Therapeutic Effect of Vitamin D3 Supplementation to Clomiphene Citrate Resistant PCOS Women: A Randomized Controlled Trial

Thesis

Submitted for Partial Fulfillment of Master Degree
in **Obstetrics & Gynecology**

By

Sara Abouelfath Abouelasrar Gad Dawoud
M.B.B.Ch. – 2013
Faculty of Medicine- Mansoura University

Under Supervision of

Prof. Dr. Ahmed Mohamed Nour El-Din Hashaad
Professor of Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Dr. Reda Mokhtar Kamal Ghanem
Lecturer of Obstetrics & Gynaecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine – Ain Shams University
2020

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Ahmed Mohamed Nour El-Din Hashaad****, Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University, for his meticulous supervision, kind guidance, valuable instructions and generous help.*

Special thanks are due to ***Dr. Reda Mokhtar Kamal Ghanem****, Lecturer of Obstetrics & Gynaecology, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Sara Abouelfath Abouelasrar Gad Dawoud

List of Contents

List of Abbreviations

Abb.	Full term
1,25(OH)2D	*1,25- dihydroxyvitamin D*
25(OH)D	*25- hydroxyvitamin D*
ACOG	*American College of Obstetrics and Gynecology*
AES	*Androgen Excess Society*
AFC	*Antral follicle count*
AGEs	*Advanced glycation end products*
AMH	*Müllerian hormone*
ASRM	*American Society for Reproductive Medicine*
BMI	*Body mass index*
CC	*Clomiphene citrate*
CNS	*Central nervous system*
D2	*Ergocalciferol*
D3	*Cholecalciferol*
ESHRE	*European Society of Human Reproduction and Embryology*
FSH	*Follicle stimulating hormone*
GDM	*Gestational diabetes mellitus*
GnRH	*Gonadotrophin-releasing hormone*
HCG	*Human chorionic gonadotropin*
IGF-1	*Insulin-like growth factor-1*
IOM	*Institute of Medicine*
IR	*Insulin resistance*
ISD	*Insulin sensitising drug*
IVF	*In vitro fertilization*
LH	*Luteinising hormone*

List of Abbreviations cont...

Abb.	Full term
DHEAS	*Dehydroepiandrosterone sulfate*
mFG	*Modified Ferriman-Gallwey*
NC-CAH	*Non-classical congenital adrenal hyperplasia*
NHANES	*National Health and Nutrition Examination Surveys*
NIH	*National Institutes of Health Criteria*
PCOM	*Polycystic ovarian morphology*
PCOS	*Polycystic ovary syndrome*
PTH	*Parathyroid hormone*
RAGE	*Receptor for AGEs*
RDA	*Recommended daily allowance*
SHBG	*Sex hormone binding globulin*
VDR	*Vitamin D receptor*

List of Tables

List of Figures

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a multifaceted condition characterized by chronic anovulation and excess ovarian activity, in contrast to other causes of anovulation that involve ovarian dormancy or primary insufficiency ***(Rocha et al., 2019).*** It is the most common cause of chronic anovulation and anovulatory infertility ***(Dumont et al., 2015).*** Signs of the syndrome can present as early as puberty ***(Ehrmann, 2005)***.

The clinical manifestations of PCOS are heterogeneous and it looks possible that patients may present some of various symptoms and signs. The heterogeneity seems to be adjusted by several factors; such as genetic factors, nutritional condition in the uterus, prenatal androgen exposure, insulin resistance, exaggerated adrenarche, and body weight changes ***(Zhang et al., 2013).*** Environmental status and other factors such as obesity, appear to exacerbate the underlying genetic predisposition.

Clinical manifestations of PCOS include menstrual irregularities, signs of androgen excess, obesity, and sometimes hirsutism. Although some of the clinical symptoms and presentations of PCOS is dependent on age, ovarian failure and hyperandrogenism are common characteristics at any age ***(Tsikouras et al., 2015).***

Clomiphene citrate is used for induction of ovulation in PCOS, administered during the early follicular phase of the menstrual cycle or during a progesterone-induced withdrawal bleeding.

For women who do not ovulate on the starting dosage of clomiphene citrate, the clinician may increase the daily dose. A change in therapy is recommended, if a pregnancy does not occur after six ovulatory cycles on the drug. ***(Thessaloniki ESHRE/ASRM-Sponsored Polycystic Ovary Syndrome Consensus Workshop Group, 2008).***

Because of its antiestrogenic properties, clomiphene citrate can be detrimental to cervical mucus and endometrial thickness, which may negatively affect conception and implantation. women need to be educated about adverse effects that include hot flashes, dry mouth, and vision changes, which may require a change in medication management.

Approximately 20% to 30% of women do not ovulate while taking clomiphene citrate ***(Tang et al., 2013)***. Women with PCOS who have not responded to clomiphene citrate may be offered one of following second-line treatments:

- Laparoscopic ovarian drilling
- Combined treatment with clomiphene citrate and metformin, if this has not already been given as a first-line treatment, or

- Gonadotrophins

It is evidenced that there is poly morphism in VDR gene associated with vitamin D levels in PCOS patients. This gene is isolated from the female reproductive organs. In VDR null mice; uterine hypoplasia, impaired folliculogenesis and infertility is noted. That's why it is thought to be contributing in the genomic regulation of reproduction.***(Kinuta et al., 2000)***

Another interesting observation is; PCOS patients have hypovitaminosis D3***(Mazloomi et al., 2012)***, with increasing evidence that vitamin D affects insulin and glucose metabolism ***(Girgis et al., 2013)***. Vitamin D intake may improve hormonal profiles in addition to having anti-inflammatory and anti-oxidant effects ***(Jamilian et al., 2017).***

AIM OF THE WORK

The aim of the work is to assess the efficacy of vitamin D supplementation in improving ovulation induction in PCOS women.

Research question

In clomihene citrate resistant PCOS women, does vitamin D supplementation improves ovulation rate?

Research hypothesis

In clomihene citrate resistant PCOS women, vitamin D supplementation may improve ovulation rate.

Chapter 1

POLYCYSTIC OVARY SYNDROME

Basic Pathophysiology of Polycystic Ovary Syndrome

Poly cystic ovary syndrome (PCOS) remains an enigmatic condition, despite years of research. The pathophysiology is complex and is thought to be a result of interactions between genetics, epigenetics, ovarian dysfunction, endocrine, neuroendocrine and metabolic alterations, amongst other changes ***(Ibáñez et al., 2017).***

PCOS is characterized by hypothalamic–pituitary–ovarian axis dysfunction and anovulation. But, unlike other causes of ovulatory failure that feature insufficient ovarian follicle growth or suppressed gonadotropin secretion (or both), PCOS typically includes androgen excess and subtle alterations (not detected by routine tests) in serum levels of gonadotropins and estrogens ***(Rocha et al., 2019).***

Furthermore, extra-reproductive manifestations of PCOS include insulin resistance (IR), metabolic syndrome (MS), and low-grade chronic inflammation ***(Durmus et al., 2017).***

Ovarian pathology is a major element of PCOS**.** In a normal fertile female, a single follicle matures and undergoes ovulation from a pool of primordial follicles present in the ovaries since birth ***(Ibáñez et al., 2017)***.

The rate at which primordial follicles are selected for growth is strictly controlled, in order to maintain ovarian reserve and ensure that fertility is intact ***(Hsueh et al., 2015).***

In PCOS, an imbalance between androgens, anti-Müllerian hormone (AMH) and follicle stimulating hormone (FSH), cause a halt of follicular growth ***(Franks et al., 2008).***

AMH is produced by ovarian granulosa cells and is important in preventing primordial follicles from transitioning into primary follicles. The characteristic polycystic appearance of ovaries in PCOS is due to large number of primordial follicles growing and undergoing subsequent growth arrest ***(Ibáñez et al., 2017).***

High luteinising hormone (LH) levels are required for androgen synthesis by ovarian theca cells. High LH combined with low FSH levels and decreased estradiol synthesis through the conversion of androgens, results in anovulation due to the absence of a dominant follicle ***(Lebbe et al., 2013).***

Insulin resistance (IR) is another important component of PCOS ***(Ibáñez et al., 2017).*** IR results from inadequate tissue utilization of insulin for glucose metabolism. Although the exact mechanisms are yet to be elucidated, genetic, intra- and extra uterine factors and adaptations to consumption of high energy food items are considered to be factors causing IR in PCOS ***(Kumari et al., 2013).***

Puberty is also thought to have a major effect on hyperinsulinaemia and IR. During puberty, there may be a temporary increase in insulin levels and IR. Subsequent elevations in insulin-like growth factor-1 (IGF-1) and growth hormone levels, mean that more amino acids are available for growth. During puberty, only glucose metabolism is affected by IR, while protein metabolism is spared ***(Saenger et al., 2000).***

In PCOS, IR affects the liver, adipose tissue and skeletal muscles. However, the steroidogenic ovaries and adrenal glands remain sensitive to the actions of insulin, another effect of insulin is to decrease sex hormone binding globulin (SHBG) synthesis in the liver; resulting in elevated levels of free androgens. Women with PCOS often have elevated serum insulin and IR, regardless of androgen concentrations and their levels of 'adiposity'.

Criteria for diagnosis

Some sets of criteria for diagnosis have been proposed for PCOS: National Institutes of Health Criteria (NIH), defined in 1990 and included only: presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhea ***(Dunaif, 1997).***

Later in 2003, The European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) developed the **Rotterdam consensus** regarding the diagnosis of PCOS,