INTRODUCTION

Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting women in the reproductive age group, is a predominant cause of anovulatory infertility, with a prevalence rate of 17-20% ***(Subarna et al., 2015)***.

Ovulation dysfunction represents one of the most common problems in couples presenting for infertility evaluation ***(Branigan and Estes, 2003)***.

PCOS is an important cause of both menstrual irregularity and androgen excess in women. When fully expressed, the manifestations include irregular menstrual cycles together with hirsutism and/or acne, obesity are a frequent concomitant ***(Ehrmann et al., 2005)***.

In 2003, the Rotterdam consensus group revised the diagnostic criteria of polycystic ovarian syndrome: any two of the following criteria are essential for diagnosis of PCOS:

1. Oligo and/or anovulation.
2. Clinical and/or biochemical signs of hyperandrogenism.
3. Polycystic ovaries and with exclusion of other cases of hyperandrogenism (congenital adrenal hyperplasia, androgen secreting tumors and cushing syndrome).

Kandil and Selim (2005), considered the diagnosis of PCOS according to the following:

1. Clinical feature: the affected women have ameno/oligomenorrhea, overweight with or without hirsutism.

2. U/s criteria: an enlarged or normal sized ovary with multiple small subcortical follicles more than 10 follicles (2-9 mm in diameter) together with dense stroma.

3. Abnormal hormonal profile: elevated LH, normal or decreased FSH and LH:FSH ratio more than 2 ***(Kandil and Selim, 2005)***.

Problems in inducing ovulation in women with polycystic ovary syndrome are well recognized ***(Berek et al., 2012)***.

The main indication for laparoscopic ovarian drilling is clomiphene citrate resistant PCOS as a second line therapy for anovulatory infertile PCOS cases; specifically, as an alternative to gonadotropins ***(Abu-Hashim et al., 2013)***.

Laparoscopic ovarian drilling is currently recommended as a safe, efficacious and cost-effective alternative to gonadotropins for ovulation induction in infertile, anovulatory, CC-resistant PCOS women without the risks of OHSS or multiple gestations ***(Subarna et al., 2015)***.

Laparoscopic ovarian drilling can lead to injuries in ovarian tissue and induce reduction of ovarian reserve ***(Fernandez et al., 2011)***.

Ovarian reserve is related to size, number and quality of oocytes within follicles. The ovarian reserve is the reproductive ability of the ovary that shows number of follicles in it. Ovarian reserve decrease with aging and subsequently the reproductive ability of women ***(Hansen et al., 2008)***.

Antimullerian hormone is reflecting the 'ovarian reserve' which meaning the number of follicles that can be recruited to grow by the administration of FSH ***(Hansen et al., 2008)***.

Antimullerian hormone is expressed by granulosa cells of the ovary during the reproductive years, and limits the formation of primary follicles by inhibiting excessive follicular recruitment by FSH ***(Dewailly et al., 2014)***.Some authorities suggest it is a measure of certain aspects of ovarian function ***(Broer et al., 2011)***, useful in assessing conditions such as polycystic ovary syndrome and premature ovarian failure ***(Visser et al., 2006)***.

Antimullerian hormone is useful to predict a poor ovarian response in In vitro fertilization (IVF), but it does not appear to add any predictive information about success rates of an already established pregnancy after IVF ***(Broer et al., 2013)***.

Additionally, AMH level is used to determine a women's remaining egg supply ***(Indichova et al., 2015)***.

Antimullerian hormone is a good predictor of oocytes quantity, but it may not provide information about egg quality. Thus, young women with low antimullerian hormone levels may have a reduced number of oocytes but normal, age-appropriate oocytes quality ***(Toner et al., 2013)***.

In a similar study, evaluating the effect of ovarian drilling on AMH and antral follicular count, the results showed that there were statistically significant difference between AMH level and antral follicular count before and after laparoscopic ovarian drilling and it may indicate a possible diminished ovarian reserve.

The authors of this study could also recommend using the AMH and AFC as a reliable markers of the ovarian reseve and measuring them for women with anovulatory PCOS undergoing LOD may provid a useful tool in evaluating the outcome of LOD as a gold standerd treatment for clomiphen citrate resistant PCO women ***(Emad et al., 2014)***.

AIM OF THE WORK

The aim of the study is to evaluate the effect of laparoscopic ovarian drilling on anti-mullerian hormone as an ovarian reserve marker in infertile women with polycystic ovarian syndrome.

Research hypothesis :

In women with PCOS and undergoing ovarian drilling, AMH as a marker of ovarian reserve may be or may not be affected by this operation.

Research question :

In women with PCOS and undergoing ovarian drilling does this operation affect AMH levels?

POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS), a common endocrine disorder affecting women in the reproductive age group, is a predominant cause of anovulatory infertility, with a prevalence rate of 17-20% ***(Subarna et al., 2015)***.

It is important to appreciate that PCOS is a syndrome, reflecting multiple potential etiologies and variable clinical presentations. Its key features are oligo- or anovulation and hyperandrogenism. Other features are polycystic ovaries on pelvic ultrasonography, infertility due to oligoovulation, obesity, and insulin resistance ***(Robert et al., 2016).***

The condition was first described in 1935 by American gynecologists Irving F. Stein, Sr. and Michael L. Leventhal, from whom its original name of Stein–Leventhal syndrome is taken ***(Marrian and Greg, 2011; Richard, 2011).*** The earliest published description of a person with what is now recognized as PCOS was in 1721 in Italy. Cyst-related changes to the ovaries were described in 1844 ***(Kovacs and Gabor, 2007).***

Epidemiology

The prevalence of PCOS depends on the choice of diagnostic criteria. The World Health Organization estimates that it affects 116 million women worldwide as of 2010 (3.4% of women) ***(Vos et al., 2012).*** One community-based prevalence study using the Rotterdam criteria found that about

18% of women had PCOS and 70% of them were previously undiagnosed ***(Teede et al., 2010).***

Ultrasonographic findings of polycystic ovaries are found in 8-25% of normal women ***(Polson et al., 1988; Clayton et al., 1992; Farquhar et al., 1994; Van et al., 1997).*** 14% women on oral contraceptives are found to have polycystic ovaries ***(Clayton et al., 1992).*** Ovarian cysts are also a common side effect of intrauterine devices (IUDs) ***(Hardeman et al., 2014).***

Prevalence estimates for PCOS, as defined by the NIH/NICHD criteria, indicate that PCOS is a common endocrinopathy affecting 4%–8% of women of reproductive age **(Azziz et al., 2004)** Recently, several groups have demonstrated that the prevalence of PCOS varies depending on the diagnostic criteria used (Table1) These studies consistently report that the prevalence estimates using the Rotterdam criteria are two to three times greater than those obtained using the NIH/NICHD criteria **(Yildiz et al., 2012)**.

Table (1): Prevalence of polycystic ovary syndrome (PCOS) using different diagnostic criteria **(Yildiz et al., 2012).**

Source	Population	NIH/NICHD criteria	ESHRE/ASRM (Rotterdam) criteria	Androgen excess and PCOS society criteria
March et al. 2010	728 Australian women	8.7%	17.8%	12.0%
Mehrabian et al. 2011	820 Iranian women	7%	15.2%	7.92%
Tehrani et al. 2011	929 Iranian women	7.1%	14.6%	11.7%
Yildiz et al. 2012	392 Turkish women	6.1%	19.9%	15.3%

The main features of PCOS are anovulation, hyperandrogenism and insulin resistance. Anovulation results in irregular menstruation, amenorrhea, ovulation-related infertility and polycystic ovaries. Hyperandrogenism results in acne and hirsutism. Insulin resistance is often associated with obesity, Type 2 diabetes, and high cholesterol levels. The symptoms and severity of the syndrome vary greatly among the affected women. Moreover, it may affect daily physical activities **(Palomba et al., 2015).**

Etiology

PCOS is a common heterogeneous disorder of uncertain cause ***(Mayo Clinic staff, 2011; Fauser et al., 2011; Legro and***

Strauss, 2002). There is evidence that it is a genetic disease. This 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; Fauser et al., 2011; Legro and Strauss, 2002).***

Although evidence of familial segregation and clustering of the disease in first-degree relatives of women diagnosed with PCOS has been presented, no particular pattern of inheritance has emerged. Some of the problems in genetic studies have been the lack of uniform criteria for diagnosis, heterogeneity of phenotypic features, and the fact that the disorder is only expressed clinically in women during their reproductive years. Even within affected families and between sisters with polycystic ovaries, there is heterogeneity in presentation ***(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 from a parent, and, if a daughter receives the variant, the daughter will have the disease to some extent ***(Hamosh, 2011; Crosignani and Nicolosi, 2001; Legro and Strauss, 2002; Strauss, 2003).***

The variable expressivity occurs when a phenotype is expressed to a different degree among individuals with the same genotype For example, individuals with the same allele for a gene involved in a quantitative trait like body height might have large variance (some are taller than others), making prediction of the phenotype from a particular genotype alone difficult ***(Tao, 2010)***.

The genetic variant can be inherited from either the father or the mother, and can be passed along to both 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; Hamosh, 2011).*** The allele appears to manifest itself at least partially via heightened androgen levels secreted by follicle theca cells from women with the allele ***(Strauss, 2003).*** The exact gene affected has not yet been recognized ***(Diamanti-Kandaraskis et al., 2006; Lergo and Strauss, 2002; Amato and Simpson, 2004).***

Although the role of genetic factors in PCOS is strongly supported, the genes that are involved in the etiology of the syndrome have not been fully investigated until now ***(Prapas et al., 2009).***

PCOS is considered a complex, polygenic trait that might result from the interaction of susceptible and protective genomic variants under the influence of environmental factors,

whose role is under intensive investigation ***(Diamanti-Kandaraskis and Piperi, 2005).***

The heritability of PCOS is probably more complex, similar to that of type 2 diabetes mellitus or cardiovascular disease. However, a positive family history appears to be the most informative risk factor for the development of PCOS ***(Mohammed et al., 2007).***

The principal genetic target for the responsible variants proposed include genes regulating secretion and action of gonadotrophin and insulin, weight and energy regulation, and androgen biosynthesis and action ***(Azziz et al., 2004).***

Some studies including a study by **Soter et al.,** have demonstrated a definite influence of interleukin-6 and interleukin-10 gene polymorphisms, interferon-c and transforming growth factor-beta1 in the development of PCOS, although no clear pattern of inheritance has been identified **(Soter et al., 2015)**. Other causal factors are epigenetic exposures, highlighting the association between intrauterine exposure and maternal androgens and phenotypes related to the syndrome **(Demissie et al., 2008)**.

Ethnic variations in PCOS may be associated with environmental factors, such as socioeconomic conditions and lifestyle **(Dumesic et al., 2015)**.

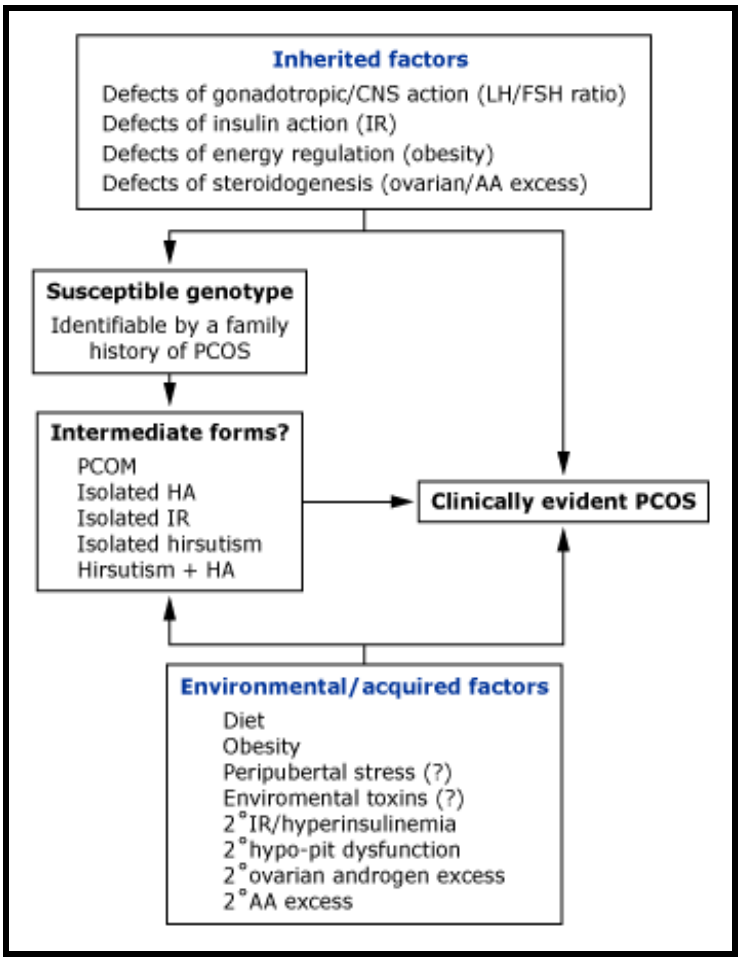

Figure (1): Potential mechanisms underlying the development of PCOS.
*AA= adrenal androgen * CNS= central nervous system *HA= hyperandrogenism
*IR=insulin resistance * PCOM= PCO morphology.

Inherited factors act to create a susceptible genotype, most commonly identifiable by a positive family history for PCOS or related features. This susceptible genotype, in isolation or in association with environmental or acquired factors, may result in intermediate forms of functional hyperandrogenism. Continued exposure to environmental

factors or an increasing load of genetic variants favoring its occurance, leade to development of clinical evidence of PCOs ***(Azziz et al., 2004)***.

Pathophysiology of PCOS:

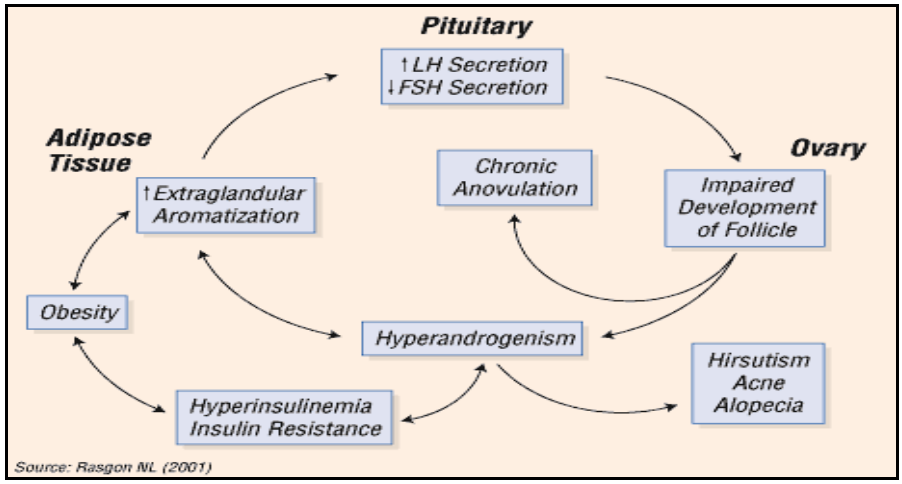

Figure (2): Pathophysiology of polycystic ovary syndrome.

Despite a large number of research studies, pathogenesis of PCOS still needs further elucidation **(Witchel et al., 2012).** However**,** some pathophysiological mechanisms are known, e.g. alterations in the secretion of gonadotropin-releasing hormone, defect in androgen synthesis and development of insulin resistance **(King, 2006)**.

One of the numerous theories proposed to explain pathogenesis of the syndrome is the disturbance of the hypothalamic-pituitary axis, resulting in disarranged gonadotropin secretion by the hypothalamus with a consequent

elevation of luteinizing hormone (LH) levels and normal or low follicle-stimulating hormone (FSH) levels **(Dumesic et al., 2015)**.

A number of studies have also indicated that insulin resistance is the key pathophysiological element for development of the syndrome. Insulin acts synergistically with LH to increase androgen production in the theca cell of the ovary (**Erhmann, 2005)**. Another site for androgen production is the adrenal cortex, due to abnormalities in cortical stereoidogenesis promoted by stimulation of adrenocorticotropic hormone **(da Silva et al., 2007)**.

And these excess androgen levels, mainly testosterone, androstenedione and dehydroepiandrosterone sulfate, cause premature atresia of ovarian follicles, forming multiple cysts and anovulation with persistent estrogen levels resulting from aromatization of androgens to estrogens without opposition of progesterone and associated with an increased risk of endometrial cancer **(Dumitrescu et al., 2015)**.

In a normal menstrual cycle, one egg is released from a dominant follicle – essentially a cyst that bursts to release the egg. After ovulation the follicle remnant is transformed into a progesterone-producing corpus luteum, which shrinks and disappears after approximately 12–14 days. In PCOS, there is a

so-called "follicular arrest", i.e., several follicles develop to a size of 5–7 mm, but not further. No single follicle reaches the preovulatory size (16 mm or more). The small ovarian follicles are believed to be the result of disturbed ovarian function with failed ovulation, reflected by the infrequent or absent menstruation that is typical of the condition ***(Enien et al., 2012).***

Intrinsic ovarian dysfunction:

Theca cells in women with PCOS produce increased androgens in response to similar levels of LH compared with normal theca cells **(Baskind and Balen, 2016)**.

Genetic role:

Some studies suggest that genetic plays an important role in pathogenesis of PCOS. The high prevalence of women with PCOS and the wide range of phenotypes can be explained by the interaction of key genes with environmental factors **(Urbanek, 2007)**. There are some evidences showed that there are association between cytochrome P450 17-hydroxylase/17, 20-desmolase (CYP17) and PCOS. Cytochrome P450 side-chain cleavage enzyme (CYP11A) is another candidate gene that some studies find a role for it in PCOS. This gene encodes the cholesterol side-chain cleavage enzyme. Mutation in cytochrome P450 21-hydroxylase (CYP21) gene has found to have a role in PCOS in many studies. This gene encodes 21-