Association between Maternal and Neonatal Vitamin D status and the Development of Congenital Anomalies

Thesis

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By

Mohamed Mahmoud Ramadan Khalifa
M.B., B.Ch,
Faculty of Medicine - Shams University (2015)

Under supervision of

Prof. Dr. Mohamed Nasr El-Deen El-Barbary
Professor of Pediatrics
Faculty of Medicine, Ain Shams University

Prof.Dr./ Sahar Samir Abd El-Maksoud
Professor of Clinical Pathology
Faculty of Medicine, Ain Shams University

Dr. Suzan Abd El-Razek Mohamed
Lecturer of Pediatrics
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
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Mohamed Khalifa

List of Contents

List of Tables

List of Tables Cont...

List of Figures

List of Abbreviations

Abb.	Full term
1,25-DHCC	1,25- dihydroxycholecalciferol
25OHD	25 hydroxyvitamin D
Ca	Calcium
CAs	Congenital anomalies
CHD	Congenital heart disease
CNS	Central nervous system
C-section	Cesarean section
CT	Computed tomography
DOHaD	Developmental origins of health and disease
GDM	Gestational diabetes mellitus
HATs	Histone acetyl transferases
HDACs	Histone deacetylases
IOM	Institute of medicine
MRI	Magnetic resonance imaging
NTDs	Neural tube defect
P	Phosphorus
PTH	Parathyroid hormone
PTHrP	PTH-related peptide
RCTs	Randomized Clinical Trials
RXR	Retinoid X receptor
SGA	Small for gestational age
VACTERL	Vertebral anomalies, anal atresia, cardiac defects, trachea-esophageal fistula, renal anomalies, limb defects
VDR	Vitamin D receptor
VDRE	Vitamin D response element

INTRODUCTION

Congenital anomalies (CAs), also known as congenital malformations or birth defects, can be defined as functional or structural anomalies that occur during intrauterine life ***(Elghanmi et al., 2020).***

Its etiology is unknown in 50% of cases and genetic in 30-40% and environmental in 5-10%. Medications, infectious agents, and environmental toxins had all been implicated as teratogens ***(Onankpa et al., 2014).***

Vitamin D is not only a lipid-soluble vitamin, but also a steroid hormone that can be synthesized endogenously. It has an important role in calcium (Ca)-phosphorus (P) homeostasis ***(Holick et al., 2016).***

Molecular and genetic studies confirm that vitamin D also has role in epigenetic modification and it modulates the risks of several other human diseases, including autoimmune disorders ***(Zeitelhofer et al., 2017).***

Epigenetic modifications are among the most important mechanisms by which environmental factors can influence early cellular differentiation and create new phenotypic traits during pregnancy and within the neonatal period without altering the deoxyribonucleic acid sequence. Epigenetic changes can not only modulate the individual adaptation to the

environment but also have an influence on lifelong health and disease ***(Indrio et al., 2017).***

Vitamin D regulates the essential pathways of cellular metabolism and differentiation via its nuclear receptor (vitamin D receptor) (VDR). In addition to this, vitamin D markedly influences the regulation of cell replication ***(Karlic et al., 2011).***

Vitamin D deficiency in pregnancy has been found to be associated with development of multiple congenital anomalies in offspring in several studies, like congenital heart disease, congenital neural tube defect, congenital diaphragmatic hernia ***(Kim et al., 2016).***

Thus, it is advisable to review Vitamin D deficiency in mothers and their offspring so that strategies can be implemented to prevent the impact of vitamin D deficiency on the fetus.

Aim of the Work

This study aims to evaluate the potential association between maternal and neonatal vitamin D status and the subsequent development of congenital anomalies.

Chapter One

VITAMIN D IN PREGNANCY

Physiology of vitamin D

Vitamin D is a fat-soluble vitamin with two major physiological forms: Ergocalciferol, (vitamin D2) and Cholecalciferol (vitamin D3) ***(DeLuca, 2014).*** These two forms basically differ in their side chain structure, While D2 is mainly obtained from plants and vegetable sources, D3 is majorly synthesized in the skin on exposure to sunlight (UVB radiation) from 7 dehydrocholesterol, Both forms of vitamin D are also available as dietary supplements ***(De-Regil et al., 2016).***

All the forms of vitamin D are activated only on enzyme-mediated hydroxylation.

The first hydroxylation reaction is mediated by 25α-hydroxylase, to produce 25 hydroxyvitamin D (25OHD) or calcidiol and takes place in the liver, This is followed by the next hydroxylation step in the kidney, mediated by 1α-hydroxylase, to produce 1,25- dihydroxycholecalciferol (1,25-DHCC) or calcitriol ***(Harvey et al., 2014).*** **(Figure 1)**

While 25OHD is the most abundant circulating form of vitamin D, 1,25-DHCC is the most active form. The hydroxylation reactions and the availability of active vitamin D are regulated by serum calcium and phosphorus and parathyroid hormone (PTH) ***(Sahota, 2014).***

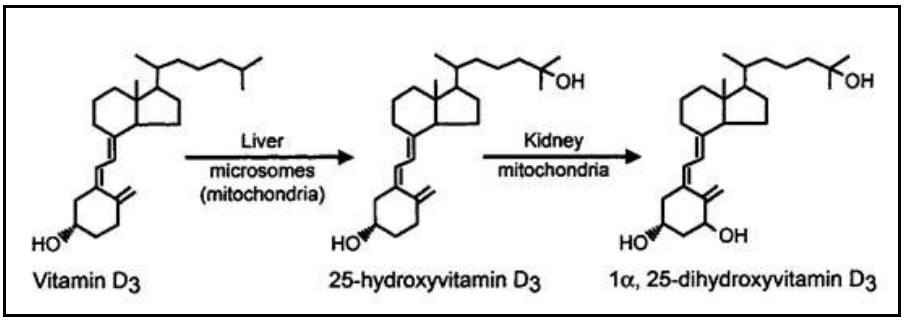

Figure (1): Vitamin D metabolism in the liver, 25-hydroxylation of vitamin D occurs leading to 25(OH)D. In the kidney, a second hydroxylation takes place by 1 α-hydroxylase leading to the formation of 1,25-dihydroxivitamin 2D, the biologically active form of vitamin D ***(Holick et al., 2006).***

Dietatic sources of vitamin D *(Dawodu et al., 2013).*

Vitamin D is also found in a number of foods:

- Oily fish – such as salmon, sardines and mackerel
- Red meat
- Liver and beef
- Milk
- Egg yolks
- Fortified foods – such as some fat spreads and breakfast cereals

Vitamin D is a secosteroid, which is also considered an important prohormone ***(Weinert et al., 2015).*** Since vitamin D receptors (VDRs) are present in many cells and tissues throughout the body, many studies support the role of vitamin D in several physiological functions beyond bone and muscle

health ***(Joergensen et al., 2014).*** During pregnancy, vitamin D plays a vital role in embryogenesis, especially fetal skeletal development and calcium homeostasis ***(Hollis et al., 2011).***

Several studies suggested the increasing prevalence of vitamin D deficiency in pregnancy and the associated adverse maternal and fetal outcomes, such as gestational diabetes mellitus (GDM), preeclampsia, small for gestational age (SGA) and preterm births ***(Palaniswamy et al., 2016).***

Vitamin D physiology during pregnancy

During pregnancy, mobilization of maternal calcium increases to meet the demands of adequate fetal bone mineralization ***(Olmos-Ortiz et al., 2015).*** As a consequence, a number of physiological adaptations take place, including increased maternal serum calcitriol, vitamin D binding protein (DBP) and placental VDR activity to maintain normal serum levels of 25OHD and calcium ***(Olmos-Ortiz et al., 2015).***

Besides the kidneys, the placenta can potentially activate 25(OH) D, since it contains the enzyme 1-α-hydroxilase producing 1, 25(OH) 2D. Moreover, placenta has a paracrine control of vitamin D metabolism and it may also inactivate 25(OH)D by 24-hydroxylation to 24,25(OH)2D. This makes it possible for a local regulation of vitamin D levels within the placental tissue that may modulate anti-inflammatory effects

and affect pregnancy development and/or perinatal outcomes ***(Liu et al., 2012) (Fig. 2).***

Plasma levels of 1.25 (OH) 2D increases in early pregnancy, reaching a peak in the third trimester and returning to normal during lactation. A potent stimulus to placental transfer of calcium and placental synthesis of vitamin D is the PTH-related peptide (PTHrP), produced in the fetal parathyroid and placental tissues, which increases the synthesis of vitamin D. The PTHrP can reach the maternal circulation and it acts through the PTH/PTHrP receptor in the kidney and bones, being a mediator in the increase of 1.25(OH) 2D and helping in the regulation of calcium and PTH levels in pregnancy.

Other signals involved in the regulation process include prolactin and the placental lactogen hormone, which increase intestinal calcium absorption, reduce urinary calcium excretion and stimulate the production of PTHrP and 1.25(OH) 2D ***(Mulligan et al., 2010).***