Clomiphene citrate - metformin versus Letrozole - metformin in Clomiphene - resistant patients with polycystic ovarian syndrome

Thesis

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Introduction

Polycystic ovary syndrome (PCOS) is a common condition, present in ١٢–٢١٪ of women of reproductive age. Up to ٧٠٪ of women with PCOS in the community remain undiagnosed. Changing definitions and a range of symptoms have made the path to diagnosis for many women difficult. ***(March et al., ٢٠١٠).***

Polycystic ovarian syndrome (PCOS) remains one of its leading causes. Using the Rotterdam criteria a clinical diagnosis of PCOS is easily reached and most often treatment can be initiated following a few basic investigations ***(Kamath and George., ٢٠١١)***.

Not all women with polycystic ovaries demonstrate the clinical and biochemical features which define the syndrome of PCOS**..** Pathophysiology of this syndrome appears to be multifactorial and polygenic. Although several definitions and various criteria have been used to define PCOS, the principal feature of this syndrome may still be considered oligoanovulation ***(Bayram et al., ٢٠٠٥).***

Although, infertility has been attributed to various factors, anovulation is still the main cause of about ٤٠٪ of female infertilities. However , the incidence of PCOS as the major cause of anovulation, has been reported to be about ٦٪ in infertile

female ***(Sohrabvand et al., ٢٠٠٦)*** with estimates of the prevalence in the general population being in the order of ٢٠-٣٣٪ ***(Bayram et al., ٢٠٠٥)***.

Diagnosis of PCOS by Rotterdam criteria includes at least two of the following criteria:

A) oligo or anovulation

B) hyperandrogenism :Laboratory confirmed or clinical symptoms

C) polycystic ovaries on ultrasound ***(ESHRE/ASRM, ٢٠٠٤).***

Clomiphene Citrate

It is an oral antiestrogen used for ovarian stimulation and has a long half-life and accumulates in the body .Its anitestrogenic effect may have adverse effect on endometrium (an estrogen responsive site) and on the quality of cervical mucus , transtubal transport oocyte plus embryo quality ***(Gardner et al., ٢٠٠٤).***

In anovulatory women, the use of clomiphene citrate is widely accepted as a first line of treatment because of its low cost and easy administration (***Homburg et al., ٢٠٠٢).***

Clomiphene, a non steroidal compound, structurally similar to estrogen, in the central nervous system,it blocks estrogenic hypothalamic receptors, resulting in blinding of the

hypothalamus pituitary axis to endogenous circulating estrogen. This in turn triggers release of FSH from the anterior pituitary following alterations in GnRH pulsatility, consequently this will lead to hyper stimulation of ovaries and ovulation. Clomiphene also has peripheral anti estrogenic action at the level of the endometrium and cervical mucus, partly explaining the discrepancy in ovulation rates and pregnancy rates ***(Gardner et al, ٢٠٠٤ & Homburg et al., ٢٠٠٥)*** .

Clomiphene citrate is given for ٥ days following the onset of spontaneous or a progestagen induced period, starting at any time from days ٢, ٣, ٤ or ٥, as there is no difference in the outcome between these time-points. The recommended starting dose is ٥٠ mg/day, as almost half of the pregnancies are achieved with this dose. Unless normal ovulation occurs the dose is increased gradually in each of the next cycles by ٥٠ mg/day up to a maximum dose of ١٥٠ mg/day ***(Boostanfar et al., ٢٠٠١).***

The clomiphene citrate dose may be increased progressively up to a maximum of ٢٠٠ mg/day for ٥ days**.** More or less than ٥٠٪ of hyporeacting patients will ovulate at this dose. Approximately ٥٠٪ of normal women will ovulate with a dose of ٥٠ mg, and an additional ٢٠٪ will ovulate with ١٠٠ mg/day, the overall ovulation rate ranging from ٧٠ to ٨٥٪. ***(Imani et al., ٢٠٠٢).*** Additionally, around ٢٠-٢٥٪ anovulatory women with

normal FSH concentrations will not respond at all to clomiphene citrate and are considered to be clomiphene-resistant ***(Imani et al., ٢٠٠٢).***

Implantation may be impeded by an antiestrogenic effect on the endometrium,and reduce the pregnancy rate ***(Wolman et al., ١٩٩٤).*** Several studies have correlated endometrial thickness and pregnancy. They have reported that no pregnancy occurred when endometrial thickness was ٦-٨ mm or less,and that the chance of pregnancy was greater with a thickness of ٩-١٠ mm or more. Thus, endometrial thickness may be a factor contributing to the discrepancy between ovulation and pregnancy rates with the use of clomiphene citrate ***(Isaacs et al., ١٩٩٦)***. Ovulation is confirmed by mid luteal serum progesterone ***(Sallam et al., ١٩٩٩)***

Metformin

It is an oral antidiabetic drugs from biguanide class used for treatment of type ٢ diabetes mellitus, it is a safe and effective drug that is recently used for the treatment of PCOS patients ***(Pasquali et al ., ٢٠٠٠)***. The administration of metformin improves clinical and biochemical features of PCOS and induces ovulation cycles in anovulatory CC-resistant patients ***(Stumvoll et al ., ١٩٩٥)*** .

Some studies have reported that hyperinsulinemia is the main cause of clomiphene resistance in PCOS patients ***(Pasquali et al ., ٢٠٠٦)*** . In PCOS patients, metformin can decrease the level of L.H. and ovarian androgen level as well as correct hyperinsulinemia ***(Heard et al., ٢٠٠٧)***. It has been shown that metformin increases ovarian response to clomiphene citrate in obese women with PCOS ***(Nestler et al., ٢٠٠٨).***

Aromatase inhibitors

Several authors have been advocating aromatase inhibitors as new ovulation-inducing agents ***(Mitwally et al., ٢٠٠٥ & Al-Fadhli et al., ٢٠٠٦).***

Aromatase inhibitors are orally administered with minimal side effects.The most widely used aromatase inhibitor is letrozole. The half-life of letrozole is ٤٥h and it clears rapidly from the body ***(Jee et al., ٢٠٠٦).***Using of letrozole as ovulation-inducing agents is associated with thicker endometrium due to absence of any antiestrogenic effect and trends towards higher pregnancy rates ***(Holzer et al., ٢٠٠٦)***

Letrozole prevents the androgen-estrogen conversion (aromatization)and therefore interferes with the negative feed back at the level of the hypothalamus and the level of pituitary leading to decrease in estrogen production. The increased pituitary

gonadotropins output will stimulate the development of ovarian follicles. In addition, androgens that are normally converted to estrogens accumulate in the ovary and these androgens increase follicular sensitivity to FSH ***(Holzer et al., ٢٠٠٦ &Mitwally et al., ٢٠٠٤).***

As the ovaries of women with PCOS produce high amounts of estrogen so the effects of aromatase inhibitors in these women are more pronounced. Unlike clomiphene citrate, aromatase inhibitors do not deplete estrogen receptors or produce negative effects on the endometrium. Also, clomiphene citrate has a longer half-life (٥–٧ days) that results in prolonged central estrogen receptor depletion ***(Mitwally et al., ٢٠٠٥ & Jee et al., ٢٠٠٦).***

Aim of the work

The aim of this study was to compare the effect of the following drugs :combination clomiphene citrate –metformin versus combination letrozole -metformin on ovulation induction in clomiphene citrate resistant patients with PCOS as regards.

- Pregnancy rate (primary outcome).
- Ovulation rate (secondary outcome).
- Number of follicles.
- Endometrial thickness on day of HCG injection.

I - Polycystic Ovary Syndrome (PCOS)

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 ***(Fauser et al., ٢٠١١)***.

PCOS produces symptoms in approximately ٥٪ to ١٠٪ of females of reproductive age (١٢–٤٥ years old). It is thought to be one of the leading causes of female subfertility ***(Boomsma et al., ٢٠٠٨).***

Definition:

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age ***(Teede et al., ٢٠١٠).*** The presentation is diverse. There is no single, unified definition of PCOS, no single diagnostic test and no consensus on the diagnostic criteria. Currently, PCOS is most commonly defined by Rotterdam criteria(٢٠٠٣), which requires at least two of three features for diagnosis – chronic anovulation, clinical and/or biochemical signs of hyperandrogenism, or polycystic ovaries ***(Elghblawi, ٢٠٠٧).***

Until recently, three definitions were followed: first is the National Institute of Child Health and Human Development (NICHD) conference diagnostic criteria and the second is

suggested by the European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM). The third definition has been proposed recently by the Androgen Excess Society, which takes into account both the criteria existent till date. The three definitions are summarized in [Table - ١]

Table ١: Diagnostic criteria for polycystic ovary syndrome according to different published definitions

Definition/year	Diagnostic criteria	Exclusion criteria
NIH/ ١٩٩٠	Requires the simultaneous presence of: ١. Clinical (hirsutism, alopecia, acne) and/or biochemical hyperandrogenism. ٢. Menstrual dysfunction.	CAH, androgen-secreting tumours, Cushing's syndrome, hyperprolactinaemia.
Rotterdam/ ٢٠٠٣	Requires the presence of at least two criteria: ١. Clincial (hirsutism, acne) and/or biochemical hyperandrogenism. ٢. Ovulatory dysfunction. ٣. PCOM.	
AES/ ٢٠٠٦, ٢٠٠٧	Requires the presence of hyperandorgenism, clinical (hirsutism) and/or biochemical, and either: ١. Oligo-anovulation. ٢. PCOM.	CAH, androgen-secreting neoplasms, androgenic/anabolic drug use or abuse, Cushing's syndrome, syndromes of sever insulin resistance, thyroid dysfunction, hyperprolactinaemia.

(Galluzzo et al., ٢٠٠٨)

PCOS is currently considered a complex metabolic disorder and a risk factor for diabetes mellitus, cardiovascular disease and endometrial cancer. It is believed that insulin resistance might be a link between carbohydrate intolerance and the increase in cardiovascular risk and PCOS ***(Barcellos et al., ٢٠٠٢).***

Prevalence:

Although polycystic ovaries can be found in approximately ٢٠٪ 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. PCOS is associated with ٧٥٪ of all anovulatory disorders causing infertility, with ٩٠٪ of women with oligomenorrhoea, more than ٩٠٪ with hirsutism and more than ٨٠٪ with persistent acne ***(Homburg, ٢٠٠٨).***

Clearly, the prevalence of PCOS will depend to a degree on the criteria used to define this disorder. The prevalence of clinically evident PCOS in unselected women of reproductive age ranges from ٦,٥ to ٨,٠٪ using the ١٩٩٠ NIH criteria. ***(Goodarzi and Azziz, ٢٠٠٦).***

In a further study of the presence of PCOS in a population of subfertile women in London the incidence was ٣٢٪ ***(Agrawal et al., ٢٠٠٤)***.

The use of different diagnostic criteria for PCOS have undermined attempts to derive an accurate, population- based polycystic ovaries at the time of ultrasound examination is relatively frequent, occurring in up to ٣٣٪ of women, although most studies report an incidence around ٢٢٪ in an unselected population ***(Rogir et al., ٢٠٠٤)***.

ETIOLOGY and PATHOGENESIS

PCOS is a common, complex genetic disorder. Common diseases such as schizophrenia, asthma, and type ٢ 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, ٢٠٠٦).***

١- Hereditary Factors:

The exact etiology of PCOS is unknown. There is, however, increasing evidence for genetic 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, ٢٠٠٤).***

Not only is PCOS itself a heritable condition, but also within PCOS insulin resistance and insulin secretion appear to be under significant genetic control. Among sisters of women with PCOS, those who had PCOS or hyperandrogenemia with regular menses had lower insulin sensitivity than unaffected sisters, assessed by fasting insulin and glucose measurements ***(Goodarzi and Azziz, ٢٠٠٦)***.

٢- Environmental Factors:

While the majority of cases appear to be genetically transmitted, the environmental factors can be involved as

PCOS may also be acquired by exposure to excess androgens at any time during the fertile years. Intra-uterine exposure of a female fetus to an excess of androgens is an etiological hypothesis finding increasing favor ***(Bruns et al., ٢٠٠٥).***

Lobo and Carmina (٢٠٠٠) investigated the prevalence of psychological stress and its possible relationship to various hormonal parameters. They hypothesized that psychological stress and neurotransmitter levels may be linked to some of the hormonal derangement including inappropriate gonadotropins secretion and elevated adrenal androgen levels in women with PCOS.

٣- Endocrinological and Metabolic Factors:

Polycystic ovary syndrome involves overproduction of ovarian androgens leading to a heterogeneous range of symptoms including hirsutism, acne, anovulation and infertility. Hyperinsulinaemia exacerbated by obesity is often a key feature ***(Homburg, ٢٠٠٨).***

Although the etiology of polycystic ovary syndrome is unknown, ٣ main hypotheses have been proposed in ٢٠٠٥ by Polycystic Ovary Syndrome Writing Committee ***(Setji and Brown, ٢٠٠٧)***:

١) Hypothalamic-pituitary axis abnormalities cause abnormal secretion of gonadotropin releasing hormone and luteinizing hormone, resulting in increased ovarian androgen production.

٢) Insulin resistance drives the metabolic and reproductive abnormalities in polycystic ovary syndrome.

٣) An enzymatic defect of ovarian (adrenal) steroidogenesis favors excess androgen production**.**

١) Hypothalamic-pituitary axis

The simple explanation for the phenomenon of antral follicles arrest in development is that serum concentrations of FSH, while rarely frankly low, are suppressed below the threshold level reguired during the early follicular phase to stimulate normal follicle maturation ***(Franks, et al., ٢٠٠١).***

LH hypersecretion is a characteristic hallmark of PCOS. LH is secreted in a pulsatile manner. Women with PCOS have an increase in both the LH pulse frequency and amplitude, resulting in increased ٢٤-hour secretion ***(Tsilchorozidou et al., ٢٠٠٤).***

This increase in LH secretion is thought to occur as a result of increased frequency of hypothalamic GnRH pulses. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary ***(Ehrmann, ٢٠٠٥)***