INTRODUCTION

Polycyctic ovary syndrome (PCOS) is the most common cause of anovulatory infertility which affects 4-7 % of women. It is the most common cause of hyper androgenic anovulatory infertility. The underlying cause of this disorder is still unknown ***(Wiels et al., 1999).***

The classic symptoms of the disease are due to increase ovarian androgen production and chronic anouvlation. There are many clinical and laboratory criteria as anouvlation, oligomenorrhia, hirsutism, acne, obesity. Also there may be an elevated total testosterone and luteinizing hormone to follicle stimulating hormone ratio ***(Tsilchorozidou et al., 2006)***.

Clomiphene citrate has been the 1st line of treatment for ovulation induction. Clomiphene citrate resistance (failure to ovulate after taking clomiphene citrate) is common, occurring in approximately 15% to 40% of women with PCOS ***(Koutsa et al., 1997; Wolf et al., 2000; Pritts, 2002)***. NICE definition is: "Anovulatory women who do not ovulate after receiving the 150 mg dose of clomiphene citrate" ***(NICE, 2004)*** Resistance is associated with an increased body mass index (BMI) and weight reduction programmes improve the success rates of clomiphene citrate therapy ***(Koutsa et al., 1997).***

The therapeutic techniques for CC –resistant patients are the addition of corticosteroid such as dexamethasone ***(Elnashar***

et al., 2006), extended duration of clomiphene citrate ***(Badway et al., 2008)***, the use of aromatase inhibitor ***(Badway et al., 2008),*** laparoscopic ovarian drilling or in vitro fertilization ***(Thessaloniki et al., 2008).***

Aromatase is a cytochrome P450 (CYP450) hemoprotein containing enzyme complex (the product of CYP 19 gene) that catalyzes rate limiting step in the production of estrogens which is the conversion of androstenedione and testosterone to estrone and estradiol, through hydroxylation steps respectively, so recent research has focused on the use of aromatase inhibitors as letrozole for induction of ovulation ***(Akhtar et al., 1993).***

They are used for ovulation induction as its administration in early follicular phase to release hypothalamus or pituitary from estrogen negative feedback GNRH leading to increase gonadotropin secretion which stimulates follicular growth ***(Okman et al., 2003).*** They also act locally in the ovary to increase follicular sensitivity to FSH as result from increase intraovarian androgen subsequently to blocked conversion of androgen to estrogen. In recent studies letrozole increase endometrial thickness by up-regulation of estrogen receptors and improve pregnancy rate. They are reversible compitive inhibitors of aromatase highly potent, selective and rapidly absorbed from GIT and excreted by the kidney with elimination half life of letrozole is about 2 days ***(Lidor et al., 2000).***

Tamoxifen (TMX) is another anti estrogen which is a triphenyl ethylene derivative which is similar to CC in structure, ovulation rates have been reported as 50-90% and pregnancy rates as 30-50%. Tamoxifen has shown reasonably good results in CC failure cases too ***(Borenstein et al., 1989).*** The better ovulation and pregnancy rates may be because of higher score of cervical mucus and better functioning of the corpus luteum.The suggested dose is 20-40 mg daily in induction of ovulation, beginning in early follicular phase of the cycle, but it is less common used for ovulation induction as this indication is not licensed yet, although it is sometimes prescribed for women who have side effect of CC ***(Brown, 2009).***

Therefore, the hypothesis of the present work is to evaluate the efficacy of TMX compared to letrozole in achieving successful ovulation and pregnancy in CC resistant women with PCOS as simple inexpensive strategy in controlled ovarian stimulation.

AIM OF THE WORK

Research question: Are the TMX and Letrozol effective to induce ovulation in infertile clomid resistant women with polycystic ovarian syndrome and achieving pregnancy which more effective.

Population of study: this study was carried out on infertile clomid resistant women with polycyctic ovarian syndrome who were assigned for treatment of their infertility by induction of ovulation. **Intervention:** Aimed to compare the ability to induce ovulation between TMX and letrozole in CC resistant women and achieving pregnancy. **To** compare between two groups 40 patients in each group in which one group received letrozol and the other received TMX. ***Outcome:*** 1ry object: achieving pregnancy**.** 2nd object: successful ovulation by occurrence of ovulation by at least one follicle (≥ 18 mm) and endometrial thickness at the time of HCG administration.

Research hypothesis: TMX or letrozole are effective in achieving successful ovulation and pregnancy in CC resistant women with PCOS.

The null hypothesis that they fail to achieve successful ovulation or pregnancy in CC resistant women or there is no significant difference between two groups.

POLYCYSTIC OVARY SYNDROME

Introduction:

Polycystic ovary syndrome (**PCOS**) is the most common endocrine disorders. PCOS is heterogeneous disorder of unknown etiology, but there is strong evidence that it is classified as a genetic disease ***(Legro and Strauss, 2002; Diamanti et al., 2006; Fauser et al., 2011).***

PCOS causes symptoms in approximately 5% to 10% of women in reproductive age (12–45 years old). It is thought to be one of the most common causes of female subfertility ***(Azziz et al., 2004; Goldenbrg and Glueck, 2008; Boomsma et al., 2008)*** and the most common endocrine problem in women in reproductive age ***(Teede et al., 2010)***.

There is vary symptoms and signs among women with PCOS and for an individual these may change over time ***(Balen et al., 1995)***.

The PCOS is familial and different aspects of the syndrome may be inherited. The PCOs can present without clinical signs of the syndrome, which may then become presented in certain conditions. There are many factors that affect expression of PCOS, for example, a increase in weight is associated with a worsening of symptoms while weight reduction may ameliorate the endocrine and metabolic profile and symptoms ***(Clark et al., 1995)***.

Genetic studies have found a link between PCOS and abnormal insulin metabolism, and indicate that the syndrome may be the expression of a complex genetic disorder. The features of obesity, hyperinsulinaemia, and hyper-androgenaemia which are commonly seen in PCOS are also known to be factors which causes an increased risk of cardiovascular disease and non-insulin dependent diabetes mellitus (NIDDM) ***(Moran et al., 2010).***

There are many studies which concloude that women with PCOS have an increased risk for these diseases which affect long-term risks for health, and this evidence has prompted indications for screening women for PCOS ***(RCOG guidelines, 2003).***

Definitions:

Historically the detection of the polycystic ovary required visualization of the ovaries at laparotomy with histological confirmation following biopsy ***(Stein and Leventhal, 1935).***

As further studies linked the association of certain endocrine abnormalities in women with histological evidence of PCOS, biochemical criteria became the indicated for diagnosis. Increase serum levels of LH, testosterone, and androstenedione, in association with low or normal levels of follicle stimulating hormone (FSH) and abnormal estrogen

secretion, described an endocrine profile which many authers believed to be diagnostic of PCOS ***(Balen et al., 2003)***.

The advent of high resolution ultrasound scan provided a non-invasive technique for the measurment of ovarian size and morphology. Good correlation has since been shown between ultrasound diagnoses of pcos morphology and the histopathological criteria for pco ovaries by studies examining ovarian tissue collected at hysterectomy or after wedge resection ***(Saxton et al., 1990; Takahashi et al., 1994)***.

The histopathological criteria was defined as the observation of: increased numbers of follicles, hypertrophy and luteinization of the inner theca cell layer, and thickened ovarian tunica. Transabdominal and/or transvaginal ultrasound have since become the most commonly used diagnostic tools for the identification of pco ovaries. And an attempt has been made to provide the ultrasound criteria for the diagnosis of pco ovaries. In essence the polycystic ovary should have at least one of the following: either 12 or more follicles measuring 2–9 mm in diameter or increased ovarian volume (> 10 cm3) ***(Balen et al., 2003).***

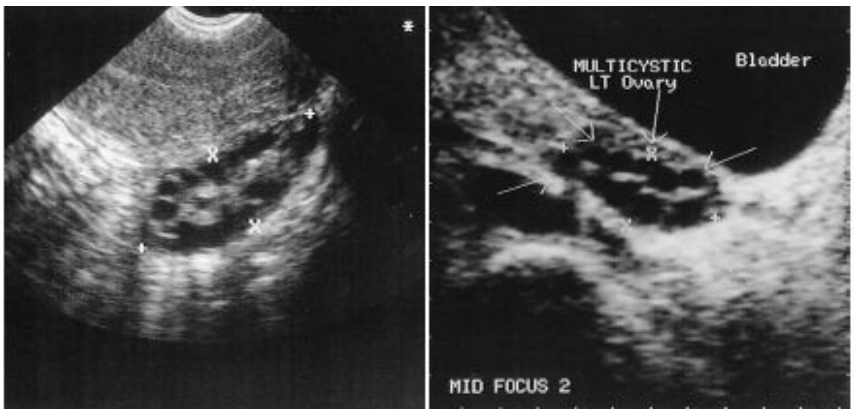

Figure (1): Transvaginal ultrasound scan of a polycystic ovary. (b) Transabdominal ultrasound scan of a multicystic ovary ***(Balen, 2008).***

The introduction of three-dimensional ultrasound and the use of color and pulsed Doppler ultrasound are techniques which may further enhance the diagnosis of polycystic ovaries and which may be more commonly used in time ***(Kyei-Mensah et al., 1996; Marrinan and Greg, 2011).***

The use of magnetic resonance imaging (MRI) for the visualization of the structure of pelvic organs has been used to have even greater sensitivity than ultrasound for the diagnosis of polycystic ovaries. However, the substantial cost and practical difficulties involved with MRI technique limit its use ***(Faure et al., 1989)***

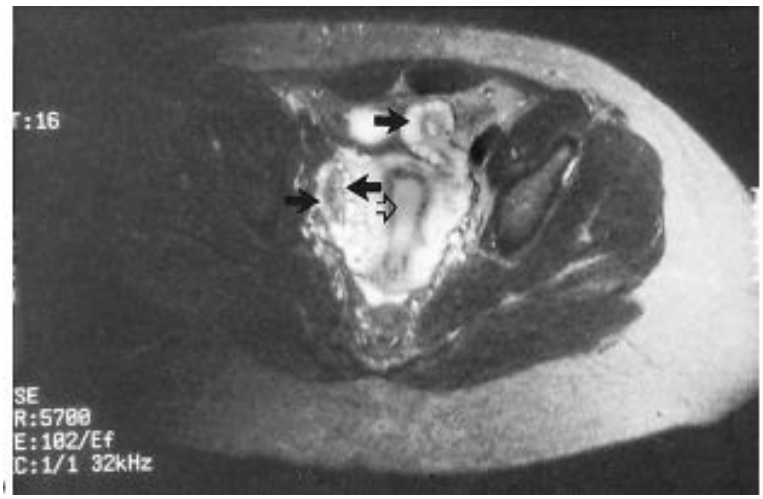

Figure (2): Magneticresonance imaging (MRI) of a pelvis, demonstrating two polycystic ovaries (closed arrows) and a hyperplastic endometrium (open arrow) ***(Balen, 2008).***

The term "polycystic ovary" in some aspects adds to the confusion that surrounds its diagnosis. The "cysts" are not cysts in the sense that they do contain oocytes. So truly it should be named a polyfollicular ovary, to reflect the finding that the "cysts" are actually follicles whose developing has been arrested. Indeed the prerequisite of a number of cysts may be of less relevant than the volume of ovarian stroma, which has been shown to correlate with serum testosterone concentrations ***(Kyei-Mensah et al., 1996).***

Furthermore, it has been suggested recently that an ultrasound measurment of the ratio of ovarian stromal area to total ovarian area gives the greatest sensitivity and specificity for the diagnosis of PCOS ***(Fulghesu et al., 2007).***

While it is now clear that ultrasound provides an good technique for the detection of pco ovarian morphology, identification of pco ovaries by ultrasound does not automatically confirm a diagnosis of PCOS. Controversy still exists over a specific definition of the syndrome and whether or not the diagnosis should require confirmation of pco ovarian morphology ***(Fulghesu et al., 2007).***

In 1990 the National Institute of Health conference on PCOS recommended that diagnostic criteria should include evidence of hyperandrogenism and ovulatory dysfunction, in the absence of non-classic adrenal hyperplasia, and that evidence of polycystic ovarian morphology is not necessary ***(Zawadski and Dunaif, 1992).***

This definition results in the condition of PCOS without polycystic ovaries. However, the more accepted theory in the UK is that a spectrum exists, ranging from women with PCO ovarian morphology and no overt abnormality at one side, to those with PCO ovaries associated with severe clinical and biochemical disorders at the other side, hence the ESHRE/ASRM Consensus of 2004 ***(Fauser et al., 2004).***

Although debate on what constitutes PCOS stills, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition. According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria: oligo-ovulation or anovulation, clinical or

biochemical evidence of hyperandrogenism, and polycystic ovaries on ultrasound assessment (> 12 small antral follicles in an ovary), with the exclusion of medical conditions such as congenital adrenal hyperplasia, androgen-secreting tumours, or Cushing's syndrome ***(ESHRE/ASRM, 2004).***

Nevertheless, it is widely recognized in the USA that positive ovarian findings predominate and there is considerable overlap between the European and US definitions (Table 1). Debate continues regarding the reliability and sensitivity of the various tests that we have ***(Barth et al., 2007).***

Table (1): Definitions of PCOS.

Source	*Criteria*
NIH (1990)[20]	To include all of the following: 1: Hyperandrogenism and/or hyperandrogenemia 2: Oligo-ovulation 3: Exclusion of related disorders
ESHRE/ASRM (Rotterdam 2003)[2]	To include two of the following, with the exclusion of related disorders: 1: Oligo- or anovulation 2: Clinical and/or biochemical signs of hyperandrogenism 3: Polycystic ovaries redefined as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume (>10 cm^3)[3]
Androgen Excess Society (2006)[77]	To include all of the following: 1: Hirsutism and/or hyperandrogenemia 2: Oligo-anovulation and/or polycystic ovaries 3: Exclusion of androgen excess or related disorders

Using a combination of clinical, ultrasonographic, and biochemical criteria, the diagnosis of PCOS is usually reserved for those women who exhibit an ultrasound picture of polycystic ovaries, and who display one or more of the clinical

symptoms (menstrual cycle disturbances, hirsutism, obesity, hyper-androgenism), and/or one or more of the recognized biochemical disturbances (elevated testosterone, androstenedione, LH or insulin). This definition of PCOS requires the exclusion of specific underlying diseases of the adrenal or pituitary glands (e.g. hyperprolactinemia, acromegaly, congenital adrenal hyperplasia, Cushing's syndrome, androgen secreting tumors of the ovary or adrenal gland) which could predispose to similar ultrasound and biochemical features ***(Fauser et al., 2004).***

Clinical manifestations:

PCOS includes a heterogeneous collection of symptoms and signs with different degree of severity in affecting the reproductive, endocrine and metabolic functions ***(Edmonds, 2012).***

Balen reported a large series of women with pco ovaries detected by ultrasound scan. All of the 1871 patients had at least one symptom of the PCOS (see Table 2). Thirty-eight percent were overweight (body mass index (BMI) > 25kg/m2). Obesity was associated with an increased risk of hirsutism, menstrual cycle irrigularity, and an increase serum testosterone concentration. Obesity was also associated with an elevated rate of infertility. Twenty-six per cent with primary infertility and 14% with secondary infertility had a BMI more than 30 kg/m^2 ***(Balen et al., 1995).***

Approximately 30% had a regular menstrual cycle, 50% had oligomenorrhea, and 20% amenorrhea. In this study the classical endocrine features of increase serum LH and testosterone were found in only 39.8% and 28.9% of patients, respectively. Ovarian volume was correlated with serum LH and with testosterone concentrations. Other studies have confirmed that markers of insulin resistance correlated with ovarian volume and stromal echogenicity, which in turn have been related with androgen production. Other groups have similarly reported heterogeneity in their populations of PCOS ***(Dewailly et al., 1994).***

Franks's series, also from UK, related to 300 women recruited from a specialized endocrine clinic ***(Frank, 1989).*** Some years earlier Goldzieher compiled a comprehensive review of 1079 cases of surgically proven pco ovaries ***(Goldzieher et al., 1981).*** The frequency of clinical signs and symptoms in these series were similar (Table 2). Clinical phenotyping of PCOS involves determining the existance of clinical and/or biochemical androgen excess (hyper-androgenism), while excluding related disorders. The primary clinical sign of hyperandroginism is the presence of hirsutism. However, at the ESHRE/ASRM consensus was agreed that normative data in large populations are still lacking ***(Fauser et al., 2004).***

The assessment of hirsutism is relatively subjective and few physicians in clinically actually use standardized scoring

methods such as Ferriman Gallwey scoring system to quantify the severity of hirsutism for research ***(Ferriman and Gallwey, 1961).***

The Ferriman Gallwey scoring system was developed in 1961 and later modified in 1981 ***(Hatch et al., 1981).***

Within this system, abnormal hair distribution is assessed in nine body areas and scored from 0 to 4. Increasing scores correspond to greater hair density within a specific area. Many authors define hirsutism as a sore of 8 or greater using the modified Gallwey. There are also significant racial differences with hirsutism being less prevalent in hyperandrogenic women of Eastern Asia and more in those from Southern Asia ***(Rodin et al., 1998).***

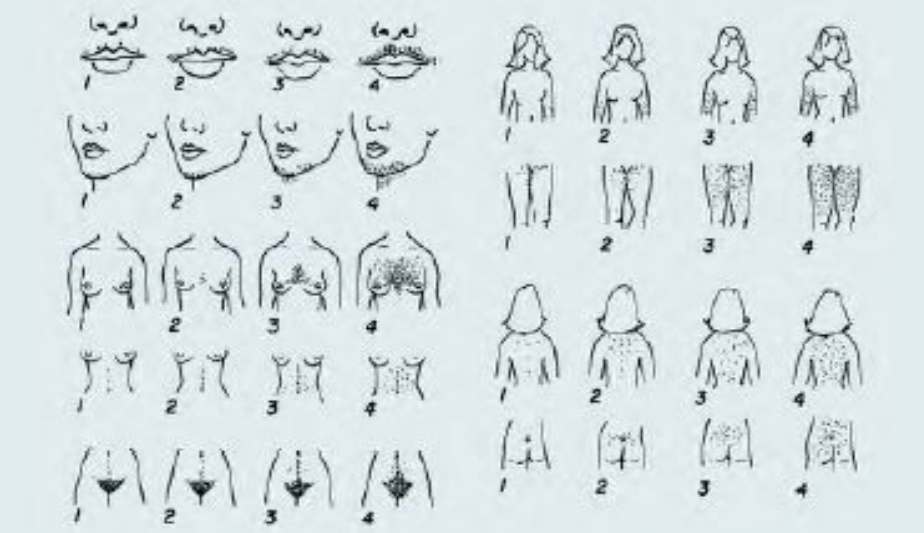

Figure (3): Depiction of the Ferriman-Gallwey system for scoring hirsutism ***(Hatch et al., 1981).***

Table (2): Clinical symptoms and sign of PCOS.

	Percentage frequency of symptom or sign			
	Balen et al (1995)[1] n = 1741	Franks (1989)[25] n = 300	Goldzieher et al (1981)[24] n = 1079	
Symptom or sign	%	%	%	No. of cases[a]
Menstrual cycle disturbance:	47	52	29[b]	(n = 547)
– oligomenorrhea	19	28	51	(n = 640)
– amenorrhea				
Hirsutism	66	64	69	(n = 819)
Obesity	38	35	41	(n = 600)
Acne	34	27	–	–
Alopecia	6	3	–	–
Acanthosis nigricans	2	< 1	–	–
Infertility (primary/secondary)	20	42	74	(n = 596)

– Denotes feature not recorded.
[a] In the Goldzieher study clinical details were not available for the entire 1079 women, thus the number of cases which were used to determine the frequency of each symptom is stated.
[b] In this series, any abnormal pattern of uterine bleeding was included.

The sole presence of acne is felt to be a relatively better indicator of hyperandrogenism, although studies are somewhat confusing regarding the exact prevalence of androgen excess in these patients. The presence of androgenic alopecia as an indicator of androgen excess has been less well studied. However, it appears to be a relatively poor indicator of androgen excess, unless present in the oligo-ovulation. In Balen's study of over 1700 women with PCOS it was found that a third had an increase serum total testosterone concentration and that the 95 percentile for total testosterone was 4.8 nmol/L ***(Balen et al., 1995).***