



Assessment of Vitamin D Levels in Women with Polycystic Ovarian Syndrome

Thesis

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Submitted by

Sanaa Shaban Yosif Elkholy

M.B.B.Ch, 2011, Ain Shams University
Resident of Obstetrics and Gynecology in
Menofiya Maternity Hospital

Under Supervision of

Prof. Dr. Rowaa Abd ElAzeem Mostafa

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

Dr. Amr Ahmed Mahmoud Riad

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

Dr. Heba Mohamed Adel Abou Zaghla

Lecturer of Clinical Pathology
Faculty of Medicine, Ain Shams University

**Faculty of Medicine
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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ لَوْلَا

لَسَبَّكَ أَنْكَ لَا تَعْلَمُ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Abbreviations

25(OH)D	: 25-hydroxy vitamin D
7-DHC	: 7-dehydrocholesterol
ACTH	: Adreno cortico trophic hormones
AE-PCOS	: Androgen Excess PCOS Society
AFC	: Antral follicular count
AMH	: Anti-müllerian hormone
ASNs	: Androgen- secreting neoplasms
ASRM	: American Society of Reproductive Medicine
AUC	: Area under curve
BMD	: Bone mineral density
BMI	: Body mass index
BV	: Bacterial Vaginosis
CAH	: Congenital adrenal hyperplasia
CHCs	: Combined hormonal contraceptives
CI	: Confidence level
CLIA	: Chemiluminescence immunoassays
COC	: Combined oral contra captive pills
CV	: Cardio vascular
CVD	: Cardio vascular disease
DA	: Diagnostic accuracy
DHEAS	: Dehydroepiandrosterone sulfata

List of Abbreviations

ELISA	: The enzyme-linked immunosorbent assay
ESHRE	: European Society for Human Reproduction & Embryology
FAI	: Free androgen index
FBG	: Fasting blood glucose
FDA	: Food and Drug Administration
FGF-23	: Fibroblast 345 growth factor
FNPO	: Follicular number per ovary
FPG	: Fasting plasma glucose
FPI	: Fasting plasma insulin
FSH	: Follicle-stimulating hormone
GH	: Growth hormone
GNRH	: Gonadotropin releasing hormone
GTT	: Glucose Tolerance Test
HDL	: High density lipoprotein
HDL	: High density lipo proten
HMG-CoA	: 3-hydroxy-3-methylglutaryl-coenzyme A reductase
HPLC	: High-pressure liquid chromatography
IGF-1	: Insulin-like growth factor 1
IH	: Idiopathic hirsutism
IOM	: Institute of Medicine

List of Abbreviations

IU	: International unit
IUCD	: Intra uterine device
IVF	: In-vitro fertilization
LDL	: Low density lipo proten
LH	: Luteinizing hormone
LOD	: Laparoscopic ovarian drilling
LR	: Negative likelihood ratio
LR	: Diagnostic odd ratio
LR+	: Positive likelihood ratio
MS	: Metabolic Syndrome
NC-CAH	: Nonclassical Congenital adrenal hyperplasia
NHANES	: National Health and Nutrition Examination Survey
NIH	: National Institutes of Health
NPV	: Negative Predictive value
OV	: Ovarian volume
PCOM	: Polycystic ovarian morphology
PCOM	: Polycystic ovarian morphology
PCOS	: Polycystic ovary syndrome
PPV	: Positive Predictive value
PRL	: Prolactin
PTH	: Parathyroid hormone

List of Abbreviations

RCTs	: Randomized controlled trials
ROC curve	: Receiving operating characteristic
RR	: Relative risk
SE	: Standard error
SHBG	: Sex hormone binding globulin
T2D	: Type 2 diabetes mellitus
TGF-β	: Transforming growth factor-beta
TMB	: Tetramethylbenzidine
TV	: Trans-vaginal ultrasonography
US	: Ultrasound
UVB	: Ultraviolet band
UV-B	: Ultraviolet-B (UV-B) irradiation
VDBP	: Vitamin D binding protein
VDD	: Vitamin D deficiency
VDR	: Vitamin D receptor

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence of 6–10% in the general population. PCOS is characterized by the following: ovulatory dysfunction resulting in oligo-amenorrhea and/or anovulation, hyperandrogenism and/or hirsutism, and the presence of polycystic ovarian morphology by ultrasound **(Li et al., 2011)**.

It may also create long-term health risks, such as type 2 diabetes, endometrial cancer and cardiovascular disease as it is associated with anovulation, hyperinsulinemia and central obesity **(Haoula et al., 2012)**.

Vitamin D has important roles in various parts of the body, especially in the bones. The active form of vitamin D plays an important role in bone metabolism, regulation of calcium-phosphorus equilibrium and cell differentiation and proliferation **(Studzinsk et al., 1993)**.

Vitamin D also plays a physiologic role in reproduction including ovarian follicular development and luteinization via altering anti-müllerian hormone (AMH) signalling, follicle-stimulating hormone sensitivity and

progesterone production in human granulosa cells (**Irani and Merhi, 2014**).

It also affects glucose homeostasis through several roles. The potential influences of vitamin D on glucose homeostasis include the presence of specific vitamin D receptor (VDR) in pancreatic β -cells and skeletal muscle, the expression of 1- α -hydroxylase enzyme which can catalyze the conversion of 25-hydroxy vitamin D [25(OH)D] to 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter (**Alvarez and Ashraf, 2010**).

It also increases insulin synthesis and secretion and regulates steroidogenesis in the human ovarian tissue (**Parikh et al., 2010**).

Vitamin D deficiency is quite common in the general population. In fact, in several studies, vitamin D levels were found to be below 20 ng/ml in 10-60% of adults (**Lips, 2010**).

Serum 25-hydroxy vitamin D (25-OH D) concentrations of below 20 ng/ml are considered as vitamin D deficiency and serum 25-OH D concentrations of 20-30 ng/ml are considered as vitamin D insufficiency (**Holick, 2007**).

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of vitamin D metabolism and responsiveness. Use of sunscreen, presence of pigment in the skin, patients with skin grafts for burns will cause a reduction in the synthesis of vitamin D. Obesity can cause decreased bioavailability due to reduced availability of vitamin D. The presence of liver failure and kidney disease will also interfere the metabolism of vitamin D (**Holick, 2007**)

The underlying pathogenesis of PCOS are insulin resistance and compensatory hyperinsulinemia (**Franks, 1995**).

Increased insulin resistance causes an increase in weight which triggers hyperandrogenism and, thus, results in clinical symptoms. Although insulin resistance more frequently appears in obese patients (65%), it is less frequent in lean patients with PCOS (20%) (**Dale et al., 1992**).

Studies comparing vitamin D levels between patients with PCOS and healthy women with normal ovulation have yielded conflicting results. Some studies have shown that vitamin D levels do not change in patients with PCOS (**Li et al., 2011**).

Others studies have reported higher levels (**Panidis et al., 2005**) or low levels of vitamin D (**Wehr et al., 2011**).

It has been found that body mass index (BMI) and insulin resistance negatively correlated with vitamin D levels and obese patients have been reported to have low levels of vitamin D (**Wehr et al., 2011**).

One study revealed that insulin resistance was not correlated with vitamin D and that obesity was associated with low vitamin D levels (**Muscogiuri et al., 2012**).

In a study on obese patients with PCOS by Palm et al. in 2012, insulin resistance parameters did not change after three-month supplementation of vitamin D while total testosterone and androstenedion levels decreased (**Palm et al., 2012**).

In an observational study on 25 women with PCOS and 27 controls, Li et al reported an inverse correlation between the 25(OH)D levels and BMI, 72% of women with PCOS had vitamin D deficiency, of which 44% with severe deficiency (**Thomson et al., 2012**).

The same association was observed by Wehr et al in an observational study involving 206 PCOS women with 72% of the population showed the evidence of vitamin D deficiency (25(OH)D serum < 30 ng/ml) and noted the existence of an inverse association between 25(OH)D levels and BMI (**Wehr et al., 2009**).