Luteal Phase Versus Follicular Phase Administration of Clomiphene Citrate in Polycystic Ovary Syndrome. A Randomized Controlled Trial

Thesis

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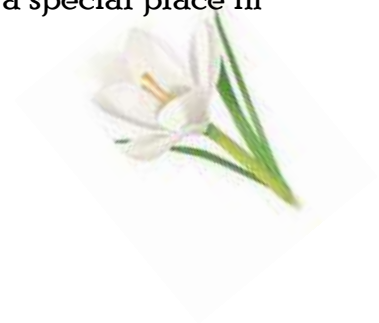

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List of Abbreviations

AGA	Androgenic alopecia
AGEs	Advanced glycation end products
ASRM	American Society for Reproductive Medicine
BBT	Basal body temperature
BMI	Body mass index
CAH	Congenital adrenal hyperplasia
CC	Clomiphene citrate
CPA	Cyproterone acetate
DHEAS	Dehydroepiandrosterone sulfate
E	Estrogen
ER	Estrogen receptors
ESHRE	Eropean Society for Human Reproduction and Embryology
FDA	Food and drug administration
FSH	Follicle stimulating hormone
GNRH	Gonadotropin releasing hormone
HAIRAN	Hyper-androgenic insulin-resistant acanthosis nigricans
HCG	Human chorionic gonadotrophin
HMG	Human menopausal gonadotrophin

HSG	Hysterosalpingography
IU	International unit
IUI	Intrauterine insemination
LH	Luteinizing hormone
LOD	Laparoscopic ovarian drilling
LOS	Laparoscopic ovarian surgery
LPD	Luteal phase deficiency
NCAH	Non classic congenital adrenal hyperplasia
NIDDM	Noninsulin-dependent diabetes mellitus
NIH	National Institutes of Health
OCP	Oral contraceptive pill
OHSS	Ovarian hyper stimulation syndrom
P	Progesterone
PCOS	Polycystic ovary syndrome
PR	Pregnancy rate
RCOG	Royal College of Obstetrician and Gynaecologist
SERM	Selective estrogen receptor modulator
SHBG	Sexual hormone binding globulin
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone
USA	United States of America
WHO	World Health Organization

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بسم الله الرحمن الرحيم

قَالَ رَبِّ أَنَّى يَكُونُ لِي غُلَامٌ وَكَانَتِ امْرَأَتِي عَاقِرًا وَقَدْ
بَلَغْتُ مِنَ الْكِبَرِ عِتِيًّا (٨) قَالَ كَذَلِكَ قَالَ رَبُّكَ هُوَ عَلَيَّ
هَيِّنٌ وَقَدْ خَلَقْتُكَ مِنْ قَبْلُ وَلَمْ تَكُ شَيْئًا

صدق الله العظيم

مريم الآية (٧-٩)

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders ***(Fauser et al., 2011).*** It is a complex, heterogeneous disorder of uncertain aetiology, but there is strong evidence that it can, to a large degree, be classified as a genetic disease ***(Fauser et al., 2011).*** Genetic and environmental contributors to hormonal disturbances combine with other factors, including obesity ***(Diamanti et al., 2006).*** Ovarian dysfunction and hypothalamic pituitary abnormalities contribute to the etiology of PCOS ***(Doi et al., 2005).***

It produces symptoms in approximately 5% to 10% of women of reproductive age 12-45 years old ***(March et al., 2010).*** It is thought to be one of the leading causes of female subfertility ***(Goldenberg and Glueck, 2008).***

Clomiphene citrate is a first line pharmacological treatment of ovulatory dysfunction associated with PCOS, because it is easily administered, relatively safe, and inexpensive ***(Norman et al., 2004).*** It is a selective estrogen receptor modulator (SERM) that increases production of gonadotropins by inhibiting negative feedback on the hypothalamus. It is used in the form of its citrate to induce ovulation ***(Homburg, 2005) (Shelly et al., 2008).***

It is known to be both an estrogen agonist and antagonist; however, its agonist properties manifest only when endogenous estrogen levels are extremely low ***(Schorge et al., 2008).***

Its administration leads to depletion of estrogen receptors at the level of the pituitary and hypothalamus, interrupting the negative feedback that estrogen normally produces. As a result, GnRH secretion is improved and stimulates pituitary production of follicle-stimulating hormone (FSH), which in turn drives follicular growth and maturation with emergence of 1 or more dominant follicles ***(Schorge et al., 2008).***

Clomiphene was effective in increasing pregnancy rate compared to placebo (Odd's ratio, OR 5.8, 95%confidence interval, CI 1.6 to 21.5) ***(Brown et al., 2009).*** The standard effective dose of CC ranges from 50 mg/d to 250 mg/d, although doses in excess of 100 mg/d are not approved by the US Food and Drug Administration (FDA) and add little to clinical pregnancy rates ***(Dodge et al., 2012).***

Most women (52%) ovulate in response to treatment with 50 mg. Those who do not ovulate with 50 mg CC may ovulate at higher doses using a step-up regimen with doses escalating 50 mg with each anovulatory cycle (22% with 100mg, 12% with 150mg, 7% with 200mg, and 5% with 250mg) ***(Gysler et al., 2011).***

Badawy at al. (2009) tested a novel protocol of luteal phase administration of CC for ovulation induction in women with polycystic ovary syndrome (PCOS), and concluded that early administration of CC in patients with PCOS will lead to more follicular growth and endometrial thickness, which might result in higher pregnancy rates.

Aim of the Work

To compare the luteal phase (early) administration of clomiphene citrate to the conventional (late) administration of the same drug in the follicular phase as regards ovarian response in PCOS.

Research Question:

Patients: Women with diagnosis of PCOS based on the 2003 ESHRE/ASRM (Rotterdam) criteria with standardized conditions.

Intervention: Early Clomiphene Citrate administration (Late luteal phase) before withdrawal endometrial shedding.

Comparison: Late Clomiphene Citrate Group (Early follicular phase) after withdrawal endometrial shedding.

Outcome: The primary outcome measures are the total number of follicles, number of follicles ≥14 mm in diameter, number of follicles ≥ 18 mm in diameter and endometrial thickness. 2ry outcome measure is the number of ovulating patients.

Research Hypothesis:

Null Hypothesis: Luteal phase administration of clomiphene citrate protocol gives same results of conventional administration of clomiphene citrate in the follicular phase as regards ovarian response in PCOS.

Alternative Hypothesis: Luteal phase administration of clomiphene citrate protocol gives better results than conventional administration of clomiphene citrate in the follicular phase as regards ovarian response in PCOS.

Chapter (I)

Polycystic Ovary Syndrome

History and Epidemiology

The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of *Stein-Leventhal syndrome* is taken ***(Marrinan and Greg, 2011).*** The earliest published description of a person with what is now recognized as PCOS was in 1721 in Italy. Cyst-related changes to the ovaries were described in 1844 ***(Kovacs et al., 2013).***

PCOS is the most common female endocrinopathy, affecting 6–7% of women in their reproductive years ***(Franks et al., 2008)***. Although polycystic ovaries can be found in approximately 20% of the female population, they are not necessarily associated with the typical symptoms, which may be expressed at some time during the fertile life span when provoked by, for example, weight gain or insulin resistance ***(Fauser et al., 2011).*** It is associated with 75% of all an ovulatory disorders causing infertility, with 90% of women with oligomenorrhoea, more than 90% with hirsutism and more than 80% with persistent acne ***(Homburg, 2008).*** It becomes symptomatic in adolescence ***(Buggs and Rosenfield, 2005)***.

Pathophysiology

A complete understanding of the pathophysiology of PCOS is still lacking. Because of the heterogeneity of this disorder, there are most likely multiple underlying pathophysiologic mechanisms. Several theories have been proposed to explain the pathogenesis of PCOS ***(Wilson et al., 2011).*** Current evidence suggests that PCOS arises as a complex trait with contributions from both heritable and uninheritable factors ***(Goodarzi and Azziz, 2009).*** Polygenic influences appear to account for about 70% of the variance in pathogenesis ***(Rosenfield, 2008).*** Insulin resistance, obesity, genetics… basically anything that disrupts hormone disruption can influence the onset of PCOS; and so does iodine deficiency ***(Li et al., 2013).***

It is a common, complex genetic disorder ***(Fauser et al., 2011).*** Common diseases such as schizophrenia, asthma, and type 2 diabetes, as well as PCOS, have a complex, multifactorial etiology, in which a variety of predisposing genes, not just one gene, interact with environmental factors to produce disease ***(Goodarzi and azziz, 2009; Insenser et al., 2013).***

I. Predisposing factors

A- Hereditary factors

The syndrome clusters in families, and prevalence rates in first-degree relatives are five to six times higher than in the

general population ***(Amato and Simpson, 2004).*** Among first-degree female relatives (on no hormonal therapy) of 93 patients with PCOS, 35% of premenopausal mothers and 40% of sisters were also affected with the disorder ***(Goodarzi and azziz, 2009).*** Studies of human ovarian theca cells have suggested dysregulation of the CYP11a gene inpatients with PCOS. This gene encodes the cholesterol side-chain cleavage enzyme, the enzyme that performs the rate-limiting step in steroid biosynthesis ***(Unsal et al., 2014).*** Evidence also suggests up regulation of other enzymes in the androgen biosynthetic pathway ***(Franks, 2006).*** In addition, the insulin receptor gene on chromosome 19p13.2 may be involved ***(Urbanek, 2005).***

B- Environmental factors

The environmental component in the pathogenesis of PCOS includes dietary factors and other exogenously derived substances. Over nutrition with consumption of calorie-rich diets leads to obesity which may accelerate the development or aggravate the clinical course of PCOS ***(Pasquali et al., 2010).*** The high intake of dietary advanced glycation end products (AGEs) may also contribute to the pathogenesis and perpetuation of PCOS ***(Diamanti-Kandarakis at al., 2008)***.

In particular, increased AGEs levels were reported in lean, normoglycemic and non-insulin resistant women with PCOS ***(Diamanti-Kandarakis at al., 2008)***, and AGEs were found to psychological stress and neurotransmitter levels may