Effect of Metformin after Laparoscopic Ovarian Drilling on Ovulation in Women with Clomiphene Citrate Resistant Polycystic Ovary Syndrome

Thesis

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By

Ahmed Mohamed Fahim Metwally
M.B.B.Ch. 2010 – Ain Shams University
Resident of Obstetrics and Gynecology
Ain Shams University Maternity Hospital

Under Supervision of

Dr. Noha Hamed Rabie
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Dr. Ahmed Mohamed Ahmed Awad Allah
Lecturer in Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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وأنزل الله عليك الكتاب والحكمة
وعلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ وكَانَ فَضْلُ اللَّهِ
عَلَيْكَ عَظِيماً

صدق الله العظيم

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Ahmed Mohamed Fahim Metwally

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List of Abbreviations

ADA	American diabetes association
ASRM	*American Society for Reproductive Medicine*
BMI	*Body mass index*
CC	Clomiphene citrate
DHEA	Dehydroepiandrosterone
E2	Estradiol
ESHRE	*European Society of Human Reproduction and Embryology*
FAI	Free androgen index
FI	Flow index
FSH	Follicle stimulating hormone
GnRH	Gonadotrophin releasing hormone
IDPP	Indian Diabetes Prevention Programme
IGF	Insulin growth factor
IGFBP	Insulin-like growth factor-binding protein
IVF	In vitro fertilization
KTP laser	Potassium titanyl phosphate
LH	Luteinizing hormone
LOD	Laparoscopic ovarian drilling
MG	Mean grayness
mL	Milli liter
Nd YAG laser	Neodymium-doped yttrium aluminum garnet
Ng	Nanogram
NIH	National Institute of Health
OGTT	Oral glucose tolerance test

List of Abbreviations *(Cont.)*

PCOS	Polycystic ovary syndrome
Pg	Picogram
rFSH	Recombinant follicle stimulating hormone
SD	Standard deviation
SHBG	Sex hormone binding globulin
t_p	Paired t-test
U/S	Ultrasound
VFI	Vascularization flow index
VI	Vascularization index
VOCAL	Virtual organ computer aided analysis
W	Watt
WHO	World Health Organization
2D	Two dimensional
3D	Three dimensional

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can to a large degree be classified as a genetic disease ***(Legro and Strauss 2002).***

The classic triad of the disorder includes infertility, menstrual dysfunction, hyperandrogenism and other symptoms. Menstrual disorders include oligomenorrhea or amenorrhea, but other types of menstrual disorders may also occur as hypermenorrhea & Infertility**;** generally results directly from chronic anovulation. Hyperandrogenism: The most common signs are acne and hirsuitism (male pattern of hair growth) ***(Teede et al., 2010).***

The exact pathophysiology of PCOS and its initiating event is still unproved. However, various biochemical abnormalities and hormonal changes have been described, and associations and linkages of one to another have been established. Many of these abnormalities reinforce each other in vicious ***(Melmed et al. 2011).*** In 2003, a workshop in Rotterdam indicated PCOS to be present if any 2 out of the following 3 criteria are met: ***(Teede et al., 2010), (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group 2004), (Azziz 2006).***

1. Oligo ovulation and/or anovulation.
2. Excess androgen activity.
3. Polycystic ovaries (by gynecologic ultrasound). According to available literature, at least one of the following criteria should be present to establish polycystic ovaries: either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (>10 cm3). Not all women with PCOS have polycystic ovaries, nor do all women with ovarian cysts have PCOS; although a pelvic ultrasound is a major diagnostic tool, it is not the only one ***(Marrinan 2011).***

In most cases ovulation can be induced with clomiphene citrate (CC), which constitutes one of the first-line treatments for ovulation induction in these patients, as it is economical, straight forward, has few adverse effects, and requires little monitoring. CC is an estrogen receptor antagonist that interferes with negative feedback of the estrogen-signaling pathway, resulting in increased availability of FSH. Increased FSH leads to follicular growth, followed by an LH surge and ovulation. CC is indicated in patients with PCOS and anovulation with normal FSH levels, but it has certain limitations in patients with a BMI 30 and advanced age ***(Homburg R., 2005),*** but approximately 25% of patients fail to ovulate and require alternative treatment. Human menopausal gonadotrophins have been used but the risk of hyper-stimulation and multi-fetal gestations are high.

Clomiphene resistance defined as failure to ovulate after receiving 150 mg of CC daily for 5 days per cycle, for at least three cycles, is common and occurs in approximately 15 to 40% in women with PCOS ***(Brown, J, 2009),(National Collaborating Centre for Women's and Children's Health / National Institute for Clinical Excellence, 2004).*** Insulin resistance, hyperandrogenemia, and obesity represent the major factors involved in CC resistance; avert the ovaries from responding to raised endogenous FSH levels following CC therapy ***(Imani, B, et al, 1998), (Parsanezhad, ME, et al; 2001)***. Moreover, a genetic predisposition was suggested ***(Overbeek, A, et al, 2009).***

A variety of surgical option laparoscopic ovarian drilling (LOD) has now widely been accepted as a second-line treatment for an-ovulatory infertility due to polycystic ovary syndrome (PCOS). This approach not only produces high ovulation and pregnancy rates but also corrects the endocrine abnormalities associated with this syndrome ***(Gjonnaess H., 1984).***

Laparoscopic ovarian drilling was first described in 1984 and involved the creation of 8 – 15 holes, each one 2 – 4mm deep on the surface and stroma of each ovary using a unipolar electrode at 30 – 40 W for 2 – 4 seconds. Several modifications of the technique have been reported including the use of laser (CO2, argon, KTP or Nd-YAG) with good results. However, the published results of

laser surgery are inferior to those of electro cautery ***(Amer et al., 2004).***

In a systematic review, the effectiveness of insulin-sensitizing drugs in improving clinical and biochemical features of PCOS has been studied, confirming that metformin is effective in achieving ovulation in women with PCOS in comparison with placebo and in improving the ovulation rate also as additional treatment in women who received CC ***(Lord J., et al, 2003).*** Metformin has encouraging effects on several metabolic aspects of the syndrome, including insulin sensitivity, plasma glucose concentration and lipid profile. Moreover, metformin improves the ovarian function in women diagnosed with polycystic ovary syndrome, and hence, metformin is considered an agent for ovulation induction among these patients. In women with PCOS treatment with metformin is effective in the lowering of hyperinsulinemia and hyperandro-genemia ***(Tarlatzis, et al, 2008)***.

Aim of the Work

The aim of the current study is to study the effect of Metformin administration after laparoscopic ovarian drilling on ovulation in Clomiphene Citrate resistant women with polycystic ovary syndrome

Research question:

Will Metformin administration after laparoscopic ovarian drilling improve ovulation in Clomiphene Citrate resistant women with polycystic ovary syndrome?

Research hypothesis:

Metformin administration after laparoscopic ovarian drilling may improve ovulation in Clomiphene Citrate resistant women with polycystic ovary syndrome.

Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common female endocrine disorders. PCOS is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can to a large degree be classified as a genetic disease***(Legro and Strauss, 2002), (Fauser et al., 2011).***

The condition was first described in 1935 by American gynecologists Irving F. Stein and Michael L. Leventhal, from whom its original name of *Stein-Leventhal syndrome* is taken***(Marrinan and Greg, 2011), (Richard, 2011).***

Other names for this syndrome include polycystic ovary disease, functional ovarian hyperandrogenism, ovarian hyperthecosis, sclerocystic ovary syndrome, and Stein-Leventhal syndrome. The eponymous last option is the original name; it is now used, if at all, only for the subset of patients with all the symptoms of amenorrhea with infertility, hirsutism, and enlarged polycystic ovaries ***(Marrinan and Greg, 2011).***

Symptoms of PCOS:

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age (12–45 years old). It is thought to be one of the leading causes of female subfertility and the most frequent endocrine problem in women of reproductive age ***(Azziz et al., 2004), (Boomsma et al., 2008), (Goldenberg and Glueck, 2008).*** The clinical severity of PCOS symptoms

appears to be largely determined by factors such as obesity***(Kandarakiset al., 2006), (Teede et al., 2010).***

The principal features are anovulation, resulting in irregular menstruation, amenorrhea, ovulation-related infertility, and polycystic ovaries; excessive amounts or effects of androgenic hormones, resulting in acne and hirsutism; and insulin resistance, often associated with obesity, Type 2 diabetes, and high cholesterol levels.The symptoms and severity of the syndrome vary greatly among affected women ***(Teede et al., 2010).***

The World Health Organization criteria for classification of anovulation include the determination of oligomenorrhea (menstrual cycle >35 days) or amenorrhea (menstrual cycle > 6 months) in combination with concentration of prolactin, follicle stimulating hormone (FSH) and estradiol. Almost 80% of anovulatory patients have normal serum FSH and estradiol levels and demonstrate very heterogeneous symptoms ranging from anovulation, obesity, biochemical or clinical hyperandrogenism and insulin resistance. PCOS is the most common cause of anovulation in women with normal serum FSH and estradiol levels ***(Nadir and Kandarakis, 2009).***

Despite the heterogenecity in symptoms associated with PCOS, the essential feature is arrested follicular development at the stage when selection of the dominant follicle should normally occur***(Wafaa et al., 2012).***