Association of Vitamin D Deficiency in Pregnancy and Risk of Preterm Labor

Thesis

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By

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Marwa Ahmed

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List of Abbreviations

Abb.	Full term
25(OH) VD	25 hyrdoxy vitamin D
ACTH	Adrenocorticotropic hormone
AI	Adequte intake
BMI	Body mass index
BV	Bacterial vaginosis
CAMP	Cathelicidin antimicrobial protein
CI	Confidence interval
CRH	Corticotropin releasing hormone
CRP	C reactive protein
CS	Cesarean section
CYP27A1	Cytochrome P27A1
CYP27B1	Cytochrome P27B1
DBP	Vitamin D binding protein
DCs	Dendiritic cells
DHEAS	Dehyrdoepiandrosterone sulphate
DNA	Double stranded nucleic acid
DRG	A multinational specialty medical equipment and diagnostics manufacturer and distributor.
DV	Daily values
E1	Estrone
E2	Estradiol
E3	Estriol
ELBW	Extremely low birth weight
ELISA	Enzyme-linked immunosorbent asssay
ER	Estrogen receptor
EUROPOP	European Programme of Occupational Risks and Pregnancy Outcome

List of Abbreviations Cont...

Abb.	Full term
FDA	US Food and Drug Adminestration
FGF-23	Fibroblast growth factor 23
GA	Gestational age
GBS	Group B streptococci
G-CSF	Granulocyte colony stimulating factor
GDM	Gestational diabetes mellitus
hCAP18	Human cathelicidin antimicrobial peptide
hCG	Human chorionic gonadotropin
HIE	Hypoxic ischemic encephalopathy
HPA	Hypothalamic pituitary adrenal
HPLC-MS	High performance liquid chromatography mass spectrometry
HS	Highly significant
IL-1	Interleukin 1
IOM	Institute of medicine
IQR	Iterquatrile range
IU	International unit
IUFD	Intrauterine foetal death
LBW	Low birth weight
MMPs	Matrix metallo proteinases
mRNA	Messenger ribo nucleic acid
NCC	Nested case control study
ng/ml	Nano gram/mille
nM	Nanomolar= 10^{-9} mol/L
nmol/L	Nano moll/liter
NS	Non significant
OR	Odds ratio

List of Abbreviations Cont...

Abb.	Full term
PAMG-1	Placental alpha macroglobulin-1
PAO	Pregnancy adverse outcomes
PAR	Protease-activated receptors
PPROM	Preterm premature rupture of membranes
PR	Progesterone receptor
PROM	Premature rupture of membranes
PTB	Preterm birth
PTD	Preterm delivery
PTH	Parathyroid hormone
PTL	Preterm labor
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized controlled trials
RDA	Recommended daily allowance
RXR	Retinoid x-receptor
S	Significant
SD	Standard deviation
SGA	Small for gestational age
SIDS	Sudden infant death syndrome
sPTB	Spontanous preterm birth
STIs	Sexually transmitted infections
TAT	Thrombin anti thrombin complex
TNFα	Tumor necrosis factor alpha
TVUS	Transvaginal ultrasound
UK	United Kingdom
UL	Upper intake level
USA	United States of America

List of Abbreviations Cont...

Abb.	Full term
USDA	United States Department of Agriculture
UV	Ultraviolet
UVB	Ultraviolet B waves
VD	Vitamin D
VDD	Vitamin D deficiency
VDRs	Vitamin D receptors
VLBW	Very low birth weight
WHO	World health organization

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INTRODUCTION

Preterm labor continues to be the leading cause of neonatal morbidity. Prematurity accounts for 50-75% of the perinatal mortality. Preterm labor is defined as onset of regular uterine contractions associated with cervical changes starting before 37 completed weeks of gestation, with or without intact fetal membranes ***(Fernandes et al., 2015).***

Estimates of preterm birth rates range from 5-10% in developed countries to 25% in developing countries ***(Beck et al., 2010).***

The pathogenesis of preterm labor is not well understood, and it is often not clear whether preterm labor represents early idiopathic activation of the normal labor process or results from a pathogenic mechanism ***(Goldenberg et al., 2008).***

Thirty to forty percent of all cases of preterm birth are due to elective delivery for a maternal or a fetal complication. The remaining 60-70% of preterm births is likely due to sub-clinical infective / inflammatory processes, cervical dysfunction, multiple gestations, idiopathic and possible social, nutritional, and environmental interactions ***(Lumley, 2003)***.

Wide spectrum of causes and demographic factors has been implicated in preterm birth. These can be categorized into four groups ***(Sangkom et al., 2015)*:**

1. Medical and obstetric complications: there are associations with placental hemorrhage and hypertensive disorders in about one-third of cases.

2. Lifestyle factors: there is an association with alcohol abuse, low maternal age, and occupational factors.

3. Amniotic fluid infection caused by a variety of micro-organisms located in the genital tract: approximately one-third of preterm births are associated with chorioamniotic infection.

4. Asymptomatic cervical dilatation. ***(Sangkom et al., 2015).***

Infections are often the most common risk factors of preterm births. Genital tract infections account for about 25-40% of preterm deliveries. Women with Chlamydia trachomatis, Gardnerella vaginalis, Trichomonas vaginalis, Neisseria gonorrhoeae, Treponema pallidum, have a higher rate of preterm births ***(Jasovic-Siveska, 2014).***

A history of a preterm delivery is one of the most significant risk factors. The recurrence risk factor of preterm birth in women with a history of preterm delivery ranges from 17% to 40% and appears to depend on the number of prior preterm deliveries ***(Goldenberg et al., 2008).***

The finding of short cervix on transvaginal ultrasound also is a known risk factor for preterm birth ***(Palatnik and Grobman, 2015).***

Multiple gestations carry one of the highest risks of preterm delivery. Approximately 50% of twins and nearly all higher multiple gestations end before 37 completed weeks. The average length of gestation is significantly shorter for twins (36 weeks), triple (33 weeks), and quadruplets (31 weeks) than it is for singletons (39 weeks) ***(Cunningham et al., 2005)***.

The therapeutic interventions in the setting of preterm labor aim to inhibit or reduce the strength and frequency of contractions, which delays the time of delivery and to optimize fetal status before preterm delivery ***(Iams et al., 2002).***

During the last 15 years, vitamin D has attracted increased attention. This is mainly due to new discoveries about the impact of vitamin D on several health outcomes beyond its known metabolic actions on bone and mineral metabolism ***(Manios et al., 2017).***

Vitamin D is either produced in the skin in response to direct exposure to sunlight from dehydrocholesterol or obtained from the diet ***(Ramagopalan et al., 2010)***.

In addition to its effects on health and metabolism, vitamin D has raised interest because of the large variation in the prevalence of vitamin D deficiency across countries

worldwide, with estimates ranging from 2 to 90% ***(Manios et al., 2017).***

Health care providers have reported large increases in vitamin D test requests ***(Basatemur et al., 2017)***. There is large heterogeneity between studies, mainly due to differences in the methods used to estimate vitamin D concentration in blood ***(Manios et al., 2017).***

Vitamin D level is defined as a serum level of 25-hydroxycholecalciferol [25(OH)D]. Vitamin D insufficiency is defined as a 25(OH)D concentration of<30ng/ml and frank vitamin D deficiency is defined as a 25(OH)D concentration of <20ng/ml ***(Adams et al., 2010)***.

Studies provide conflicting evidence for adverse maternal and child health outcomes related to vitamin D deficiency. However, the current state of evidence suggests unclear benefits of routine vitamin D supplementation for most maternal or child health outcomes. Despite that controversies, most Western countries recommend vitamin D supplementation during pregnancy ***(Eggemoen et al., 2016).***

Multiple epidemiologic studies have found an association between higher maternal serum 25-hydroxyvitamin D concentration, the physiological measure of vitamin D status, and lower Preterm birth risk ***(McDonnell et al., 2017).***

Aim of the Study

This study aim to assess the association between vitamin D status and preterm labor.

Chapter 1

VITAMIN D

During the first third of the twentieth century, a major focus of research in physiological chemistry was the identification of vitamins, compounds that are essential to the health of humans but cannot be synthesized by them and must therefore be obtained in the diet. Early nutritional studies identified two general classes of such compounds: fat soluble vitamins and water soluble vitamins. Eventually the fat soluble group was resolved into the four vitamin groups A, D, E, and K, all of which are isoprenoid compounds synthesized by the condensation of multiple isoprene units. Two of these (D and A) serve as hormone precursors (prohormones) ***(Nelson and Cox, 2018).***

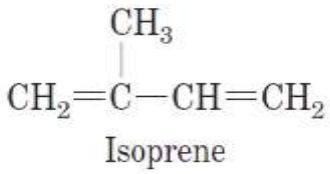

Figure (1): Isoprene ***(Nelson and Cox, 2018).***

Vitamin D was first discovered in1920 by Mellanby. It was first identified as a vitamin early in the 20thcentury, but now recognized as a prohormone. A unique aspect of vitamin D as a nutrient is that it can be synthesized by the human body through the action of sunlight. It is also naturally present in very few nutriments, and available as a dietary supplement. In