of falling in older individuals, due to improved neuromuscular function [225]. Hypovitaminosis D myopathy is a prominent symptom of vitamin D deficiency, and severely impaired muscle function may be present even before biochemical signs of bone disease develop [229]. There is evidence showing that hormones including VD as well as sex hormones modulate the functional relation between bone and muscle tissues. Also, there is evidence suggesting a relationship between osteoporosis, cardiovascular disease, and mortality, and low VD levels may be an underlying mechanism that are associated with increased bone turnover and increased risk of mortality and mortality [230]. Meanwhile, as both menopause and low level of vitamin D are related to musculoskeletal symptoms, it is suggested that vitamin D supplementation may benefit for joint pain, muscle mass, and function in peri- and postmenopausal women. Moreover, vitamin D supplementation might recover muscle function which leads to better bone mineral density and a lower risk of falling. Also, it has a positive effect on impaired cognitive function and depression, which may *per se* decrease the risk of falling [225]. Thus, randomized trials investigating vitamin D effects in peri- and early postmenopausal women on musculoskeletal symptoms and diseases are highly needed.

4.5. Vitamin D, cancer, and menopause

The incidence of cancer rises in women with increasing age. Besides other factors, this is aggravated by several lifestyle aspects such as reduced physical activity, a sedentary lifestyle, increased caloric intake, as well as obesity [224]. There is accumulating evidence suggesting that the low level of vitamin D is one of important risk factors for cancer and cancer-related mortality [231]. High 25(OH)D levels are related to reduction in mortality in patients suffering from colon, lung, and breast cancer [232, 233]. The underlying pathophysiology is not completely understood, but it is suggested that antiproliferative and apoptotic effects of vitamin D on cancer cells, inhibition of metastatic distribution and tumor invasion, and promotion of

sensitivity to radiation and chemotherapy influence on decreased mortality in cancers [233]. Since the increased risk of hypovitaminosis D in peri- and early postmenopausal women as well as the fact that underlying risk factors are also associated with an increased risk of cancer, one might speculate that an adequate vitamin D levels in those women might also be helpful regarding the risk of cancer.

4.6. Vitamin D, menopause, and mood disorders

It is well documented that women are more at a higher risk compared to men who develop psychological problems such as mood disorders and depression, which has been related to the effect of estrogen fluctuation during reproductive cycle. As well, some studies reported an increased prevalence of depression and anxiety in women across the menopausal transition [234]. It has been suggested that vitamin D may affect mood and cerebral function and the low level of vitamin D is related to vascular neuropathology [225]. Increased phagocytosis of amyloid plaques, antioxidative effects, modulation of neurotrophins, neuronal calcium regulation, immunomodulation and vascular protection [235], and changes in calcium homeostasis [236] are observed. Vitamin D deficiency and the decline in estrogens during menopausal transition are conditions associated with an increased risk of mood disorders such as depression. In this respect, more research is needed.

5. Vitamin D and male fertility

There is extensive evidence demonstrating that calcium is essential in the male reproductive system, where it is crucial for spermatogenesis, sperm motility, and acrosome reaction [237]. In this respect, the role of vitamin D, as an important modulator of calcium metabolism, in semen quality and spermatogenesis is not completely understood.

The basis of the interplay between vitamin D and reproduction lays on the presence of both VDR and 1α-hydroxylase (CYP27B1) in various tissues of the reproductive system in both sexes. VDR expression has been shown in the testis of rat [238]. Human studies demonstrated that vitamin D receptors are found in testis, epididymis, prostate, seminal vesicles, and Leydig cells. The level of expression differs, which is higher in epididymis and seminal vesicles compared to others [239]. Vitamin D receptors were also expressed in normal and abnormal sperm [239]. Acrosomal region, head, especially the nucleus, and the neck of the sperm are the sites with the most numerous mRNA VDR expression [240].

The precise role of vitamin D receptors in the sperm nucleus is unclear. It has been shown that it has a protective genomic factor, which is essential for the proper control of sperm DNA integrity and maintenance of genome stability [240]. The 1,25 (OH) 2D3 molecules seem to regulate cholesterol efflux in human sperm, affect tyrosine and threonine phosphorylation of sperm proteins, and enhance sperm bioavailability. Further, it increases intracellular calcium levels, sperm mobility, and acrosin activity, and decreases triglyceride in sperm to contribute in fertilizing capacity within the female reproductive system [241]. Vitamin D receptors are also found in the cytoplasm of epithelial cells of the epididymis and ductal prostate epithelium [242].

Meanwhile, it is shown that the mRNA encoding CYP2R1 [243] and CYPB1 is presented in all tissues of the reproductive tract [243]. The exact role of CYPR1 is unclear, but it has been suggested that it is related to vitamin D functions, as its expression progressively reduces in testicular damage [243]. Vitamin D appears to be implicated in amino acid accumulation, which is achieved either through its genomic effect, triggered by protein kinase A and C (PKC), or by a rapid, nongenomic effect, contributing in calcium/potassium channels in the plasma membrane [244]. The cyclic AMP/PKA complex is a mediator of 1,25(OH)2D3 in both genomic and nongenomic actions. As such, 1,25(OH)2D3, membrane depolarization occurs, inducing the opening of L-calcium channels and entry of calcium [241]. However, in sertoli cells, vitamin D could induce calcium uptake through an unknown receptor activity [245]. Further, vitamin D acts on sertoli cells through chloride channel activation, which is mediated through a PKA/PKC-dependent, nongenomic pathway [246]. Vitamin D enhances gamma-glutamyl transpeptidase activity, an enzyme contributed in the synthesis of proteins produced by sertoli cells. Literature supported a protective effect of vitamin D from oxidative stress and cellular toxicity, as well as maintenance of the number and motility of sperm [247]. Lastly, it has been suggested that vitamin D induces the expression of calcium-binding protein CaBP28k in testis, which is contributed in the process of spermatogenesis and steroidogenesis [248].

Recent literature suggested that men suffering from severe hypospermatogenesis or idiopathic sertoli cell-only syndrome (SCOS), despite normal levels of total testosterone and estradiol, had lower plasma 25(OH)D concentrations, higher concentrations of bone resorption markers, and lower T-scores both in femoral neck and in lumbar spine compared to healthy controls [240, 249]. Researchers showed that there are positive correlation of 25(OH)D serum levels with sperm motility and progressive motility. Moreover, men with vitamin D deficiency (<10 ng/ml) had a lower proportion of motile, progressive motile, and morphologically normal spermatozoa [250]. Further investigations are needed to evaluate the positive role of vitamin D supplementation in men's infertility.

6. Vitamin D supplementation

There are no specific guidelines regarding vitamin D supplementation for women or men affected by endocrine disturbances. Thus, according to positive vitamin D effects on bone health, the Institute of Medicine [251] and the Endocrine Society [22] suggest a vitamin D level of at least 50 nmol/l (20 ng/ml). Based on the Recommended Daily Allowance (RDA, covering requirements of R97.5% of the population), the daily intake of vitamin D should be 600 IU/day for each person up >70 years and 800 IU/day for older adults. The Endocrine Practice Guidelines Committee [22] recommend a daily intake of 1500–2000 IU vitamin D3 daily for adults older than 18 years up to 70 years in order to raise the blood level of 25(OH)D to more than 30 ng/ml. It is documented that vitamin D supplementation with 1000 IU/day increases 25(OH)D levels/10 ng/ml [133]. However, in severe vitamin D deficiency, higher doses of vitamin D 50,000 IU weekly for up to 8 weeks are recommended. Notably, vitamin D intoxication, which leads to hypercalcemia, renal damage, and vascular calcification, occurred

in 25(OH)D levels to more than 150 ng/ml [18]. Regarding several adverse effects of the low level of vitamin D on different health aspects, vitamin D supplementation in order to reach an adequate vitamin D level is highly recommended.

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