Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder ***(March et al., 2010; Teede et al., 2011),*** affecting approximately 5% to 15% of women in reproductive age ***(Shannon and Wang, 2012)***.

Stein and Leventhal originally described PCOS noting varying degrees of enlarged ovaries, obesity, hirsutism, and chronic anovulation in obese women seeking treatment for infertility. They suggested surgery (wedge resection of the ovaries) for management of the condition, resulting in restoration of ovulation in the majority of cases ***(Stein and Leventhal, 1935).***

Since then, many researchers have initiated to pay close attention to this syndrome, a lot of related studies on its etiology, diagnosis, and management have been conducted. it is supposed that the pathogenesis of PCOS is associated with both heredity and environment; however, the exact pathogenesis remains uncertain ***(Barber et al., 2010)***.

PCOS is a genetically heterogeneous syndrome in which the genetic contributions remain incompletely described , PCOS is an inherently difficult condition to study genetically because of its heterogeneity, difficulty with

retrospective diagnosis in postmenopausal women, associated subfertility and incompletely understood etiology ***(Barber et al., 2010).***

A disordered ovarian environment characterizes PCOS. In women with PCOS, ovarian follicles arrest in a state of preovulation, this state of arrest is caused primarily by an overabundance of androgens, which impedes follicle growth and ovulation. current opinion suggests that insulin resistance is the culprit because it is observed in many women with PCOS ***(Dunaif et al.,1989; Johnson, 2014)***.

Insulin resistance causes an abnormal response in the ovary that results in an increase in the amount of circulating androgens that lead to hyperandrogenism ***(Fritz & Speroff, 2011).***

The additional metabolic derangements, such as insulin resistance, impaired glucose tolerance and dyslipidemia significantly increase the risks of diabetes, cardiovascular disease, hypertension, metabolic syndrome and endometrial cancer among PCOS patients. there fore, PCOS is defined not only as a gynecologic endocrinopathy but also as a kind of metabolic disorder ***(Chen and shi, 2010).***

Women with PCOS have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production. high serum concentrations of androgenic hormones, such, as: testosterone, androstenedione, and dehydro-epiandrosterone sulfate (DHEA-S), may be encountered in these patients ***(Toulis et al., 2009).***

The European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine sponsored in Rotterdam in 2003 issued that the diagnosis of PCOS should be made when two of the following characteristics are satisfied:

(1) Oligoamenorrhea and / or anovulation.

(2) The presence of hyperandrogenemia or clinical hyperandrogenism

(3) Polycystic ovarian morphology on ultrasound after excluding other related diseases that can induce ovarian dysfunction and hyperandrogenism ***(Rotterdam ESHRE/ ASRM- Sponsored PCOS consensus workshop group, 2004).***

Clomiphene citrate(CC) is still considered first-line therapy for ovarian stimulation in PCOS due to its structural similarities to estrogen, CC competitively attaches to nuclear

estrogen receptors and by lowering the negative feedback of estrogen, it activates mechanisms that change the secretion pattern of gonadotropin-releasing hormone, which in turn result in increased pituitary gonadotropin hormones. This process ultimately causes ovarian follicles to grow ***(Fritz ,2011)***.

However, lifestyle modification is widely accepted as the first line of treatment for women with PCOS to optimize their health before and concurrent with any fertility treatment ***(American College of Obstetricians and Gynecologists, 2009; Costello et al., 2012;; Moran et al., 2011).***

Studies have shown a significant difference between rate of ovulation and pregnancy and a higher abortion rate in patients undergoing clomiphene citrate therapy. Thus the use of a simpler oral drug, as a safe alternative to clomiphene citrate can produce a new horizon in ovulation induction ***(Casper and Mitwally, 2011).***

Aromatase is a microsomal enzyme that mediates conversion of androstenedione to estrogen and testosterone to estradiol, it is present in several tissues including the ovary, brain, placenta, adipose tissue, muscle, liver and breast. Aromatase is a good target to control estrogen level and

several studies have demonstrated the effectiveness of aromatase inhibitors in induction of ovulation ***(Roy et al., 2012).***

Letrozole, a newly designed selective aromatase inhibitor which can be used to induce ovulation in infertile women with PCOS ***(Casper and Mitwally, 2011).***

Letrozole is rapidly absorbed from the gastrointestinal tract and excreted by the kidney. The elimination half-life of letrozole is about 2 days ***(Mitwally and Casper, 2001).***

Also, letrozole act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens, since conversion of androgen substrate to estrogen is blocked. Recent data support a stimulatory role for androgens in early follicular growth ***(Al-Omari et al., 2001 ; Metawie, 2001).***

Letrozole does not have any adverse effects on the fetus and is safe, Letrozole decreases the secretion of estrogen both in the ovaries and in the periphery, and causes an increase in gonadotropins, which in turn causes maturation of the ovarian follicles ***(Jirege and Patill, 2010).***

Aim of work

The aim of this study is to compare the efficacy of letrozole on ovulation induction to that of clomiphene citrate in women suffering polycystic ovary syndrome.

Research question:

In women with PCOS, Is Letrozole effective in ovulation induction as Clomiphene citrate?

Researcher hypothesis:

In women with PCOS , Letrozole may be as effective as Clomiphene citrate in ovulation induction.

Chapter (1)
polycystic ovary syndrome (PCOS)

Definition

polycystic ovary syndrome (PCOS), also called hyperandrogenic anovulation (HA) or Stein–Leventhal syndrome ***(Kollmann et al., 2014),*** is one of the most common endocrinal disorder that affecting approximately 5% to 15% of women in reproductive age ***(Shannon and Wang, 2012)***.

Stein and Leventhal were the first to recognize an association between the presence of polycystic ovaries and signs of amenorrhea and hirsutism ***(Stein et al.,1935).***

Stein and Leventhal described PCOS as a frequent cause of irregular ovulation in women seeking treatment for subfertility and they published their report of seven women with amenorrhea, hirsutism, obesity, and enlarged polycystic appearing ovaries. Since then, much has been learned about this complex disorder ***(Chang, 2004).***

PCOS is mainly associated with menstrual dysfunction, anovulation infertility, hyperandrogenism and insulin resistance leading to metabolic problems such as diabetes melliutes (DM) and cardiovascular diseases ***(Pangaribuanis et al., 2011).***

PCOS appears to be a heterogeneous disorder in which ovarian, and possibly adrenal hyperandrogenism is present along with varying degrees of gonadotropic and metabolic disorders , additionally infertility problems and psychosocial disorders are presented as other clinical consequences associated with PCOS ***(DuRant et al., 2009).***

Clinically; PCOS characterized by chronic anovulation, menstrual irregularities, infertility and obesity in combination with some evidence of hyperandrogenism such as hirsutism and acne ***(Iwasa et al., 2009).***

PCOS is considered an inherently difficult condition to study genetically because of its heterogeneity, difficulty with retrospective diagnosis in postmenopausal women, associated infertility plus incompletely understood etiology ***(Barber et al., 2010).***

The accepted diagnostic definition of PCOS is the Rotterdam criteria supported by the European Society of Human Reproduction and Embryology, The American Society for Reproductive Medicine, The National Institute of Health (NIH), and the Australian PCOS Alliance ***(Geisthovel et al., 2007)***

The 2003 revised diagnostic criteria for PCOS reached at a consensus conference held in Rotterdam jointly by the European Society for Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ ASRM) are compared to the earlier definition reached at the 1990 National Institute of Health (NIH) international workshop , In 2006, The Androgen Excess Society (AES) Task Force on the Phenotype of PCOS narrowed the Rotterdam criteria to exclude women who did not have androgen excess and revised all the data described in the literature and attempted to give an evidence-based definition of PCOS in order to direct diagnosis, clinical management and future studies (Table1) ***(Brien et al., 2008).***

Table (1): Criteria for the diagnosis of PCOS

efiniti-on/Year	Diagnostic criteria	Exclusion criteria
NIH, 1990	Requires the simultaneous presence of : 1-Clinical (hirsutism, alopecia, acne) and / or biochemical hyperandrogenism 2-.Menstrual dysfunction .	- Congenital adrenal hyperplasia . - Androgen-secreting tumours , Cushing's syndrome.
ROT, 2003	Requires the presence of at least two criteria among : 1-Clinical(hirsutism, acne) and/or-biochemical hyper-androgenism 2- Ovulatory dysfunction. 3-Polycystic ovarian morphology.	- Hyperprolactinaemia. - Congenital-adrenal hyperplasia . - Androgen-secreting tumours Cushing's syndrome.
AES, 2006	Requires the presence of clinical (hirsutism) and/or biochemical hyperandrogenism and either: 1- Ovulatory dysfunction. 2- Polycystic ovarian Morphology .	-Congenital-adrenal hyperplasia. -Androgen-secreting neoplasms. -Androgenic/anabolic drug use or abuse . - Cushing's syndrome . - Thyroid dysfunction - Syndromes of severe insulin-resistance. - Hyperprolactinaemia.

(Brien et al., 2008).

Nowadays, a common perception among medical experts dealing with the syndrome, is that the name PCOS constitutes a distraction that impedes progress, and that this name of polycystic ovaries does not reflect the complex interactions that characterize this syndrome ***(Dunaif and Fauser, 2013).***

Furthermore, the emergence of new definitions with the use of ovarian morphology, besides chronic anovulation and hyperandrogenism, as diagnostic criteria has increased the phenotypic variety of PCOS presentation ***(Conway et al., 2014).***

However, the NIH Experts Panel recommended the maintenance of the broad diagnostic criteria of Rotterdam ***(The Rotterdam Eshre / Asrm-Sponsored PCOS consensus workshop group, 2004)***, but focused on the need for specific identification of the phenotype of each patient.

By using the possible combinations of these criteria, four different phenotypes of PCOS are now identified:

Hyperandrogenism (clinical or biochemical) and chronic anovulation [H-CA].

Hyperandrogenism and polycystic ovaries on ultrasound (PCOm) but with ovulatory cycles [H-PCOm].

Chronic anovulation and polycystic ovaries without hyperandrogenism [CA-PCOm].

Hyperandrogenism, chronic anovulation, and polycystic ovaries [H-CA-PCOm].

(Final report National Institute of Health. Evidence-based Methodology Workshop on PCOS ,2012).

The identification of specific phenotypes in PCOS patients seems to be justified from the metabolic point. In contrast to chronic anovulation, metabolic abnormalities may dominate the syndrome throughout the subject's lifespan, although no data regarding adolescence are available ***(Legro et al., 2013).***

Epidemiology

Several groups have demonstrated that the prevalence of PCOS varies depending on which diagnostic criteria used ***(Yildiz et al., 2012)***.

As an example, in a report of 827 women with World Health Organization (WHO) class2 oligo-ovulation (euestrogenic normogonadotropic ovulatory dysfunction)

456 (55 %) were classified as having PCOS by the National Institutes of Health (NIH) 1990 criteria (irregular menses, biochemical and/or clinical hyperandrogenism, other causes of hyperandrogenism excluded).

In contrast, 754 (91%) women were considered to have PCOS using the broader Rotterdam 2003 criteria (which requires two out of three of the following: oligo- and/or anovulation, clinical and/or biochemical hyperandrogenism,

and polycystic ovarian morphology by ultrasound (Other causes of hyperandrogenism must also be excluded) ***(Broekmans et al., 2006)***.

It is reported that, the prevalences of PCOS in unselected women in many populations around the globe ranging from 6 to 10 % with few exceptions (***Tehrani et al., 2011).***

Type 1, type 2 and gestational diabetes have been associated with an increased prevalence of PCOS , Escobar-Morre- ale et al screened 85 Caucasian women with type 1 diabetes mellitus for PCOS using the NIH/NICHD criteria , PCOS was diagnosed in 16 of these women (18.8%) ***(Escobar et al., 2000)***

Approximately 10% of women with PCOS have type 2 diabetes mellitus, and 30-40% of women with PCOS have impaired glucose tolerance by 40 years of age ***(Ehrmann et al., 1999; Legro et al., 1999)***.

Etiology of PCOS

There are no certainties about the origin of PCOS ***(Dumesic et al.,2007).***

Even though the name of PCOS suggests that the ovaries are central to disease pathology, cysts are actually a symptom instead of the cause of the disease. Some symptoms of PCOS will persist even if both ovaries are removed ***(Dunaif and Fauser, 2013).***

However there is strong evidence that PCOS is a genetic disease. Such evidence includes the familial clustering of cases, greater concordance in monozygotic compared with dizygotic twins and heritability of endocrine and metabolic features of PCOS ***(Diamanti-Kandarakis et al., 2006).***

The genetic component appears to be inherited in an autosomal dominant fashion with high genetic penetrance but variable expressivity in females, this means that each child has a 50% chance of inheriting the predisposing genetic variant (s) from a parent, and, if a daughter receives the variant (s), she will have the disease to some extent ***(Legro and Strauss,2002).***

The genetic variant(s) can be inherited from either the father or the mother, and can be passed along to the sons (who may be asymptomatic carriers or may have symptoms such as early baldness and/or excessive hair) and daughters, who will show signs of PCOS ***(Crosignani and Nicolosi, 2001).*** The exact gene affected has not yet been identified ***(Amato and Simpson, 2004; Legro and Strauss, 2002).***

In rare instances, single-gene mutations can give rise to the phenotype of the syndrome ***(Draper et al., 2003).*** However, it is unlikely that PCOS represents a single gene defect but it is more likely to be polygenic or oligogenic ***(Urbanek M, 2007).***

PCOS may be related to or worsened by exposures during the prenatal period, epigenetic factors, environmental impacts ***(Palioura and Diamanti-Kandarakis,2013)*** such as bisphenol A, certain drugs and obesity***(Rutkowska and Rachoń, 2014; Hoeger KM, 2014).***

PCOS may also be acquired by exposure to excess androgens at any time during the fertile years ***(Abbott et al., 2005).***