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Vitamin D as Prenatal Suplementation Preventing Recurrent Pregnancy Loss Literature Review

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ABSTRACT

Recurrent pregnancy loss is spontaneous or induced demise of three or more successive pregnancies under 20 weeks gestation age or estimated fetal weight less than 500 grams which can be caused by various factors such as maternal age, genetic disorders, immunological problems, previous illness, or nutritional intake. Vitamin D or calciferol is an important nutrient for maternal and neonatal prosperity. Vitamin D is a fat-soluble vitamin that can be obtained from sunlight or food intake and can be metabolized in various cells including reproductive cells so that vitamin D has a role in modulating immune systems, hormone secretion, cell differentiation, cell proliferation, and maintenance of pregnancy. Examination of vitamin D levels before planning a pregnancy can reduce the risk of pregnancy loss because the low status of vitamin D in pregnant women can interfere the placentation process and become one of the pregnancy loss causes. Vitamin D supplementation has proven to reduce the risk of recurrent pregnancy loss in preparation for pregnancy and during pregnancy, especially in women with low status of vitamin D.

1. INTRODUCTION

Pregnancy loss is interpreted as spontaneous or induced fetal demise that occurs before the fetus viable to survive outside the uterus when the gestational age has not reached 20 weeks or the fetus weight less than 500 grams [1- 3]. Most cases occur in the first trimester and it is estimated that one in four pregnant women has had a pregnancy loss with incidence ranges from 10-28% [3]. Roughly 15% of pregnant women encounter unknown pregnancy loss, 2% women have two pregnancy loss in a row, and 0.4-1% women have three pregnancy loss in a row [1]. Recurrent pregnancy loss can defined as miscarriage that occurs three or more times in a row before 20 weeks of gestation (World Health Organization) or experience of two miscarriages with clinical evidence (sonography or histopathological results of pregnancy) (American Society for Reproductive Medicine) [4]. Maternal age and history of prior pregnancy loss are two independent risk factors for recurrences. The percentage increased significantly with increasing maternal age, from 10-15% in women 20 to 24 years to 51% in women 40 to 44 years. The risk increase in women who have previous miscarriages. The risk of pregnancy loss after two consecutive miscarriages is 17-25%

and after three consecutive miscarriages is 25-46% [5]. Other factors that play a role in increasing the risk of pregnancy loss are paternal age, history of smoking, caffeine or alcohol consumption, severe nutritional problems, uterine or cervical anatomical abnormalities, hormonal disorders, hemostasis disorders, immunological problems, infectious diseases, chronic diseases, physical and psychological trauma, and fetal anomalies or severe chromosomal abnormalities [3- 5].

These risk factors can be avoided with good pregnancy preparation. Lifestyle before and during pregnancy will determine the nutritional status of the mother and affect both maternal and neonatal health conditions [6]. During pregnancy, nutritional needs will increase to maintain maternal metabolism, tissue growth, and fetal development so that micronutrient intake during preconception also has an important role in supporting pregnancy [6,7]. Vitamin D is one type of micronutrient which responsible for maternal and neonatal well-being, including in prevent pregnancy loss.

The literature review was compiled based on existing research in the last 10 years identified from an electronic search in the PUBMED database. *Medical Subject Heading* keywords include vitamin D, antiphospholipid syndrome, and recurrent pregnancy loss. References were collected manually from all selected articles that were relevant to the subject of vitamin D mechanisms against recurrent pregnancy loss and excluded irrelevant or duplicate articles.

2. Discussion

2.1 Pathophysiology of APS in RPL

Antiphospholipid syndrome (APS) can be described as autoimmune condition with production of antiphospholipid antibodies (aPL) including anticardiolipin antibodies (aCL), lupus anticoagulant (LA), and anti-β2glycoprotein I (aβ2GPI) antibodies [8]. The mechanism is variable and usually associated to thrombotic events. APS can occur primary and secondary in association with SLE another autoimmune diseases or in other life-threatening condition from extensive thrombosis [9]. APS is associated with 15-20% prevalence of recurrent pregnancy loss [8].

Thrombosis in APS occur due to antibodies that disrupt coagulation homeostasis and antibodies that induce activation of endothelial cells, monocytes, and platelets [10]. Manifestations of thrombosis in APS suggest platelet activation as part of aPL-induced immunopathology. aPL shows glycoproteins expression on the platelet membrane as GPIIb/IIIa and GPIIIa. Different cellular adhesion molecules and tissue factors expression will activate endothelial cells and monocytes. aPL also induces placental and vascular thrombosis by interfering anexin anticoagulant on the phospholipid-expressing surface then causing clotting factors transfer and blocking the formation of procoagulant complexes [10], [11]. aPL impairs spiral artery formation, trophoblast invasion, secretion of Human Chorionic Gonadotropin, Growth Factors, syncytiotrophoblast apoptosis, and inflammatory response by activating complement in both mother and fetus [12].

The aβ2GPI antibody is the main pathogenic antibody in APS. Endothelial cell exposure to aβ2GPI and peptides causes inhibition of endothelial cell activation such as decreased expression of E-selectin adhesion molecule, intercellular adhesion molecule, vascular cell adhesion molecule, and monocyte adhesion [13]. Aβ2GPI antibodies are also associated with activation of complement and the coagulation-complement pathway. C5a induces procoagulant activity which depend on neutrophil tissue factor and inhibit fibrinolysis, endothelial cells activation, induction of adhesion molecules expression, procoagulant and platelet activity. This condition will cause inflammation and placental injury as a sign of fetal growth failure

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in APS patients [13], [14].

2.2 Metabolism of Vitamin D

Vitamin D can be obtained directly from the sun exposed skin and various foods like fish, eggs, and fortified food products in smaller amounts [15], [16]. Sunlight will sythesize the initial form of vitamin D, 7-dehydrocholestrol into vitamin D3. It binds to vitamin D binding protein circulates in blood vessels and binds to albumin and lipoproteins to transport in liver. In the liver, the CYP2R1 enzyme makes vitamin D3 hydroxylated to 25(OH)D3 (calcidiol), by the CYP27B1 enzyme which is mostly found in the kidneys, placenta, macrophages, lungs, and brain, calcidiol is hydroxylated to the active form of vitamin D, 1,25(OH)2D3 (calcitriol) [16], [17]. Calcidiol describes total vitamin D reserves in the body with a longer half-time than calcitriol so it can be used to determine vitamin D status individuals in the category of deficiency (<20 ng/mL), insufficiency (21-30 ng/mL), or sufficient (>30 ng/mL) [18]. Various factors can influence vitamin D status including race, ethnicity, culture, skin color differences, sun exposure, and nutritional intake [19].

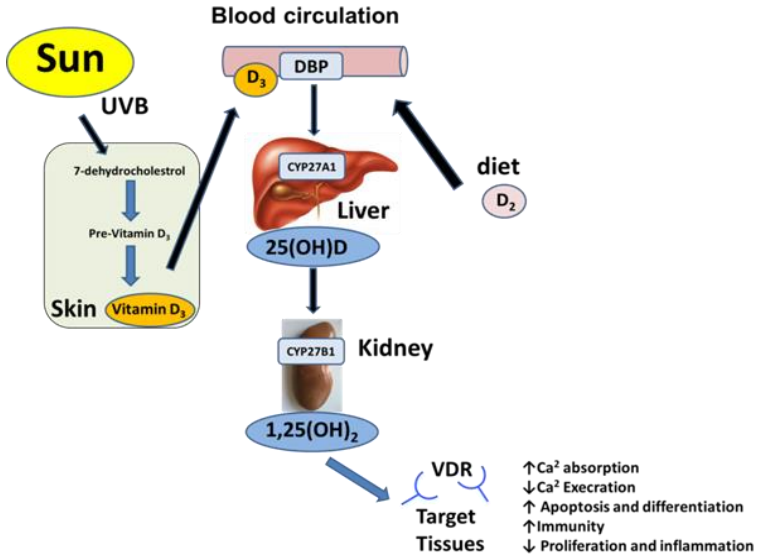

Figure 1 Metabolism of Vitamin D [20]

Calcitriol and vitamin D receptor is transcribed in target tissues to elicit biological response [16]. Vitamin D is widely known in bone metabolism through its ability to maintain a balance of phosphate and calcium [15] but its receptors can also be found in other cells and tissues such as mononuclear cells, endometrial stroma, vascular endothelial cells, pancreatic cells, keratinocytes, and nervous tissue. Therefore, vitamin D also can modulate a major immune (innate immune response and acquired immune response), secrete hormone, differentiate cell, and proliferate cell [16]. In a pregnancy, maternal physiological condition changes, it adjusts the nutritional needs of the fetus and affect vitamin D homeostasis and its availability to both the mother and the fetus. Vitamin D homeostasis is responsible for providing an optimal environment for fetal growth and successful delivery. Deficiency vitamin D in pregnancy cause a big impact to the mother and fetus as increasing risk of gestational diabetes, preeclampsia, premature birth, fetal growth restriction, abortion, impaired ovarian function, impaired fertility, and affects fecundity [19]. Clinical studies show that adequate levels of vitamin D from preconception can maintain immune balance and fetal development [20].

2.3 Vitamin D Action in APS

Immunoglobulin G (IgG) in APS patients will induce endothelial dysfunction, monocyte and platelet

activation, and overexpression of tissue factors, adhesion molecules, and proinflammatory cytokines through TLR4 activation. aPL can also activate endothelial cells via TLR2 and TLR4 signaling. LPS increases aβ2GPI expression in vascular tissues and triggers aPL-mediated thrombosis. Vitamin D is able to suppress the expression of TLR4 which is responsible for the activation of NFkB and the signaling cascade that ultimately induces a prothrombotic state in endothelial cells by aPL. Vitamin D is also able to reduce expression of tissue factors induced by proinflammatory agents such as TNF-α or LPS in monocytes, reduce inflammatory pathways and the risk of endothelial cell damage [21].

During pregnancy, vitamin D has an important role as placentation (trophoblast migration and spiral artery remodeling), immune function, maternal calcium homeostasis and fetal development. Vitamin D deficiency in pregnancy can cause abnormal or insufficiency placentation and abnormal fetal development leading to health problems after birth [17]. Women with prior pregnancy loss without infertility problem can be scheduled for preconception vitamin D to decrease recurrency, morbidity, and mortality in pregnancy [21]. Vitamin D will inhibit signaling, tissue factor expression, endothelial activation, and cell inflammation that can improve vascular thrombotic problems. Vitamin D which is produced by trophoblast in early pregnancy will also create an anti-inflammatory environment and induce decidualization, both increase successfully in pregnancy [22].

Vitamin D has a role in CD4 T cells differentiation and activity and produces a response of Th1/Th2 which prevent inflammation and autoimmunity [17]. Besides, vitamin D also has antithrombotic effect through its suppressive effect on aβ2GPI expression. Complement inhibitor expression of CD55 (decay accelerating factor) in human monocytes and complement activity inhibition by vitamin D also proven to prevent pregnancy disorders [23].

2.4 Vitamin D Action in Pregnancy

Activity of vitamin D in pregnant women will show three striking manifestation as increase in calcitriol doubled, decrease in 25(OH)D in placenta barrier quarter, and increase in vitamin D receptor expression and metabolic enzymes regulator in the placenta [19]. Metabolism of vitamin D which is expressed in female reproductive tissues such as ovaries, decidua, endometrium, placenta, and some immune cells provides immunomodulatory effects from periconception to pregnancy time in the form of increasing immune balance, tolerance and maintenance of pregnancy through effects on B cells, T cells, macrophages, and dendritic cells [18]. These proinflammatory mediators can assist calcitriol synthesis and are also involved in fertilization process, implantation, and maintenance of pregnancy [21].

Currently the immune system has become one factor that has an important role in fertility, implantation, and pregnancy. Sperm fluid induce proinflammatory immune response and contributes to endometrial remodeling in preparation for implantation as well as activation of neutrophils, macrophages, cytokine pathways, and chemokines [18]. The immune system in maternal called Treg cells plays an important role in tolerating the father's antigens to support the success of embryo implantation. Calcitriol can suppress IL-6 production which inhibits Tregs development and upregulates TGF-β. The presence of Tregs will repress cytotoxic T cells, Th1 cells, macrophages, dendritic cells, and NK cells that prevent embryo resorption in early pregnancy. Calcitriol will also increase Th2 differentiation and lowering the Th1/Th2 ratio and causing the maternal immune system more sensitive to pathogens [16- 18].

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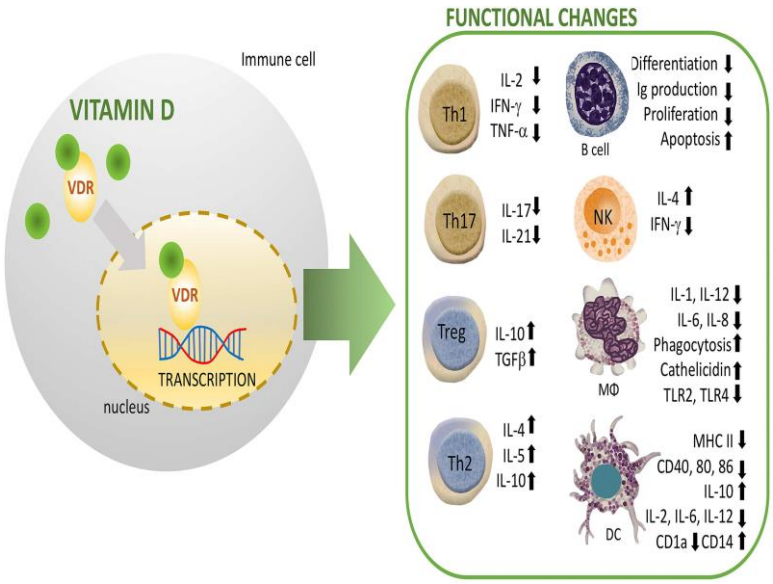

Figure 2 Vitamin D as Immunomodulatory on Immune Cell Lineages [17]

Lower vitamin D is common in reproductive age women. It can pose a risk to infertility and pregnancy failure. Research by Eggemoen (2016) shows that circulating vitamin D levels in pregnant women is less than 25 nmol/L, either in South Asia (45%), Middle East (40%), or Sub-Saharan Africa (26%) [24]. Pregnant women who have vitamin D deficiency or insufficiency need vitamin D intake to avoid complications during pregnancy. According to Mumford (2018), pre-pregnancy vitamin D levels higher than 75 nmol/L can increase chances of pregnancy and live birth, and avoid pregnancy loss [25].

2.5 Vitamin D Supplementation

During pregnancy, a pregnant woman requires more nutritional intake than when she is not pregnant, which is best achieved through the consumption of healthy balanced nutritious foods. However, it is undeniable that during pregnancy there are hormonal changes which affect the appetite of pregnant women. Therefore, to reach their needs, additional vitamins can be given as supplementation, including vitamin D. Vitamin D supplementation is available in two forms as vitamin D2 or ergocalciferol and vitamin D3 or cholecocalciferol. Cholecalciferol supplementation is known to be more effective in increasing serum vitamin D [26].

There is currently no dose of routine prenatal vitamin D supplementation for those at risk or during the antenatal period, but previous research data suggest that every 10 ng/mL increase in preconception, vitamin D levels is associated with a 12% reduction in the risk of pregnancy loss [27]. Recommendation of vitamin D as nutritional intake for pregnant women based on The Food and Agriculture Organization of the United Nations is as much as 5 grams (200 IU) per day [28]. The United States Institute of Medicine recommends pregnant women to take 600 IU vitamin D to achieve higher serum vitamin D than 50 nmol/L (20 ng/mL). Meanwhile, the US Endocrine Society recommends a minimum intake of vitamin D for pregnant women as much as 1,500-2,000 IU to maintain serum vitamin D levels of more than 75 nmol/L (30 mg/dL) for adequate vitamin D status [27]. Mostly, multivitamin supplement for pregnancy contain vitamin D in 200-400 IU. This dose is sufficient for the general population who is sufficiently exposed to sunlight, but too low for consumption by populations with vitamin D deficiency, especially in pregnant women whose maintain vitamin D levels higher of 30 ng/mL [29].

Some health organizations recommend at least 400 IU/day of vitamin D used as a supplement with the

maximum total intake should between 1,000-2,000 IU/day including food sources like fish or egg yolks [30]. Supplementation during pregnancy with 1,000 IU of vitamin D can overcome deficiency in pregnant women but should be monitored regularly because there are other factors that also affect the adequacy of vitamin D in pregnant women including race, ethnicity, and period of supplementation [27]. Based on studies of adult samples, vitamin D supplementation was shown to have minimal toxicity at a dose of 10,000 IU per day and more pronounced toxicity at a dose of 20,000 IU per day such as hypercalcemia, hypercalciuria, and an increase in serum calcidiol levels reaching 200 nmol/L [28]. Excessive intake of vitamin D in pregnancy will inrease risk of hypercalcemia and hypercalciuria in the fetus. It can be avoided by consuming maximum dose of vitamin D 4,000 IU which started in 12th or 16th week gestational age until delivery. Higher doses can be used only for a limited short period during the third trimester (because doses are cumulative) [27,30].

3. Conclusion

Recurrent pregnancy loss is influenced by many factors such as vitamin D deficiency which can affect immune cell imbalance. Vitamin D supplementation should be started in preparing pregnancy and during pregnancy to prevent pregnancy loss by keeping placentation process and preventing excessive inflammatory response, especially in women with high risk of vitamin D deficiency.

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