1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is recognized as the most common endocrine disorder of reproductive-aged women around the world ***(Stein and Leventhal, 1935)***. It affects 2% to 7% of women in the general population ***(Schmidt et al., 2016)***. The pathogenesis underlying these clinical features is poorly understood. Gonadotropic dysregulation, genetics, and environmental factors have been implicated ***(Norman et al., 2007)***.

The diagnostic criteria for PCOS continue to evolve, but the 2003 Rotterdam consensus criteria remain widely used. These criteria require at least 2 of the following findings for diagnosis; oligoanovulation, polycystic ovaries on transvaginal ultrasonography, and clinical signs or biochemical evidence of hyperandrogenism ***(Rotterdam et al., 2004).***

Patients with PCOS are frequently first seen by a dermatologist. It is estimated that 72% to 82% of women with PCOS are seen with cutaneous signs classically associated with hyperandrogenism such as acne, hirsutism, and androgenic alopecia ***(Carmina et al., 2003)***. Hyperandrogenism may also manifest as acanthosis nigricans ***(Lee et al., 2007)***.

Hirsutism is the most common clinical manifestation of hyperandrogenism in women ***(Rosenfield, 2005)***. Approximately 60% to 70% of women with PCOS have hirsutism ***(Azziz et al., 2006)***. Hirsutism is defined as excessive terminal hair growth

that takes on a male pattern distribution ***(Marla et al., 2008)***. The hair type present in most women with a hormonal hyper androgenic disorder is coarse, thickened, pigmented, and long and is called terminal hair. Typically, the onset of hirsutism in PCOS follows menarche, although a minority of premenarche girls have earlier onset of pubic hair development and some degree of hirsutism. The hirsutism in PCOS is more pronounced. The presence of substantial numbers of terminal hairs over the chin, neck, lower face, and side burns indicates the presence of androgen excess. Similarly, excessive hair growth on the lower back, sternum, abdomen, shoulders, buttocks, perineal area, and inner thighs is considered abnormal. Several clinical assessment scales have been used in the grading of hirsutism ***(Hatch et al., 1981).***

During adolescence, acne should not be considered a substitute of hyperandrogenism ***(Carmina et al., 2003)***, although girls with severe acne or acne that is resistant to oral and topical agents, including isotretinoin, may have a 40% likelihood of developing PCOS ***(Borgia et al., 2004)***. About one third of women with PCOS, particularly younger women, demonstrate acne ***(Strauss et al., 2007)***. When acne persists after adolescence or is exacerbated in the mid-20s or -30s, hyperandrogenemia is common, and acne may be considered a clinical sign of hyperandrogenism. Those presenting with acne alone may have serum free T levels as high as those seen in

hyperandrogenic disease states, demonstrating hirsutism without acne ***(Lucky et al., 1983)***.

Alopecia in females may present as diffuse pattern of thinning hair over the vertex of the scalp with the frontal hair line commonly preserved. It is a poor predictor of biochemical hyper androgenemia, and low serum iron levels and aging are more common causes of hair loss in women ***(Barth et al., 2007)***. In the setting of androgen excess, androgen sensitive hair follicles shorten during the anagen phase, resulting in miniaturization of the scalp hair, less scalp coverage, and alopecia. The pattern of hair loss in women with hyperandrogenism is variable. For example, although hair loss patterns in women with hyperandrogenemia typically involve the vertex, crown, or a diffuse pattern, women with more severe hyperandrogenemia may experience bitemporal hair loss and loss of the frontal hairline ***(Goodman et al., 2001).*** While the actual prevalence of alopecia in women with PCOS is relatively low compared with other androgenic symptoms (approximately 5%), an association with polycystic ovaries has been reported ***(Cela et al., 2003)***.

Acanthosis nigricans is characterized by brown and velvety hyperpigmentation of the skin with accentuation on skin folds. It is most commonly observed in the neck and intertriginous areas, such as armpits, groins and inframammary region. It is reported in 5% of the patients with PCOS ***(Fraser and Kovacs, 2004).*** Excessive binding of serum insulin to IGF-1 receptors in peripheral tissues determines the proliferation of

keratinocytes and fibroblasts; hence, acanthosis nigricans is a cutaneous manifestation of hyperinsulinemia, and not just of obesity. Despite being mostly associated with obesity, PCOS and diabetes, acanthosis nigricans may be associated with genetic diseases, drug reaction (nicotinic acid) and malignancies ***(Lee et al., 2007)***.

PCOS shows reproductive and metabolic complications that must be diagnosed and treated early due to the risk of infertility, endometrial cancer and plurimetabolic syndrome. Besides these complications, PCOS is associated with high morbidity due to aesthetic aspects that negatively affect women's selfesteem. Knowledge about the physiopathologic mechanisms of this syndrome is very important for an appropriate therapeutic approach ***(Moura et al., 2011)***.

Early detection of PCOS cases could be aided by picking up cutaneous lesions that are specifically associated with PCOS. In addition, many skin manifestations were regarded clinically suspecious as to diagnose PCOS such as acne, hirsutism, androgenic alopecia, acanthosis nigricans and seborrhic dermatitis. However some of these skin lesions are present in female patients who have not been diagnosed as having PCOS.

2. AIM OF THE WORK

The aim of the current study was to determine the prevalence of cutaneous disorders of PCOS and indicate the specific cutaneous lesions that have reliable association with PCOS. These could be used as a specific marker for early diagnosis of highly suspect patients with PCOS.

3. REVIEW OF LITERATURE

Polycystic ovary syndrome (PCOS)

3.1. Historical background

The presence of male secondary sexual characteristics in women has been recognized from ancient times, but it was not until 1921 when the association of hyper androgenic symptoms with abnormalities in glucose metabolism had been reported, highlighting the presence of polycystic ovaries (PCO) in some of these patients ***(Escobar-Morreale et al., 2005)***.

In 1935, seven women with amenorrhea, hirsutism, obesity and a characteristic polycystic appearance of their ovaries, was the first description of a complex phenotype known as the polycystic ovary syndrome (PCOS) ***(Stein and Leventhal, 1935)***.

3.2. Introduction:

Polycystic ovary syndrome (PCOS) is a complex, heterogeneous disorder of uncertain etiology, but there is strong evidence that it can be classified as a genetic disease ***(Legro and Strauss, 2002; Fauser et al., 2011).***

Three features are generally recognized to compose this syndrome, including androgen excess, ovulatory dysfunction and polycystic ovaries. Androgen excess (or hyperandrogenism) is detected either by laboratory analysis, generally measuring

circulating androgen levels, or by clinical examination, primarily in the form of hirsutism. Ovulatory dysfunction is generally detected by the presence of clinically evident oligomenorrhea. Finally, classical polycystic ovaries are diagnosed by ultrasonography ***(Trivax and Azziz, 2007).***

3.3. 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 the population) ***(Vos, 2012).*** One community-based prevalence study using the Rotterdam criteria found that about 18% of women had PCOS, and that 70% of them were previously undiagnosed ***(Teede et al., 2010).***

Prevalence estimates range from 8% using the National Institutes of Health criteria to 18%when the broader Rotterdam diagnostic criteria are applied ***(Housman et al., 2014)***.

Ultrasonographic findings of polycystic ovary are found in 8-25% of normal women ***(Clayton et al., 2004; Santbrink et al., 2007)*** and 14% of women on oral contraceptives are found to have polycystic ovary ***(Clayton et al., 2004).***

3.4. Etiology and Pathogenesis

The heterogeneity of the disorder has led to multiple mutually inconsistent theories regarding its etiology. These include :

3.4.1. Primary defect in insulin action and/or binding to receptors leading to hyperinsulinemia ***(Tsilchorozidou et al., 2004)***.

3.4.2. Primary neuroendocrine defect leading to an exaggerated leutinzing hormone (LH) pulse frequency and amplitude ***(Tsilchorozidou et al., 2004)***.

3.4.3. Primary defect in ovarian/adrenal androgen biosynthesis resulting in hyperandrogenism ***(Tsilchorozidou et al., 2004)***.

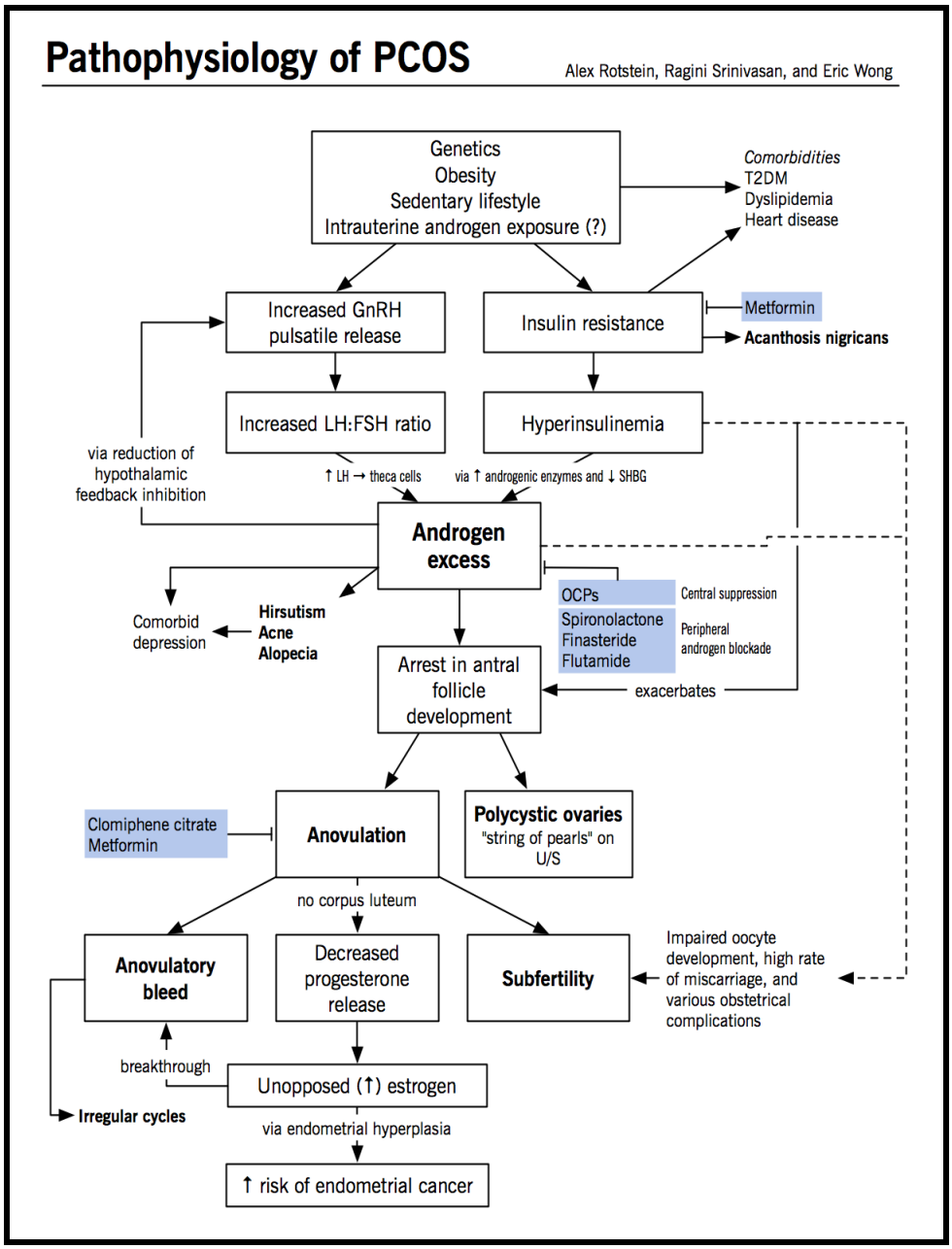

Figure (1): Detailed pathophysiology of PCOS ***(Rotstein et al., 2010).***

3.4.1. Insulin Resistance

It is defined as a subnormal response to both endogenous and exogenous insulin ***(Steiner et al., 1990)***, and is generally accepted as an important risk factor for the development of the metabolic syndrome ***(Wild et al., 2010).*** It is found in 95% of obese women with PCOS ***(Carmina and Lobo, 2004)***.

A family history of type 2 diabetes is more widely met among PCOS women with impaired glucose tolerance (IGT) compared with those with normal glucose tolerance ***(Ehrmann et al., 2005).*** Clinical features that suggest the presence of severe insulin resistance include acanthosis nigricans, ovarian hyperandrogenism, lipodystrophy, accelerated or impaired linear growth, autoimmunity and muscle cramps ***(Mantzoros, 2008).***

3.4.3. Hyperandrogenism

Biochemical hyperandrogenism was defined as an elevation of the serum testosterone concentration above the criteria where total testosterone should be more than 0.68 ng/mL or free testosterone more than 1.72 pg/mL ***(Chae et al., 2008)***.

3.4.3.1. Adrenal hyperandrogenism:

There is a body of evidence to suggest that adrenal hyperandrogenism by putative dysregulation of 17α-hydroxylase/17, 20 hydroxylase is a genetically determined trait in PCOS ***(Goodarzi et al., 2007)***. Increased peripheral metabolism of cortisol has also, been proposed to contribute to

the functional adrenal hyper-androgenism ***(Tsilchorozidou et al., 2003)***.

In particular, the enhanced inactivation of cortisol by 5α-reductase or the impaired reactivation of cortisone by 11-β-hydroxy-steroidogenase 1 could lead to decreased feedback suppression of adrenocorticotropic hormone (ACTH) secretion. Notably, insulin resistance may in part account for the enhanced 5α-reduction of cortisol without affecting cortisol production. In this setting, the hypothalamic–pituitary–adrenal axis may be stimulated, leading to increased adrenal androgen production in PCOS ***(Yildiz et al., 2004)*** (Fig 2).

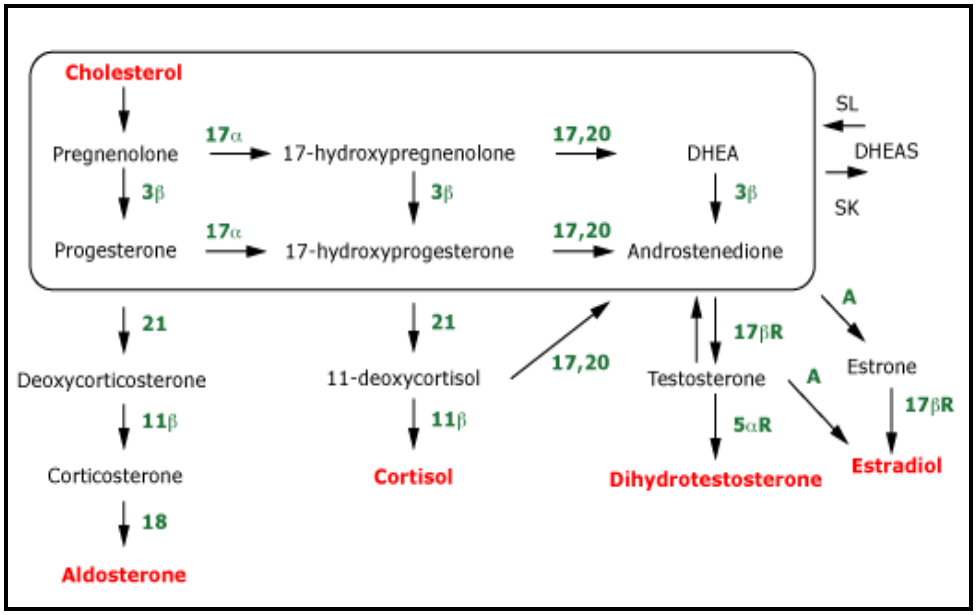

Figure (2): Synthetic pathways for adrenal steroid synthesis ***(Barbieri, 2006).***

3.4.3.2. Ovarian hyperandrogenism:

Women with PCOS also have relatively steady circulating levels of gonadotropins resulting in increased ovarian production of total testesterone, androstenedione, DHEA, dehydroepiandrosterone sulphate (DHEA-S), 17α-hydroxyprogesterone, and estrone (E_1) ***(De Vane et al., 1975; Heineman et al., 1984)***.

Sekar et al. in (2000), demonstrated that LH and insulin synergistically can up-regulate low density lipoprotein (LDL) receptor in granulosa-luteal cells via intracellular mechanisms that include the protein kinase A (PKA), PI3K, and mitogen-activated protein (MAP) kinase signaling pathways (Fig. 3).

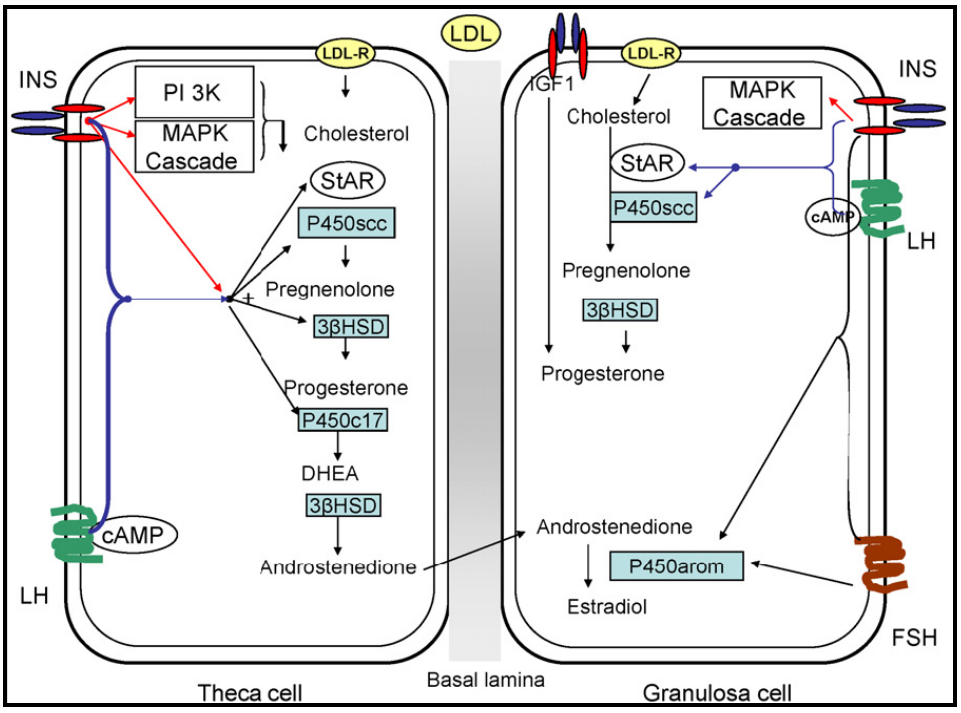

Figure (3): Intracellular pathways that affecting the regulation of ovarian steroid synthesis ***(Diamanti-Kandarakis et al., 2008).***

3.4.4. Hyperinsulinemia and Hyperandrogenism

Several studies have demonstrated a positive correlation between fasting insulin levels and androgen levels and whether hyperandrogenism results from the hyperinsulinaemia of insulin resistance, or vice versa, has been debated, since this correlation was demonstrated ***(Burghen et al., 1980; Lobo et al., 1983)***.

Most of authorities hypothesize that in affected individuals, hyperinsulinemia secondary to insulin resistance is the primary factor driving increased androgen production ***(Bremer and Miller, 2008)***.

This concept is supported by data showing that bilateral oophorectomy ***(Nagamani et al., 1986)***, or the administration of a GnRH agonist ***(Geffner et al., 1986),*** or an antiandrogenic compound, do not alter the insulin resistance or hyperinsulinemia of women with PCOS ***(Diamanti-Kandarakis et al., 1995)***.

Insulin may act alone to stimulate ovarian androgen secretion directly and/or augment LH stimulated androgen secretion ***(Hernandez et al., 1998)***, or it may act indirectly to:

1) Enhance the amplitude of GnRH stimulated LH pulses ***(Soldani et al., 1994)***.

2) Decrease hepatic production of serum sex hormone binding globulin (SHBG) ***(Nestler et al., 1991)***.

3) Decrease IGF binding protein-1 ***(Lee et al., 1993)***.

This insulin would increase the availability of free IGF-1, which can also stimulate androgen production ***(Ibanez et al., 1997)***. Furthermore, the hyperinsulinemia of PCOS may contribute to mid-antral follicular arrest, a characteristic feature of the polycystic ovary ***(Franks et al., 1999)***.

Conn et al. (2000) showed that women with PCOS had clinical evidence of hyperandrogenism and/or menstrual disturbance, suggesting that hyperinsulinaemia alone is not sufficient for the expression of the syndrome. In another study in a more genetically homogenous group of Asian women, ***Rodin and colleagues (1998)*** reported that the effects of type 2 DM and PCO on insulin sensitivity were independent, suggesting that these changes in insulin sensitivity involve different mechanisms. It is possible that the insulin resistance and the reproductive disturbances reflect separate genetic defects and that insulin resistance unmasks the syndrome in genetically susceptible women.

Many studies strongly suggest that only women with the endocrine syndrome of hyperandrogenism and chronic anovulation appear to be insulin-resistant ***(Dunaif et al., 1987; Robinson et al., 1993; Sampson et al., 1996)***. Other reports indicate that ovulatory women with hyperandrogenism or PCO in US are not insulin-resistant ***(Tsilchorozidou et al., 2004)***.

3.4.5. Abnormal ovarian morphology:

Approximately six to eight times more, pre-antral and small antral follicles are present in the polycystic ovary compared with the normal ovary ***(Webber et al., 2003).*** They are arrested in development at a size of 2–9 mm. An enlarged stromal volume is invariably present and a total ovarian volume >10 cm^3 is often witnessed ***(Balen et al., 2003)***.

Excess androgens probably play a key role in the etiology of the abnormal ovarian morphology. Androgens encourage the development of primary follicles with arrest of growth to the stage of pre-antral and small antral follicles, and, in the presence of excess androgens, this process is accelerated compared with the normal ovary ***(Homburg, 2008).***

3.4.5. Neuroendocrine Effects

Gonadotropin-dependent functional ovarian hyper-androgenism is the major source of the hyperandorgenemia in the majority of PCOS cases ***(Ehrmann, 2005; Buggs and Rosenfield, 2005).***

Excessive LH secretion relative to FSH by the pituitary gland was the first laboratory abnormality identified in classic PCOS. It is thought to play a role in the pathogenesis of PCOS by increasing androgen production and secretion by ovarian theca cells ***(Rosenfield, 2008).***