THE ROLE OF ROSIGLITAZONE IN INDUCTION OF OVULATION IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME

Thes*is submitted for partial fulfillment of the MD degree in Obstetrics and Gynecology*

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2010

Abstract

The Polycystic Ovary Syndrome (PCOS) is a heterogeneous disorder, whose principal features include androgen excess, ovulatory dysfunction, and/or polycystic ovaries, and is recognized as one of the most common endocrine/metabolic disorders of women. The pathophysiology of PCOS appears to be multifactorial and polygenic**.** Current evidence suggests that insulin resistance is an important pathophysiological feature of the polycystic ovary syndrome (PCOS). An important implication of insulin resistance in PCOS is that insulin-sensitizing agents are a useful therapeutic approach in this disorder, as documented by multiple clinical trials.

Clomiphene citrate (CC) is currently the first-line therapeutic modality for women with infertility and PCOS. Overall, approximately 80% of all patients receiving clomiphene ovulate and 40% (one-half of those ovulating) conceive. Data suggest that decreased insulin sensitivity, hyperandrogenemia, and obesity, all associated with PCOS, are prominent factors involved in reducing the probability that the ovaries will respond to clomiphene.

Key Words:

Definition and Diagnosis of PCOS, Insulin Resistance and PCOS, Clinical Pharmacology, the Role of Insulin Sensitizers in PCOS.

ACKNOWLEDGEMENT

*First and above all thanks to **GOD**, the most beneficial and merciful for helping me bring this work to light.*

*Words fail to express my sincere appreciation to **Prof. Dr.Maher Mohamed Abdel Wahab**, Professor of Obstetrics and Gynecology, Faculty of Medicine, Cairo University. It was both a great honour and a pleasure to work under his supervision. His great encouragement, kind guidance and unforgettable help will always be remembered.*

*My Deepest thanks and appreciation goes to **Prof. Dr. Samia Moustafa Mohamed**, Professor of Biochemistry Faculty of Medicine, Cairo University, for her generous supervision and fruitful assistance during the course of this research.*

*I would like to express my gratitude to **Prof. Dr.Mohamed Mahmoud Waly,** Professor of Obstetrics and Gynecology Faculty of Medicine, Cairo University, for his kind help and encouragement in performing this work.*

*Many thanks to **Prof. Dr. Ahmed Sayed El-Gazar,** Assistant Professor of Obstetrics and Gynecology Faculty of Medicine, Cairo University for his generous effort, valuable instructions and great help .*

DEDICATION

To My Father,

Prof. Dr. Mahmoud Kotb,

for his endless love, guide and support.

LIST OF ABBREVIATIONS

17-HP	17α-hydroxyprogesterone
ACTH	Adrenocorticotropic hormone
AES	Androgen Excess Society
AN	Acanthosis nigricans
ASRM	American Society of Reproductive Medicine
BMI	Body mass index
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CC	Clomiphene citrate
DCI-IPG	D-chiro-inositolphosphoglycan
DHEAS	Dehydroepiandrosterone sulfate
ESHRE	European Society for Human Reproduction and Embryology
EGF	Epidermal growth factor
FSH	Follicle-stimulating hormone
GnRHa	Gonadotropin-releasing hormone agonist
HCG	Human chorionic gonadotropin
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IGF-1	Insulin growth factor-1
IGFBP-1	Insulin growth factor binding protein-1
IRSs	Insulin receptor substrates
LH	Luteinizing hormone
MAPK	Mitogen activated protein kinase
MFO	Multifollicular ovaries
NAFLD	Nonalcoholic fatty liver disease
NCAH	Nonclassic congenital adrenal hyperplasia
NIH	National Institutes of Health
OGTT	Oral Glucose Tolerance Test
OHSS	Ovarian hyperstimulation syndrome
OSA	Obstructive Sleep Apnea
PCOS	Polycystic Ovary Syndrome
PI	Pulsatility index
PKA	Protein kinase A

PPARγ	Peroxisome proliferator-activated receptor γ
PSU	Pilosebaceous unit
RI	Resistive index
RIA	Radioimmunoassay
RXR	Retinoid X receptor
SHBG	Sex hormone-binding globulin
StAR	Steroidogenic acute regulatory protein
TG	Triglyceride
TSH	Thyroid-stimulating hormone
TZDs	Thiazolidinediones
WHR	Waist-to-hip ratio

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder of chronically abnormal ovarian function and hyperandrogenism affecting 5–10% of the female population of reproductive age ***(Wallace and Sattar, 2007)***. It is a heterogeneous disorder characterized by menstrual irregularities, clinical and/or biochemical hyperandrogenism and hyperinsulinemia secondary to reduced insulin sensitivity ***(Homburg, 2003)***

Women with PCOS demonstrate peripheral resistance to insulin, which generally presents with hyperinsulinemia a compensatory increase in plasma insulin levels. The degree of hyperinsulinemia is more profound in obese patients although the presence of insulin resistance appears to be independent of weight. Hyperinsulinemia contributes significantly to the ovarian hyperandrogenism and chronic anovulation commonly observed with PCOS ***(Ghazeeri et al., 2003).***

Clomiphene citrate (CC) is currently the first line therapeutic modality for women with infertility and PCOS. Ovulation occurs in 70-85% of women but 33-45% achieves pregnancy ***(Costello and Eden, 2003)***.

However a significant proportion of PCOS patients are resistant to the usual doses of CC ***(Ghazeeri et al., 2003).*** Often, the only alternative is to proceed with ovulation induction using exogenous gonadotropins which carry the risk of high-order multiple pregnancy and ovarian hyperstimulation, as well as excessive financial cost.

Therefore, attention has turned to the correction of hyperinsulinemia as a method of ovulation induction, particularly in obese women who demonstrate the greatest degree of insulin resistance (***Ghazeeri et al., 2003).***

Recently, the American Society for Reproductive Medicine concluded that "based on the clinical evidence to date, the use of novel insulin sensitizers such as biguanides and thiazolidnediones promise new treatment option for PCOS for both fertility and long-term disease prevention ***(Rouzi and Ardawi, 2006).***

Rosiglitazone is a thiazolidinedione, a new class of drugs which improve insulin resistance in patients with type-II diabetes mellitus and has also been tried for treatment of PCOS. It is a potent and highly selective agonist for the nuclear peroxisome proliferator activated receptor gamma (PPAR-γ). PPAR-γ increases transcription of certain insulin-sensitive genes, thereby improving insulin sensitivity. It also helps in resumption of ovulation in premenopausal anovulatory women with insulin resistance ***(Singh et al., 2008)***.

Unlike metformin, rosiglitazone decreases hepatic fat content and increases insulin sensitivity in muscles. These effects make the drug more useful in patients with insulin resistance ***(Rouzi and Ardawi, 2006).***

AIM OF THE WORK

This study was undertaken to evaluate the therapeutic effects of rosiglitazone treatment in conjunction with clomiphene citrate in induction of ovulation in patients with Polycystic ovary syndrome (PCOS).

DEFINITION AND DIAGNOSIS OF PCOS

The Polycystic Ovary Syndrome (PCOS) is a heterogeneous disorder, whose principal features include androgen excess, ovulatory dysfunction, and/or polycystic ovaries, and is recognized as one of the most common endocrine/metabolic disorders of women ***(Azziz, 2007).***

This syndrome was first described by Stein and Leventhal in 1935 ***(Stein and Leventhal, 1935).***

DEFINING PCOS

The first useful definition of PCOS arose from the proceedings of an expert conference sponsored by the US National Institutes of Health (NIH) in April 1990. Participants were surveyed, and tabulation of the results indicated that most felt that the features of PCOS were (in order of importance): (a) hyperandrogenism and/or hyperandrogenemia, (b) chronic anovulation, and (c) exclusion of related disorders such as hyperprolactinemia, thyroid disorders and congenital adrenal hyperplasia ***(Zawadzki and Dunaif, 1992)***.

Polycystic ovaries were suggestive, not diagnostic, of the syndrome. We should note that these proceedings did not provide clear guidelines on how to define each criterion. Three principal phenotypes of PCOS are recognized using the NIH 1990 criteria, including women with: (a) hirsutism,

hyperandrogenemia, and oligo-ovulation, (b) hyperandrogenemia and oligo-ovulation, or (c) hirsutism ***(Azziz, 2007).***

Another expert conference was organized in Rotterdam in May of 2003, in part sponsored by ESHRE and ASRM. (ESHRE is European Society for Human Reproduction and Embryology, ASRM is American Society of Reproductive Medicine). The proceedings of the conference noted that PCOS could be diagnosed, after the exclusion of related disorders, by two of three features:

(a) Oligo- or anovulation: clinically diagnosed as oligo-/amenorrhea, i.e., menstrual cycles longer than 35 days or less than 10 menstruations per year

(b) Clinical and/or biochemical signs of hyperandrogenism, or

(c) Polycystic ovaries: 12 or more follicles in an ovary, with each follicle measuring 2-9 mm in diameter and/or ovarian volume more than 10 ml. Neither stromal density nor distribution of the follicles is included in this definition. One polycystic ovary is sufficient for diagnosis. As for the NIH 1990 criteria, other disorders should be excluded. It should be noted that these recommendations did not replace the NIH 1990 criteria; rather they expanded the definition of PCOS ***(The Rotterdam ESHRE/ASRM workshop 2003).*** Additional phenotypes now considered as being PCOS by this criteria included: (a) women with polycystic ovaries with clinical and/or biochemical evidence of androgen excess, but no signs of ovulatory dysfunction and (b) women with polycystic ovaries and ovulatory dysfunction, but no signs of androgen excess.