Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of ovulatory infertility, affects 4–7% of women ***(Ehrmann, 2005).*** Since the first description by ***Stein and Leventhal in (1935),*** this syndrome has, over the years, been defined in different ways. In 1990 the National Institutes of Health (NIH) established new diagnostic criteria for this disorder, which were based on the presence of hyperandrogenism and chronic oligoanovulation, with the exclusion of other causes of hyperandrogenism ***(Goudas and Dumesic, 1996)***. More recently, a consensus conference held in Rotterdam in 2003 re-examined the 1990 criteria and agreed to the appropriateness of including ultrasound morphology of the ovaries as a further potential criteria to define PCOS ***(The Rotterdam ESHRE/ASRM, 2004).***

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., 2005).***

A majority of patients with PCOS have insulin resistance ***(Dunaif and Finegood, 1996).*** Their elevated insulin levels contribute to or cause the abnormalities seen in the hypothalamic-pituitary-ovarian axis that lead to PCOS. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance,

increased ovarian androgen production, decreased follicular maturation, and decreased SHBG binding; all these steps contribute to the development of PCOS ***(Willis et al., 1996; Dunaif, 1997).*** Insulin resistance is a common finding among patients of normal weight as well as overweight patients ***(Nafiye et al., 2010).***

Reducing insulin resistance by improving insulin sensitivity through medications such as metformin, and the newer thiazolidinedione (glitazones), have been an obvious approach and initial studies seemed to show effectiveness ***(Lord and Flight, 2003).***

First-line agents for ovulation induction and treatment of infertility in patients with PCOS include clomiphene ***(Atay et al., 2006; Dehbashi et al., 2006)*** and metformin ***(Palomba et al., 2005)*** alone or in combination, as well as pioglitazone ***(Dereli et al., 2005; Cataldo et al., 2006).***

In women with PCOS, metformin administered at doses of up to 1500 mg/day decreases insulin, testosterone and LH levels and it also appears to favor some weight loss ***(De Leo et al., 2003).*** Most importantly, the majority of studies have shown that metformin may significantly improve menstrual cycles and ovulation rates, both spontaneous and clomiphene-induced ***(Kashyap et al., 2004)*** while multiple small studies report that clomiphene and metformin treatment is associated with similar ovulation and pregnancy rates ***(Palomba et al., 2007; Neveu et al., 2007).***

Obese PCOS women underwent treatment with rosiglitazone and pioglitazone was found to increase ovulatory frequency and improve hyperandrogenemia ***(Romualdi et al., 2003; Brettenthaler et al., 2004; Sepilian and Nagamani, 2005).*** However, when compared with metformin, the effect of rosiglitazone in improving frequencies of ovulation was lower, whereas the effect of the two drugs on hyperandrogenemia was similar ***(Baillargeon et al., 2004).*** Similar results were found by comparing the effect of pioglitazone with that of metformin in a group of obese women with PCOS, where both drugs decreased insulin resistance and hyperandrogenemia to the same extent ***(Ortega-Gonzalez et al., 2005).***

Aim of the Work

To compare the efficacy of clomiphene citrate, combined clomiphene citrate and metformin, combined clomiphene citrate and pioglitazone as first line therapy for induction of ovulation and achievement of pregnancy in infertile obese women with polycystic ovary syndrome.

Chapter (1)
Polycystic Ovary Syndrome

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; Diamanti et al., 2006; Fauser et al., 2011)***

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 ***(Azziz et al., 2004; Goldenbrg and Glueck, 2008; Boomsma et al., 2008)*** and the most frequent endocrine problem in women of reproductive age ***(Teede et al., 2010).***

There is considerable heterogeneity of 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 various aspects of the syndrome may be differentially inherited. The PCOs can exist without clinical signs of the syndrome, which may then become expressed in certain circumstances. There are a number of factors that affect expression of PCOS, for example, a gain in

weight is associated with a worsening of symptoms while weight loss may ameliorate the endocrine and metabolic profile and symptomatology ***(Clark et al., 1995)***.

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

There are studies which indicate that women with PCOS have an increased risk for these diseases which pose long-term risks for health, and this evidence has prompted debate as to the need for screening women for PCOS ***(RCOG guidelines, 2003).***

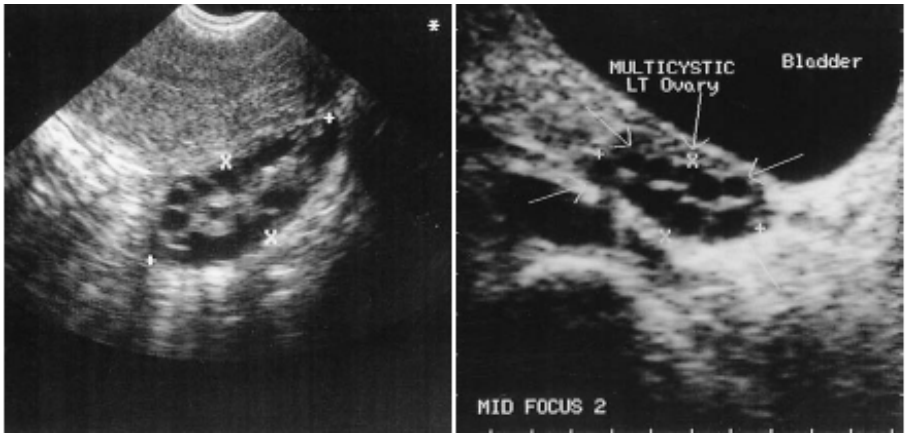
Historically the detection of the polycystic ovary required visualization of the ovaries at laparotomy with histological confirmation following biopsy ***(Stein and Leventhal, 1935).***

As further studies identified the association of certain endocrine abnormalities in women with histological evidence of polycystic ovaries, biochemical criteria became the mainstay for diagnosis. Raised serum levels of LH, testosterone, and androstenedione, in association with low or normal levels of follicle stimulating hormone (FSH) and abnormalities of

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

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

The histopathological criteria have been 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 methods for the identification of polycystic ovaries. And an attempt has been made to provide the ultrasound criteria for the diagnosis of polycystic 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).***



(a) **(b)**

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

The innovation of three-dimensional ultrasound and the use of color and pulsed Doppler ultrasound are techniques which may further enhance the detection of polycystic ovaries and which may be more commonly employed 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 claimed to have even greater sensitivity than ultrasound for the detection of polycystic ovaries. However, the substantial cost and practical problems involved with this imaging technique limit its use ***(Faure et al., 1989).***

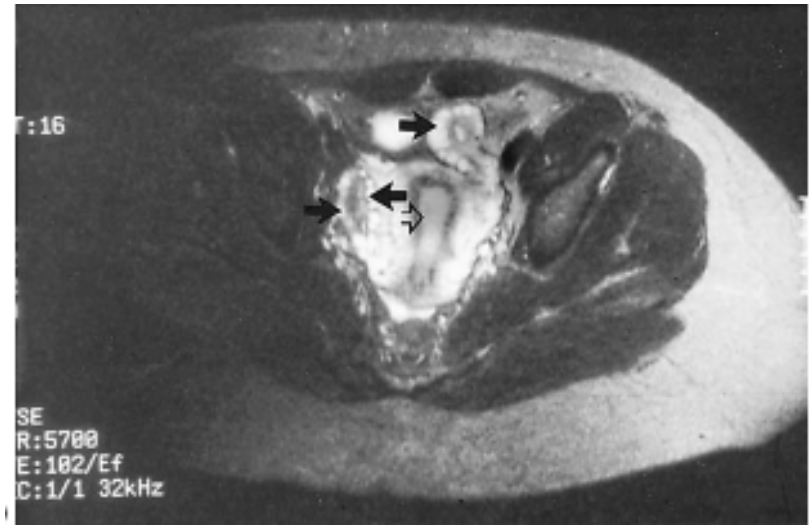


Figure (2): Magneticresonance imaging (MRI) of a pelvis, demonstrating two polycystic ovaries (closed arrows) and a hyperplastic endometrium (open arrow) ***(Balen, 2008).***

The term "polycystic ovary" in some respects 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 called a polyfollicular ovary, to reflect the finding that the "cysts" are actually follicles whose development has been arrested. Indeed the prerequisite of a certain number of cysts may be of less relevance than the volume of ovarian stroma, which has been shown to correlate closely with serum testosterone concentrations ***(Kyei-Mensah et al., 1996).***

Furthermore, it has been suggested recently that an ultrasound assessment 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 excellent technique for the detection of polycystic ovarian morphology, identification of polycystic ovaries by ultrasound does not automatically confer a diagnosis of PCOS. Controversy still exists over a precise definition of the syndrome and whether or not the diagnosis should require confirmation of polycystic ovarian morphology ***(Fulghesu et al., 2007).***

In North America 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 essential ***(Zawadski and Dunaif, 1992)***.

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

Although debate on what constitutes PCOS continues, 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 reproducibility of the various tests that we have at our disposal ***(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 signs and symptoms with varying degree of mildness and severity in affecting the reproductive, endocrine and metabolic functions ***(Edmonds, 2012).***

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

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

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.

Franks's series, also from England, related to 300 women recruited from a specialist endocrine clinic ***(Frank, 1989).*** Some years earlier Goldzieher compiled a comprehensive review of 1079 cases of surgically proven polycystic ovaries ***(Goldzieher et al., 1981).*** The frequency of clinical symptoms and signs in these series was similar (Table 2). Clinical phenotyping of PCOS involves determining the presence of clinical and/or biochemical androgen excess (hyper-androgenism), while excluding related disorders. The primary clinical sign of androgen excess is the presence of hirsutism. However, at the ESHRE/ASRM consensus meeting it 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 clinical practice actually use standardized scoring methods such as Ferriman Gallwey scoring system to quantify the degree of hirsutism for research purposes ***(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 numeric scores correspond to greater hair density within a given area. Many investigators define hirsutism as a sore of 8 or greater using the modified version. There are also significant racial differences with hirsutism being significantly less prevalent in

hyperandrogenic women of Eastern Asia origin and more so in those from Southern Asia ***(Rodin et al., 1998).***

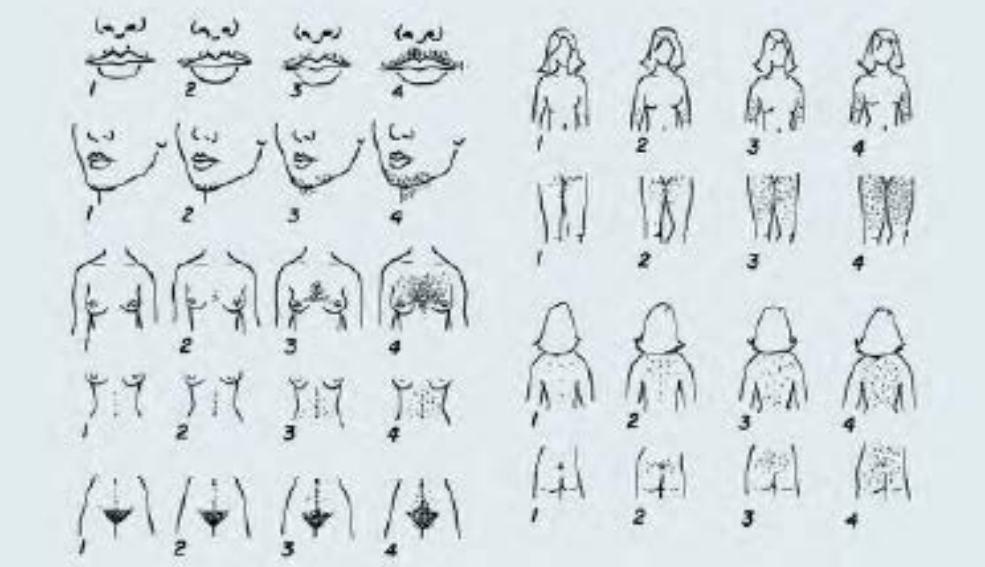


Figure (3): Depiction of the Ferriman-Gallwey system for scoring hirsutism ***(Hatch et al., 1981).***

Ovarian function in PCOS:

The presence of enlarged polycystic ovaries suggests that the ovary is the primary site of endocrine abnormality, particularly the hyperandrogenism. ***Rosenfield et al. (1990)*** suggested that derangement of P450c17α activity played a central role in excess ovarian androgen production.

This was subsequently confirmed by other workers who assessed the response of the pituitary and ovary to a single dose of the gonadotropin releasing hormone agonist (GnRHa), nafarelin, in hyperandrogenemic women with PCOS in whom adrenal androgen production had been suppressed by