Role of Vitamin D Deficiency in Occurrence of Intra Uterine Growth Restriction

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Abstract

Background: Intrauterine growth restriction (IUGR) is a major problem in midwifery medicine for which no effective treatment has been established. This problem has been associated with significant morbidity and mortality, as well as perinatal mortality. IUGR could be prevented when the treatment is administered before the occurrence of irreversible changes. Hence appropriate methods for early detection and successful treatment deem necessary. **Aim of work:** The purpose of this study is to evaluate the relationship of vitamin D serum level with IUGR in pregnant women. **Conclusions:** Serum levels of vitamin D can affect the risk of IUGR; therefore, the incidence of IUGR in babies whose mothers have enough vitamin D level during pregnancy is lower than that in other babies

KeyWords: Vitamin D, Intrauterine growth restriction, Pregnancy.

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Introduction

Maternal vitamin D deficiency has become a significant problem in modern day obstetrics; the rates of vitamin D deficiency have increased in recent decades. Increased interest in the potential role of vitamin D for prevention of non-skeletal disorders, in addition to its effects on bone health. Disorders that complicate pregnancy, such as gestational diabetes mellitus (GDM), preeclampsia, preterm delivery and fetal growth abnormalities are in this wide rang (1) Although vitamin D has traditionally been associated with bone health through its regulation of calcium and phosphate absorption, it also plays central roles in immune regulation (2) vascular function (3) and cellular proliferation and differentiation (4).

Vitamin D Receptor VDR and the 1-α-hydroxylase enzyme are expressed in pancreatic β-cells, and it has been reported that 1,25(OH)2D may have a role in the regulation of insulin production and secretion in particular, it has been demonstrated that 1,25(OH)2D acts on pancreatic islets stressed by inflammation and vitamin D deficiency. Moreover, it is well established that normal levels of vitamin D are essential for keeping extracellular calcium concentrations and calcium influx into β-cells for insulin secretion, while VDR signaling might play a direct role in glucose-induced insulin secretion addition to regulating insulin synthesis and secretion, VDR signaling promotes insulin-induced glucose uptake in liver, adipose and skeletal muscle tissues and 1,25(OH)2D directly activates the transcription and expression of the insulin receptor gene and protein in humans (5).

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Also, vitamin D is important for placenta funcation, calcium homestasis and bone mineralization which are all important deteriminent for fetal growth and development (6).

There is evidence to indicate that inflammatory cytokines are implicated in the development of preeclampsia and that vitamin D, which has anti-inflammatory effects, may play a role in preventing it., One mechanism of the anti-inflammatory effect is down regulation of uncommitted helper T cells and promotion of the proliferation of immunosuppressive regulatory T cells. There is also evidence that vitamin D plays a role in promoting IL-10 production, which is anti-inflammatory and suppresses the production of inflammatory cytokines such as eg, tumor necrosis factor α [TNFα], interleukin [IL]-6, , and IL-1β ,Many cytokines associated with preeclampsia are influenced by vitamin D, such as TNFα, ratio of IL-2 to IL-10, IL-6, and IL-8. Therefore, higher concentrations of maternal serum vitamin D and its metabolites can potentially protect against the development of preeclampsia (7).

Gestational vitamin D deficiency on infant associated with fetal growth restriction Vitamin D may influence fetal and postnatal growth through effects on calcium absorption, parathyroid hormone expression, phosphate metabolism, growth-plate function, and regulation of the insulin-like growth factor axis. Observational studies and clinical trial have suggested that vitamin D may have a beneficial effect on fetal growth (8).

Vitamin D deficiency and placental development and function:

Nguyen et al., (9) showed that placental vitamin D receptor (VDR) when decrease associated with abnormal trophoblast expression of cell-cycle regulatory gene, in vitro and expression is down regulated in pregnancies complicated by fetal growth restriction. This suggests that vitamin D homeostasis during pregnancy likely involves communication between maternal, placental and fetal compartments.

During pregnancy, vitamin D homeostasis is regularized by three adaptations including increase in maternal calcitriol vitamin D binding protein (VDBP) concentrations, and adequate availability of maternal 25(OH)D. These variations are evident at systemic and placental circulation levels, suggesting that the placenta is a main site for vitamin D metabolism (10).

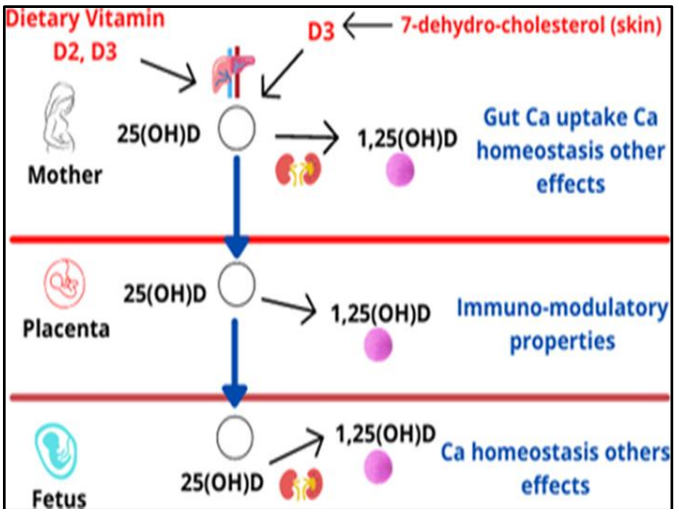

Figure (1): Effects of vitamin D during pregnancy (11).

Along with the transmission of oxygen and nutrients, the placenta also mediates the immune-tolerance adaptation during pregnancy. Fetus cannot synthesize its own vitamin D (calciferol), therefore maternal vitamin D or its other biological metabolites must be transferred to the fetus through placenta. It is not transferred in its activated form, i.e., 1,25(OH)2D, through placental tissue, rather as the inactivated precursor form, 25(OH)D, which crosses the placental barrier to the fetal compartment The placenta contains the enzyme 1-α-hydroxylase that can possibly activate 25(OH)D-producing 1,25(OH)2D (12). Moreover, placenta can also convert 25(OH)D by 24-hydroxylation to inactivated 24,25(OH)2D. 1,25(OH)2D can also be synthesized within the placenta to regulate placental metabolism.

The importance of vitamin D during pregnancy is for maintaining maternal calcium homeostasis and therefore for foetal bone development (13).

Both Vitamin D Receptor (VDR) and cytochrome P450 family 27 subfamily member B1(CYP27B1) have been noted in the placenta and decidua (14).

Importance of vitamin D in pregnancy in part result from its function in gestational uterine decidua at the maternal fetal interface, fetal maternal exchange of nutrient, waste product and also source of secretory product such as hormones (prolactin steroidal lactogen and growth factor (15).

Vitamin D and glucocorticoid interaction:

During pregnancy activity of the hypothalamic pituitary adrenal (HPA) increase and increases cortisol, corticosterone in human (16).

There are multiple pathways that influence fetal exposure to glucocorticoids with vitamin D deficiency.

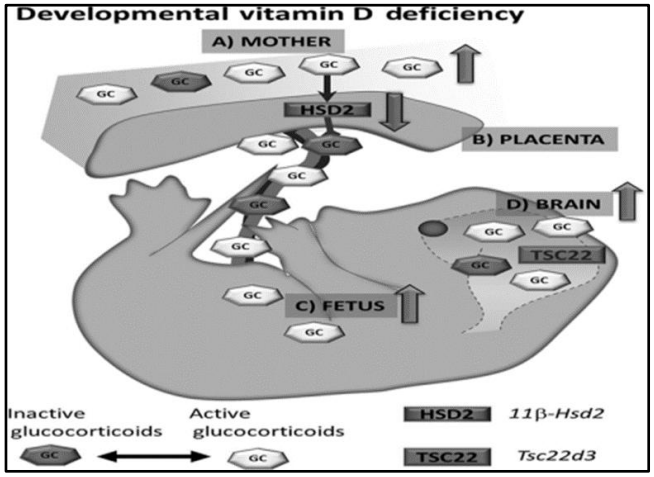

Figure (2): Proposed effects of developmental vitamin D deficiency on glucocorticoid metabolism and levels in the mother and fetus. (16) (A) In gestational vitamin D deficiency, maternal circulating active glucocorticoids (GCs) and glucocorticoids GC release in response to stress is elevated, likely increasing placental GC exposure and transport. (B) In the placenta, in 11-beta hydroxysteroid dehydrogenase 2 (11β-Hsd2) (a key enzyme that inactivates glucocorticoids (GCs) is decreased by vitamin D deficiency, which decreases the conversion of active glucocorticoids GCs to inactive forms. (C) In the fetus, the combination of increased maternal GC levels and decreased GC inactivation due to vitamin D deficiency lead to increased fetal glucocorticoids GC exposure. (D) Ultimately, vitamin D-deficient fetuses exhibit a likely increase in GC exposure in the brain, as indicated by increases in the GC-responsive gene Tsc22d3. (17).

Vitamin D Deficiency and Intra Uterine Growth Restriction

Vitamin D deficiency during pregnancy causes potentially harmful implications in the mother and the fetus (18,19). Several studies have referred to the relationship between vitamin D deficiency and the incidence of IUGR (20,21,22).

Some studies have shown that increasing the amount of 25-hydroxy vitamin D in the bloodstream before and during pregnancy contributes to nesting and causes stability in pregnancy, as well as increased calcium uptake required for fetal growth and development (23).

Studies have also indicated that the decreased expression of vitamin D receptors results in functional impairment and limitation in the beneficial effects of vitamin D in regulating the fetus-placental growth (24,25).

In the study of **Hutabarat et al,** maternal vitamin D deficiency was observed in all pathological pregnancies with a decrease in the staining levels of placental VDR in IUGR (26).

As **Zhang et al** have shown, severe vitamin D deficiency may play an important role in placental inflammation, which in turn may lead to a higher risk of IUGR and other neonatal side effects (27). The influence of taking vitamin D supplements during pregnancy in women with vitamin D deficiency for reducing the adverse effects of IUGR is recommended in future clinical trials. In their study, the correlation between vitamin D deficiency and IUGR was approved; hence, the use of vitamin D supplements before and during pregnancy could be the clinical application of this research. This study suffers from some limitations.

Conclusion:

Serum levels of vitamin D can affect the risk of IUGR; therefore, the incidence of IUGR in babies whose mothers have enough vitamin D level during pregnancy is lower than that in other babies. Therefore, it could be predicted the occurrence of IUGR by measuring the vitamin D serum levels in the early pregnancy and prevented its occurrence by using possible methods.

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