Comparison between metformin and clomiphene citrate therapy for treatment of anovulatory infertility in cases of polycystic ovary syndrome

Thesis
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Abstract

Clomiphene citrate is considered first line therapy for ovulation induction for women with PCOS and infertility the benefits of metformin on insulin sensitivity have been demonstrated in non diabetic women with PCOS. The present study was designed to compare the efficacy of metformin and clomiphene citnte in treatment of anovulation.

Key Words : Infertility PCOS - Clomiplone citrtes - Metformin - A novulation

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List of Abbreviations

ALT	**:**	Alanine Transaminase
AMPK	**:**	50-AMP-activated protein kinase
AST	**:**	Aspartate Transaminase
BMI	**:**	Body Mass Index
CC	**:**	clomiphene citrate
CVD	**:**	Cardio Vascular Disease
DHEAS	**:**	dehydroepiandrosterone sulphate
ER	**:**	Estrogen Recepter
ERs	**:**	estrogen receptors
FSH	**:**	Follicle-stimulating hormone.
GLUT-4	**:**	Glucose transporter type 4.
GnRH	**:**	gonadotrophin-releasing hormone
HMG	**:**	Human menopausal gonadotrophins
HOMA-IR	**:**	homeostatic assessment model for insulin
IGF-1	**:**	Insulin-like growth factor I
IGFBP-1	**:**	Insulin-like growth factor binding protein-1
IR	**:**	Insulin resistance
IUI	**:**	Intra Utrine Insmination
LDL	**:**	low density lipoprotein

LH	**:**	luteinizing hormone
LKB1	**:**	liver kinase B1
MS	**:**	metabolic syndrome
NAFLD	**:**	Non Alcoholic Fatty Liver Disease
NASH	**:**	Non Alcoholic steatohepatitis
OHSS	**:**	Ovarian Hyperstimulation Syndrome
OSA	**:**	Obstructive sleep apnea
PCOS	**:**	Polycystic Ovary
SHBG	**:**	Sex Hormone Binding Globulin
SHP	**:**	Small heterodimer partner
STK11	**:**	Serine/threonine kinase 11
T2DM	**:**	Type two Diabetes Mellitus
TSH	**:**	Thyroid Stimulating Hormone
TVS	**:**	Transvaginal sonography

List of Tables

List of Figures

Contents

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility and affects 4-7% of women **(Ehrmann, 2005)**.

It is by far the most common cause of hyperandrogenic anovulatory infertility and was described more than half a century ago.The underlying cause of this disorder is still uncertain **(Yen, 1999).**

The diagnostic criteria for PCOS were revised at a consensus conference jointly sponsored by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) in Rotterdam, The Netherlands in 2003.

The diagnosis now requires the presence of at least two of the following features:

- polycystic ovaries
- oligo-ovulation or anovulation
- Clinical and/or biochemical evidence of androgen excess.

Metformin is a biguanide currently used as an oralantihyperglycemic agent and is approved by US Food & Drug Administration to manage type 2 DM.

Introduction and Aim of the work

The benefits of metformin on insulin sensitivity have been demonstrated in non-DM women with PCOS.

The use of metformin in cases of PCOS is associated with increased menstrual cyclisity, improved ovulation and a reduction in circulating androgen levels **(Nestler, 2008)**.

Clomiphene citrate (CC) this compound has had a remarkably sustained career as the first-line treatment for women with absent or irregular ovulation due to hypothalamic–pituitary dysfunction associated with normal basal levels of endogenous estradiol (WHO group II).

CC was the first medication capable of inducing ovulation and as such created a welcome revolution in the treatment of infertility associated with anovulation.

AIM OF THE WORK

The aim of work is to compare the efficacy of Metformin and Clomiphene citrate therapies in treatment of anovulation in infertile patients with PCOS and to determine which of them is better as a first line medication .

POLYCYSTIC OVARY SYNDROME

Introduction:

Polycystic ovary syndrome (PCOS) was first described in 1935 by **Stein and Levanthal (1935)** in the American Journal of Obstetrics and Gynecology. Yet, it remains a syndrome that is confusing to many patients and practitioners in terms of its presentation, work-up, and management. There is a spectrum of presenting complaints and physical findings as well as overlap with other disorders, such as the metabolic syndrome **(Benjamins and Barratt, 2009).**

PCOS, a heterogeneous syndrome, is the most frequently encountered endocrine disturbance in women of reproductive age. Its prevalence ranges from 5% to 10%, it affects all ethnic groups, and it is not only a reproductive disorder but a metabolic one **(Azziz et al., 2004).** PCOS is associated with infertility, uterine changes, and endocrinopathies **(Diamanti- Kandarakis, 2008).**

Recognition of the syndrome affords the health provider an opportunity for not only reducing the emotional impact of manifestations such as acne, hirsuitism, alopecia, and infertility, but for reducing the distinct development of type 2 diabetes mellitus (T2DM) in 40% of the affected women and the potential of subsequent strokes and myocardial

infarction **(Legro et al., 1999).**

❖ Pathophysiology:

The prevalence of PCOS in the general population has been estimated to be 5% to 10% of women of reproductive age **(Azziz et al., 2004).**

Screening of an unselected population in the southwestern United States showed an incidence of 4%. Studies in first-degree relatives of patients who have PCOS have shown that 24% of mothers and 32% of sisters are affected, suggesting a major genetic association **(Kahsar-Miller et al., 2001).**

The cause of PCOS remains unknown, and this is an area of active investigation. Theories focus on the impact of luteinizing hormone (LH) stimulation and the role of insulin in the production of ovarian hyperandrogenism. Increased LH pulse amplitude and frequency have been demonstrated in women and adolescents who have PCOS, suggesting an aberrant pattern of hypothalamic gonadotropin-releasing hormone (GnRH) secretion as a causative factor. This increase in LH leads to increased production of androgens from the theca cell of the ovary **(Veldhuis et al., 2001).**

Preferential LH secretion from GnRH pulsatility may be explained by observations in rats showing that variations of GnRH pulse

frequencies result in differential expression of subunit genes. A rapid frequency of GnRH leads to an increase in α and β mRNA expression, thereby favoring LH secretion. Some nonobese patients who have PCOS have an elevated LH/follicle-stimulating hormone (FSH) ratio (>2) **(Azziz, 2000).**

Insulin resistance has been implicated in the pathophysiology of PCOS because of the evidence that insulin stimulates androgen production from the ovary in hyperandrogenic women. Ovarian stroma obtained from hyperandrogenic women has been shown to produce high levels of androgens when exposed to insulin. Insulin had no effect on androgen production from ovarian stroma from non hyperandrogenic women, however, in a case report of an adolescent female patient who had severe type II diabetes and hyperandrogenism, intravenous administration of insulin to control blood glucose was shown to increase serum androgen levels significantly. These androgen levels returned to baseline when the insulin infusion was stopped **(DeClue et al., 1991).**

Women who have PCOS have decreased sensitivity to insulin in muscle and adipose tissue, leading to a compensatory increase in insulin levels. Decreased insulin sensitivity has been demonstrated in lean and obese women, suggesting that the defect is intrinsic to PCOS. Insulin resistance has been described in 20% to 60% of women who have PCOS

(Azziz, 2003).

It has also been proposed that all women who have PCOS have insulin resistance; however, because of differences in populations studied and the sensitivity and specificity of the methods used to measure insulin resistance, not all women who have PCOS manifest insulin resistance **(Dunaif, 2003).**

In PCOS, insulin resistance is selective: insulin action on glucose transport and metabolic pathways is affected, whereas insulin's action on ovarian steroidogenesis is preserved. There are several theories to explain this apparent paradox. Insulin resistance in PCOS seems to be attributable to a post-binding defect in insulin receptor signaling **(Dunaif and Thomas, 2001).**

Binding to the insulin receptor results in tyrosine phosphorylation before stimulating insulin action. If, however, serine phosphorylation occurs, insulin action is inhibited by decreasing its kinase activity **(Dunaif, 1997).**

In the ovary, serine phosphorylation stimulates lyase activity, the enzyme responsible for converting 17-hydroxy progesterone to androstenedione, which results in increased production of androgens from the ovary. Therefore, serine phosphorylation inhibits insulin action in the metabolic pathways and stimulates insulin action to produce androgens in