Role of Vitamin D Supplementation Therapy on Ovulation and Insulin Resistance in Women with PCOS: A Randomized Controlled Trial

Thesis

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بسم الله الرحمن الرحيم
قالوا
سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم
صدق الله العظيم
سورة البقرة الآية: ٣٢

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Dedication

I dedicate this work with sincere thanks and appreciation to my ***parents, my wife and my daughters*** *for providing me with unfailing support and continuous encouragement throughout my years of study and the process of researching and writing the thesis.*

Tarek Hesham

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List of Abbreviations

Abbr.	Full-term
AMPK	: 5′AMP activated protein kinase
ASRM	: American Society of Reproductive Medicine
BMI	: Body mass index
CI	: Confidence interval
CRP	: C-reactive protein
DM	: Diabetes mellitus
DPP-4	: Dipeptidyl peptidase 4
ESHRE	: European Society of Human Reproduction and Endocrinology
FAI	: Free androgen index
GHS	: Growth hormone secretagogue
HMW	: High molecular weight
IGT	: Impaired Glucose Tolerance
IL	: Interleukin- 6
IU	: International unit
LH	: Luteinizing Hormone
mRNA	: Messenger RNA
NIH	: National Institute of Health
PCOS	: Polycystic ovarian syndrome
PPAR-α	: Peroxisome proliferator-activated receptor-alpha
PTH	: Parathyroid hormone
QOL	: Quality of life
RELM	: Resistin-like molecule
RNA	: Ribonucleic acid

SHBG : Sex hormone binding globulin

SPSS : Statistical package for social science

TNF : Tumor necrosis factor

TZDs : Thiazolidinediones

VDD : Vitamin D deficiency

VDRs : Vitamin D receptors

25OHD : 25-hydroxyvitamin D

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most prevalent worldwide female endocrine disorder, affecting nearly 5%-12% of reproductive-aged women. PCOS is the most common cause of anovulatory infertility and its foremost clinical symptoms include anovulation or oligo-ovulation, infertility, menstrual irregularity, polycystic ovaries and hyperandrogenism. PCOS is also common among infertile Arabian female population and it is associated with significant elevations in markers of metabolic syndrome, insulin resistance and cardiovascular risks Unfortunately, PCOS is not a simple pathophysiologic process for which one treatment is sufficient to control all manifestations. Therefore, when choosing a treatment regimen, it should target specific manifestations and individualized patient goals. **Aim of the Work:** The aim of this study is to assess the safety and the efficacy of vitamin D supplementation therapy on ovulation and metabolic changes in women with PCOS.

Study design: Prospective randomized controlled clinical trial. **Patients & Methods:** The current study was conducted in the infertility clinics of Ain Shams University Maternity Hospital in the period between May 2015 and May 2017. It included 300 women diagnosed with polycystic ovary syndrome attending the infertility clinics of Ain Shams University Maternity Hospital.

Results: Being a classification criterion, 25OHD level was significantly lower in the vitamin D deficient subgroup compared to the normal vitamin D subgroup; whereas no significant differences were found between the vitamin D deficient group and the control group. In the same context, 25OHD level was statistically significantly lower in the control group compared to the normal vitamin D subgroup. Vitamin D deficient PCOS women tended to have higher degree of insulin resistance. Fasting glucose was statistically significantly higher in the vitamin D deficient subgroup compared to the normal vitamin D subgroup and the control group; and higher in the control group compared to the normal vitamin D subgroup. Fasting insulin level was statistically significantly higher in the vitamin D deficient subgroup and the control group compared to the normal vitamin D subgroup; whereas no statistically significant differences were found between the former two groups. HOMA2-IR was statistically significantly higher in the vitamin D deficient subgroup and the control group compared to the normal vitamin D subgroup; whereas no statistically significant differences were found between the vitamin D deficient subgroup and the control group. No statistically significant differences were found between the three groups in the various components of the lipid profile.

Conclusion: Results of the thesis showed that Cumulative ovulation rate was significantly higher in the vitamin D deficient subgroup following vitamin D supplementation compared to the normal vitamin D subgroup and the control group with a rate ratio of 1.27 and 1.22 respectively. Number needed to treat was calculated to be 5.34 and 6.38 compared to normal vitamin D subgroup and control group respectively, i.e. 6.38 women are needed to be supplemented with vitamin D for one of them to benefit compared to control women. No significant differences were found between the three subgroups regarding the median ovulating dose of clomiphene citrate. Also, no significant differences in the cumulative clinical pregnancy rate between the ovulatory women of the three subgroups.

Key words: Vitamin D, PCOS, Ovulation.

Introduction

Polycystic ovarian syndrome (PCOS) is the most prevalent worldwide female endocrine disorder, affecting nearly 5%-12% of reproductive-aged women ***(Costello and Ledger, 2012).***

PCOS is the most common cause of anovulatory infertility and its foremost clinical symptoms include anovulation or oligo-ovulation, infertility, menstrual irregularity, polycystic ovaries and hyperandrogenism ***(Lerchbaum and Obermayer-Pietsch, 2012).***

PCOS is also common among infertile Arabian female population and it is associated with significant elevations in markers of metabolic syndrome, insulin resistance and cardiovascular risks ***(Rouzi and Ardawi, 2009).***

Unfortunately, PCOS is not a simple pathophysiologic process for which one treatment is sufficient to control all manifestations. Therefore, when choosing a treatment regimen, it should target specific manifestations and individualized patient goals ***(Kale-Gurbuz et al., 2013).***

There are many considerations to explain the underlying bases of PCOS, particularly the well-known roles of hypothalamic-pituitary gonadal dysfunctions, metabolic abnormalities and the genetic factors. However, the definite pathogenesis and real underlying etiologies of PCOS remain

uncertain and ripe with opportunities for further research ***(Kale-Gurbuz et al., 2013).*** Moreover, there is variation in the prevalence and phenotypes of PCOS in many ethnic/racial groups ***(Diamanti-Kandarakis and Dunaif, 2012).***

Recently, a special emphasis has recently been directed to the potential role of vitamin D and some regulatory peptides (e.g. adipokines and follistatin) and their associated metabolic roles and genetic factors in the development of PCOS and its related co-morbidities. In this concept, the discovering of vitamin D receptors (VDRs), which are nuclear receptors present in nearly every tissue in the body and regulates the expression of about 229 genes of the whole human genome, has revolutionized the importance of vitamin D and provided new insights into its functions ***(Yang et al., 2013).***

Several recent accumulating evidences indicate that vitamin D deficiency or genetic alterations in its receptors are one of the most important causal factors in the pathogenesis of PCOS and reproductive dysfunctions in both girls and women ***(Anagnostis et al., 2013)***.

Vitamin D deficiency is very common in PCOS patients, with a prevalence of 67–85%, and is significantly associated with development and exacerbation of PCOS symptoms and abnormalities; including ovulatory and menstrual irregularities,

infertility, hirsutism, insulin resistance, type 2 diabetes, dyslipidemia, obesity and elevated cardiovascular disease risk factors (***Lerchbaum and Obermayer-Pietsch, 2012).***

More importantly, some emerging data from small uncontrolled intervention studies show a beneficial effect of vitamin D supplementation in the management of PCOS and an improvement in its associated endocrine and metabolic disturbances ***(Thomson et al., 2012)***. However, further investigations and additional large randomized controlled trials are essentially required to better understand and confirm the potential benefits of vitamin D supplementation in this syndrome and its co-morbidities ***(Anagnostis et al., 2013).***

Now, there is a compelling body of evidence that PCOS is significantly characterized by obesity and metabolic diseases. Adipose tissues have profound paracrine and endocrine effects and produce several hormones and cytokines termed adipokines that have widespread effects on body tissues. The disturbance of these adipokines can cause endocrine diseases including PCOS ***(Mattu and Randeva, 2013)***.

Recent studies have shown that there is a strong link between the blood levels of some adipokines, particularly adiponectin, ghrelin and resistin, and the clinical and hormonal indices of PCOS and its associated risks and metabolic disturbances ***(Wang et al., 2012).***