Correlation between Vitamin D Deficiency and First Trimester Miscarriage at Ain Shams University Maternity Hospital

Thesis Submitted for Partial Fulfillment of Master Degree in Obstetrics and Gynecology

By

Dina Hussein Ibrahim El-Araby

M.B., B.Ch. Faculty of Medicine, Alexandria University, 2011
Resident of Obstetrics and Gynecology in El-Amreyah Hospital
Ministry of Health

Under supervision of

Prof. Dr. Karam Mohammed Bayoumy

Professor of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Dr. Nermeen Ahmed Mostafa El-Ghareeb

Lecturer of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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LIST OF ABBREVIATIONS

25(OH)D	**:**	25-hydroxyvitamin D
ACOG	**:**	American College of Obstetricians and Gynecologists
AGS	**:**	American Geriatrics Society
BMI	**:**	Body mass index
CAMP	**:**	Cathelicidin antimicrobial peptide
CDC	**:**	Centers for Disease Control and Prevention
CI	**:**	Confidence interval
CYP24	**:**	24-alpha-hydroxylase
CYP27B1	**:**	1-alpha-hydroxylase
EMT	**:**	Epithelial–mesenchymal transition
EVT	**:**	Extra villous trophoblastic
FGF23	**:**	Fibroblast growth factor 23
GDM	**:**	Gestational diabetes mellitus
GMCSF-2	**:**	Granulocyte-macrophage colony-stimulating factor 2
HOXA10	**:**	Homebox A10
HVDRR	**:**	Hereditary vitamin D-resistant rickets
ICSI	**:**	Intracytoplasmic sperm injection
IL	**:**	Interleukin
IOF	**:**	International Osteoporosis Foundation
IOM	**:**	Institute of Medicine
IVF	**:**	In vitro fertilization
MMP	**:**	Matrix metallo-proteinases
NOF	**:**	National Osteoporosis Foundation
PL	**:**	Pregnancy losses

PTH	**:**	Parathyroid hormone
PTHrP	**:**	Parathyroid hormone-related protein
RDA	**:**	Recommended Dietary Allowance
RPL	**:**	Recurrent pregnancy loss
RXR	**:**	Retinoid X-receptor
SA	**:**	Spontaneous abortion
Th1	**:**	T helper 1
Th2	**:**	T helper 2
TIMP-1	**:**	Tissue inhibitor of metalloproteinase-1
TNF-a	**:**	Tumor necrosis factor a
UL	**:**	Upper level
UV	**:**	Ultraviolet
VDD	**:**	Vitamin D deficiency
VDI	**:**	Vitamin D insufficiency
VDR	**:**	Vitamin D receptor

ABSTRACT

Objective: To assess the role of vitamin D deficiency and early pregnancy loss.

Patient and Method : A nested case control study conducted in outpatient antenatal care clinic under supervision of Ain Shams University Maternity hospital from the period of March 2020 to June 2020. Pregnant ladies in the first trimester were screened for eligibility criteria. Blood samples were taken from the participants at the time of presentation. All participants were followed till the end of the first trimester to report cases of miscarriage. Vitamin d was assessed for the 40 women who suffered from miscarriage (cases) and for 40 selected controls. The primary outcome was the relation between vitamin d level and early pregnancy loss. Secondary outcome was the relation between vitamin d deficiency and obesity.

Results: Our findings showed that the miscarriage group was significantly older than control group as $p<0.001$ and BMI was significantly higher as $p<0.007$. The mean value of 25(OH)D was significantly lower among miscarriage group (21.0 ± 8.5) than control group (26.5 ± 8.3) as $p=0.005$. And the majority of miscarriage group (42.5%) had 25(OH) D deficiency while (40.0%)&(17.5%) of cases had either 25(OH)D insufficiency or sufficiency which significantly different than control group ($p=0.049$). 25(OH)D ≤24.5 (ng/mL) was a significant factor that increased the likelihood of first-trimestric miscarriage with sensitivity 80%. No significant differences according to BMI grades regarding 25(OH) D grades.

Conclusion: Vitamin d deficiency is one of modifiable risk factors for first trimestric abortion. . Preconceptional vitamin D supplementation is an easy method for decreasing incidence of early pregnancy loss.

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Keywords: vitamin D deficiency, early pregnancy loss, risk factors for miscarriage.

INTRODUCTION

Miscarriage is the most common adverse outcome of pregnancy, with a reported prevalence of 12–20%. Miscarriage is multifactorial of origin, with acquired or environmental factors probably exceeding genetic factors in its causation. Identifying modifiable risk factors for miscarriage is potentially important for public health. ***(Amro and Almahdi, 2019)***

The human fetus represents a semi-allograft, which cannot survive without maternal immune tolerance**.** Controlled invasion of fetal cytotrophoblast and differentiated extra villous trophoblastic (EVT) cells into the maternal decidua and myometrium in the first trimester of pregnancy is a key process in placentation and is essential for successful pregnancy. A complex network of communications among trophoblast, decidual stromal and immune cells is reported to facilitate implantation and maintenance of pregnancy, with key roles in tissue remodeling, cell trafficking and immune tolerance being evident. ***(Ander et al., 2019)***

Vitamin D may be implicated in the risk of miscarriage due to its function as an immune modulator and its potential importance for the maternal-fetal immunologic response. Vitamin D deficiency arises from multiple causes including inadequate dietary intake and inadequate exposure to sunlight. ***(Ji et al., 2017)***

In addition, vitamin D may play a potential role in the prevention of miscarriage due to its combined immunomodulatory and anti-inflammatory properties during early pregnancy. Vitamin d deficiency might cause multiple adverse health problems in mothers (like preeclampsia, gestational diabetes, bacterial vaginosis and maternal postnatal depression) and infants (like intrauterine growth restriction and abnormal fetal bone metabolism) and that may persist into later life. ***(Schröder-Heurich et al., 2020)***

1, 25 dihydroxy vitamin D_3 (1, 25 (OH_2) D_3) has a well-established classic function in maintaining calcium homeostasis and promoting bone mineralization. In addition, vitamin D_3 has significant roles in regulating cell proliferation and differentiation and modulating innate and adaptive immune responses. The vitamin D has a regulatory role associated with placental invasion, normal implantation, and angiogenesis. ***(van de Peppel et al., 2018)***

About 50% to 90% of vitamin D is absorbed through the skin via sunlight while the rest comes from the diet. Twenty minutes of sunshine daily with over 40% of skin exposed is required to prevent vitamin D deficiency. ***(Eberhardt and Blepharitis, 2019)***

Vitamin D undergoes hydroxylation to become 25-hydroxyvitamin D (25(OH)D) in the liver, which is subsequently converted to its active form 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) in the kidney, the placenta and other target organs. ***(Bikle and Christakos, 2020)***

Some studies suggested that obesity is associated with low serum vitamin d levels. This association is likely due to the decreased bioavailability of vitamin D_3 from cutaneous and dietary sources because of its deposition in body fat compartments as it is a fat-soluble vitamin. ***(Savastano et al., 2017)***

AIM OF THE WORK

This nested case control study aims to assess the relationship between vitamin D deficiency in gravid women and pregnancy loss in the first trimester.

Study hypothesis: In gravid women, vitamin D deficiency has higher rates among early pregnancy loss cases.

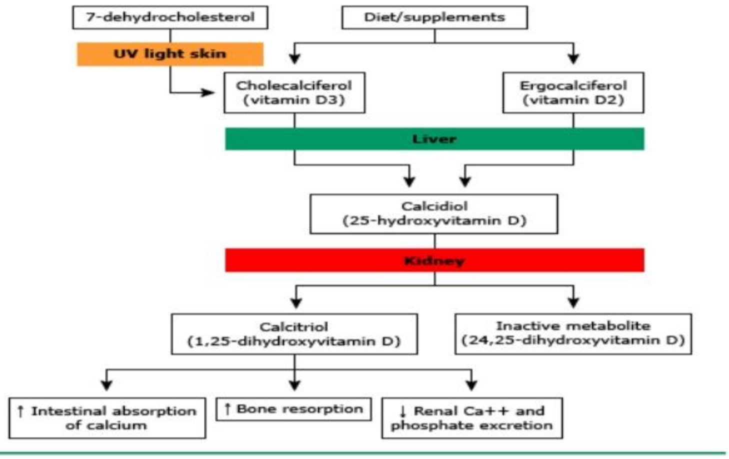
Study question: In gravid women, is the rate of vitamin D deficiency higher among early pregnancy loss cases?

Chapter (1)
Vitamin D

Chemistry:

Vitamin D, or calciferol, is a generic term and refers to a group of lipid soluble compounds with a four-ringed cholesterol backbone. 25-hydroxyvitamin D (25[OH]D) is the major circulating form of vitamin D. It has a half-life of two to three weeks, compared with 24 hours for parent vitamin D. It has activity at bone and intestine but is less than 1 percent as potent as 1,25-dihydroxyvitamin D, the most active form of vitamin D. The half-life of 1,25-dihydroxyvitamin D is approximately four to six hours. 1,25-dihydroxyvitamin D binds to intracellular receptors in target tissues and regulates gene transcription. ***(Lowe et al., 2019)***

It appears to function through a single vitamin D receptor (VDR), which is nearly universally expressed in nucleated cells. The receptor is a member of the class II steroid hormone receptor and is closely related to the retinoic acid and thyroid hormone receptors. Its most important biological action is to promote enterocyte differentiation and the intestinal absorption of calcium. Other effects include a lesser stimulation of intestinal phosphate absorption, direct suppression of parathyroid hormone (PTH) release from the parathyroid gland, regulation of osteoblast function, and permissively allowing PTH-induced osteoclast activation and bone resorption. ***(DeLuca, 2020)***



Metabolic activation of vitamin D to calcitriol and its effects on calcium and phosphate homeostasis. The result is an increase in the serum calcium and phosphate concentrations.

Figure (2): Pathways of vitamin D synthesis

Sources:

Very few foods naturally contain vitamin D (fatty fish livers are the exception); dermal synthesis is the major natural source of the vitamin. Previtamin D3 is synthesized nonenzymatically in skin from 7-dehydrocholesterol during exposure to the ultraviolet (UV) rays in sunlight. Previtamin D3 undergoes a temperature-dependent rearrangement to form vitamin D3 (cholecalciferol). This system is exceedingly efficient, and it is estimated that brief casual exposure of the arms and face is equivalent to ingestion of 200 international units per day. ***(Haddad, 2019)***

- **Natural sources Vitamin D Content:** ***(Holick, 2019)***
  - Salmon Fresh, wil 600–1000 IU/3.5oz of vitamin D3
  - Salmon Fresh, farmed 100–250 IU/3.5oz of vitamin D3 or D2
  - Canned 300–600 IU/3.5oz of vitamin D3
  - Sardines, canned 300 IU/3.5oz of vitamin D3
  - Mackerel, canned 250 IU/3.5oz of vitamin D3
  - Tuna, canned 230 IU/3.5oz of vitamin D3
  - Cod liver oil 400–1000 IU/teaspoon of vitamin D3
  - Shiitake mushrooms Fresh 100 IU/3.5oz of vitamin D2
  - Egg yolk 20 IU/3.5oz of vitamin D3 or D2

However, the length of daily exposure required to obtain the sunlight equivalent of oral vitamin D supplementation is difficult to predict on an individual basis and varies with the skin type, latitude, season, and time of day. ***(Terushkin et al., 2010)***

Prolonged exposure of the skin to sunlight does not produce toxic amounts of vitamin D3 because of photoconversion of previtamin D3 and vitamin D3 to inactive metabolites (lumisterol; tachysterol; 5,6-transvitamin D; and suprasterol 1 and 2). In addition, sunlight induces production of melanin, which reduces production of vitamin D3 in the skin. Infants, disabled persons, and