Maternal plasma 25-hydroxyvitamin D level and pregnancy outcome

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For girls
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ ﴾(32)

سورة البقرة

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Abbreviation	Meaning
1,25(OH)2D	1,25-dihydroxyvitamin D, or calcitriol (active state)
25(OH)D	25-hydroxyvitamin D, 25-hydroxycalciferol
AAP	American Academy of Pediatrics
ACOG	American College of Obstetrics and Gynecology
ACTH	Adrenocorticotrophic Hormone
ADA	American Diabetic Association
AFI	Amniotic Fluid Index
AI	Adequate Intake
BV	Bacterial Vaginosis
BMR	Basal Metabolic Rate
BMI	Body mass index (kg/m2)
CAMP	Cyclic Adenosine Monophsphate
CDC	Centers for Disease control and Prevention
Cr e B	caMP-response element-binding protein
c MYC	c- myocproto-oncogene
DBP	Vitamin D binding protein
DRI	Dietary Reference Intakes
FL	Fundal Level
FNB	Food and Nutrition Board
GDM	Gestational diabetes mellitus
HCG	Human Chorionic Gonadotropine
HCS	Human Chorionic somatomammotropin
HPL	Human Placental Lactogen
IGF	Insulin Growth Factor
IOM	Institute of Medicine (U.S.)
IRGT – 4	Insulin regulateable glucose transfers 4
IRS -1	Insulin receptor substrate 1
IU	International Unit
IUGR	Intrauterine Growth Restriction
IQ	Intelligence Quotient
NTD	Neural Tube Defects
NLS	Nuclear Localization Signs
OGTT	Oral Glucose Tolerance Test
PE	Preeclampsia
PROM	Premature Rupture of Membrane
PTH	Parathyroid hormone
raa system	Renin angiotensin aldosterone system
RANK	receptor activator of nuclear factor Kappa

List of Abbreviations

Abbreviation	Meaning
RDA	Recommended Daily Allowance
RXR	Retinoid X Receptor
SBP	Systolic Blood Pressure
SGA	Small for Gestational Age
SNP	Single Nuclear Polymorphism
SPF	Sun Protection Factor
T2DM	Type 2 Diabetes Mellitus
T3	Triiodothyronine
T4	Thyroxin
UL	Tolerable Upper Intake Limit
UVB	Ultraviolet beta solar radiation
VDR	Vitamin D Receptor
VDRE	Vitamin d response element
Vitamin D2	Ergocalciferol
Vitamin D3	Cholecalciferol

Introduction

Vitamin D is a steroid hormone that is derived primarily from synthesis in the skin through exposure to ultraviolet B radiation. Vitamin D undergoes hydroxylation in the maternal liver to form 25-OH-vitamin D (25-OH-D) which is an inactive supply form of this hormone. The active form of vitamin D (1,25-[OH] 2-vitamin D) results from the activity of 1-α-hydroxylase in the maternal kidney or placenta ***(Hollis B et al,2007).***

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent hypocalcemic tetany. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults ***(Institute Of Medicine¸2010).***

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert 25(OH)D to $1,25(OH)_2D$ ***(Holick MF¸2008).***

The vitamin D deficiency during pregnancy is caused by a lack of adequate sunlight exposure needed to synthesize vitamin D_3 (cholecalciferol) in the skin, coupled with oral intakes that are too low to meet the increased demands of pregnancy, even with regular use of prenatal vitamins containing 400 IU vitamin ***D_3*** ***(Bodnar LM et al, 2007).***

An adequate 25-OH-D level has been determined to be ≥32 ng/mL. Vitamin D insufficiency and deficiency are diagnosed at levels of <32 ng/mL and <20 ng/mL 25-OH-D, respectively. According to these criteria, vitamin D deficiency is very common in pregnancy; up to 50% of

the women are classified as vitamin D deficient (***Mulligan ML et al 2010***).

Because the half-life of 1,25-(OH)2 -vitamin D is only several minutes, the more accurate assessment of an individual's vitamin D status is determined through measurement of 25-OH-D, which has a half-life of approximately 3 weeks ***(Hollis BW et al, 2007).***

While the function of vitamin D is best understood through its effect on bone metabolism and mineral homeostasis, the influence of vitamin D on biologic processes is diverse. Indeed, vitamin D has been linked with a wide range of adverse health outcomes, including cancer, cardiovascular disease, diabetes, mental health disorders, infectious diseases, and autoimmune disorders ***(Bischoff-Ferrari HA et al, 2004)***.

Less work has been done to explore the impact on pregnancy outcome. Nevertheless, the fact that the placenta-decidua has VDR and expresses 1α-hydroxylase for synthesis of 1,25 (OH)2D highlights many potential pathways linking vitamin D to birth outcomes (preeclampsia, spontaneous preterm birth, gestational diabetes, and fetal growth restriction***) (Lisa M. Bodnar and Hyagriv N. Simhan, 2010).***

Aim of work

This study aimed to assess the causal relation between 25 hydroxyvitamin D (25-OHD) levels and adverse maternal and fetal outcomes including (preeclampsia ,preterm birth ,GDM and SGA).

Pregnancy is a dynamic, anabolic state. Within several weeks of conception, a new endocrine organ, the placenta, is already formed and is secreting hormones that affect the metabolism of all nutrients. These adjustments in nutrient metabolism, in addition to changes in the anatomy and physiology of the mother, support fetal growth and development while maintaining maternal homeostasis and preparing for lactation. Depending on the nutrient, one or more of the following adjustments occur:

1. Accretion in new tissue or deposition in maternal stores
2. Redistribution among tissues
3. Increased turnover or rate of metabolism.

To support these adjustments, the use of nutrients from the diet may be altered either by increasing intestinal absorption or by reducing excretion via the kidney or gastrointestinal tract. These adjustments in nutrient metabolism are complex and evolve continuously throughout pregnancy ***(Jant C King, 2000).***

The changes in nutrient metabolism can be described by several general concepts: adjustments in nutrient metabolism are driven by hormonal changes, fetal demands, and maternal nutrient supply; more than one potential adjustment exists for each nutrient; maternal behavioral changes augment physiologic adjustments; and a limit exists in the physiologic capacity to adjust nutrient metabolism to meet pregnancy needs, which when exceeded, fetal growth and development are impaired ***(Dale Kline and Rachel Warren¸2012).***

- **Hormonal Changes**

The first half of pregnancy is primarily a time of preparation for the demands of rapid fetal growth that occurs later in pregnancy. The corpus luteum and the placenta secrete hormones that maintain pregnancy and influence metabolism. Also the pituitary gland enlarges by approximately 135 percent, the thyroid undergoes moderate enlargement caused by glandular hyperplasia and increased vascularity and the maternal adrenal

glands undergo little, if any, morphological change ***(Willimas Obstetrics ,2010).***

Hormonal changes in reproductive system

1. Human chorionic gonadotropin (hCG)

Human chorionic gonadotropin is detected in the serum and urine within a few days of implantation. Human chorionic gonadotropin interacts with the HCG receptor and promotes the maintenance of the corpus luteum during the beginning of pregnancy. This allows the corpus luteum to secrete the progesterone hormone in the first trimester. Progesterone enriches the uterus with a thick lining of blood vessels and capillaries so that it can sustain the growing fetus. Also due to its highly negative charge, hCG may repel the immune cells of the mother, protecting the fetus during the first trimester ***(Jant C King, 2000)***.

2. Human chorionic somatomammotropin (hCS)

The placental hormone **Human chorionic somatomammotropin (**hCS), also known as human placental lactogen (h PL), is secreted by the fifth week of pregnancy. It reaches a peak secretion of 1 to 2 gm/day, paralleling the growth of the placenta. Metabolically, hCS plays a weak role in causing the deposition of protein into tissues (growth hormone is 100 times more effective than hCS in promoting tissue growth) ***(Rasmussen KM et al, 2009)***.

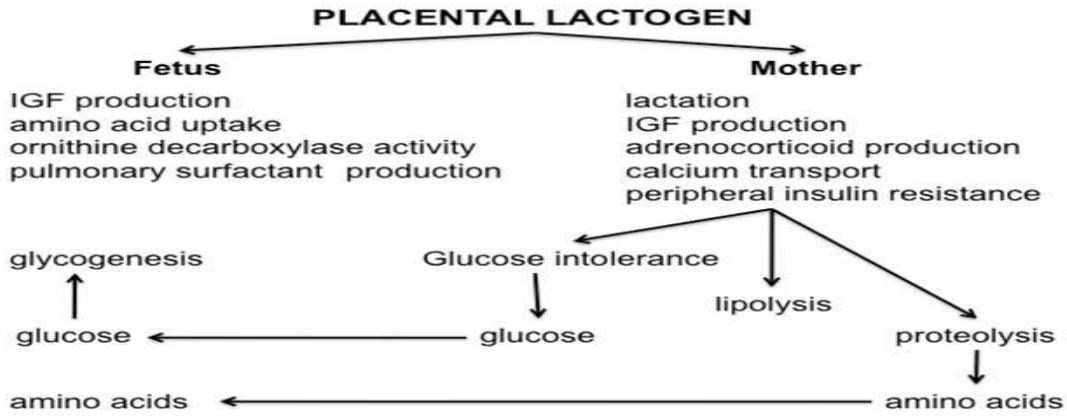

Figure 1.The biologic actions of Placental Lactogen (PL) in the mother and fetus. ***(Stuart Handwerger, 2011)***.

3. **Estrogen**

Biosynthesis of the estrogens (ie, estrone, estradiol, and estriol) is a complicated process involving the mother, fetus, and placenta. In addition to influencing the uterus and other reproductive organs, estrogens cause a rise in certain binding hormones, which result in the elevation of total hormone concentrations, whereas the amounts of unbound and biologically active hormones remain unchanged. Estrogens also influence carbohydrate, lipid, and bone metabolism ***(Jant C King, 2000)***.

4. **Progesterone**

Increase in progesterone level is responsible for an elevation in basal body temperature, which slightly increases caloric needs and stimulates maternal respiration. Unlike estrogen, progesterone stimulates the kidneys to excrete sodium, due in part to increased aldosterone production, which is involved in water balance. The net result is a slight loss of sodium from the kidneys, affecting sodium requirements during pregnancy. The most noticeable effect of increased progesterone is a decrease in activity of smooth muscles, found in the colon. Lead to constipation. The cardio-esophageal sphincter , is relaxed, lead to heartburn ***(Dale Kline and Rachel Warren¸2012).***

Hormonal changes in non reproductive endocrine systems

1. Pituitary gland

- **Growth hormone**

During the first trimester, growth hormone is secreted predominantly from the maternal pituitary gland, and concentrations in serum and amnionic fluid are within nonpregnant values. As early as 8 weeks, growth hormone secreted from the placenta becomes detectable and maternal serum values increase slowly to plateau in 28^{th} weeks***(Williams Obstetrics¸2010).***

- **Prolactin**

Maternal plasma levels of prolactin increase markedly during the course1 of normal pregnancy. Serum concentration levels are usually 10-fold greater at term compared with normal nonpregnant women ***(Williams Obstetrics¸2010).***