INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age, affecting approximately 6%–17% of the population. In recent years, efforts have focused on helping patients to gain increased awareness of PCOS, with a greater understanding of the potential long-term health consequences associated with this disorder. Women with PCOS can have an increased risk of metabolic syndrome, hypertension, insulin-resistant diabetes, cardiovascular diseases, and endometrial cancer. Therefore, identification of women at risk of PCOS is of utmost importance for early diagnosis and intervention ***(Safier et al., 2016)***.

In 2003, a little known g-protein- coupled receptor, GPR54, was found to have a key regulatory position in the hypothalamic-pituitary-gonadal axis. Several lines of evidence supported the role of GPR54 as the gatekeeper of the reproductive cascade. In humans, loss of function point mutations and deletions within the coding sequence of the GPR54 gene were identified in patients with idiopathic hypogonadotropic hypogonadism ***(De Roux et al., 2003; Chen et al., 2010))***.

Kisspeptin is one of the ligands of GPR5. It is a 54-amino-acid peptide which was first isolated in 2001 ***(Ohtaki et al., 2001)*** and has recently shown to regulate the secretion of luteinizing hormone during the promotion of ovulation by stimulating gonadotropin releasing hormone (GnRH) release from the hypothalamus ***(Castellano et al., 2006, Navarro et al., 2005b).***

Women with PCOS commonly display deregulated gonadotropin secretion with higher LH pulsatility and perturbed LH/FSH ratios, which likely contributes to the ovarian phenotype and might be indicative of disrupted GnRH secretory activity. Given the complex relationship between kisspeptin and hypothalamic-pituitary-gonadal axis, this study aimed to investigate if kisspeptin levels are increased in women with polycystic ovary syndrome than in healthy individuals and see its correlation with other hormonal changes which characterize this syndrome.

AIM OF THE WORK

Research hypothesis:

In women with PCOS, kisspeptin levels may be higher than in normals.

Research question:

In women with PCOS, are kisspeptin levels higher than in normals?

Aim of the study:

This study aims to assess the assosciation between kisspeptin level and PCOS.

Chapter One

POLYCYSTIC OVARY SYNDROME (PCOS)

Also called hyperandrogenic anovulation (HA) ***(Kollmann et al., 2014)***, is one of the most common endocrine disorders among women. PCOS has a diverse range of causes that are not entirely understood, but there is evidence that it is largely a genetic disease ***(Fauser et al., 2011)***.

Historical background:

The presence of male secondary sexual characteristics in women has been recognized from ancient times, but it was not until 1921 when Achard and Thyers reported the association of hyperandrogenic symptoms with abnormalities in glucose metabolism, highlighting the presence of polycystic ovaries (PCOS)in some of their patients ***(Escobar et al., 2005)***.

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

Criteria of diagnosis:

National Institute of Health (NIH) 1990 Criteria for PCOS:

In 1990 a consensus workshop sponsored by the NIH/NICHD suggested that a person has PCOS if she has all of the following ***(Richard et al., 2011)***:

- Oligo ovulation.
- Signs of androgen excess (clinical or biochemical).
- Exclusion of other disorders that can result in menstrual irregularity and hyperandrogenism.

Rotterdam criteria:

In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any 2 of 3 criteria are met ***(Azziz et al., 2006)***:

- Oligoovulation and/or anovulation.
- Excess androgen activity.
- Polycystic ovaries (by gynecologic ultrasound) (Rotterdam Consensus Workshop, 2004).
- Androgen Excess Society (AES) 2006 criteria for PCOS:

Finally, in 2006, the Androgen Excess & PCOS Society suggested a tightening of the diagnostic criteria to all of: ***(Teede et al., 2010)***.

1- Excess androgen activity.
2- Oligo-ovulation\ anovulation and/ or polycystic ovaries.
3- Other entities are excluded that would cause excess androgen activity

(AES, 2006)

Prevelance:

Prevelance of 20-48% among the general adult population ***(Forrest et al., 2011)***. But this figure may not reflect the true prevelance, as there have been no specific population based studies, and the criteria used for diagnosis are varied. An international consensus definition of PCOS defined a set of agreed criteria used for diagnosis ***(ESHRE/ASRM-sponsored PCOS consensus workshop group, 2004)***.

The prevalence of PCOS has increased with the use of different diagnostic criteria and has recently shown to be 18% in the first community based prevalence study based on the current Rotterdam diagnostic criteria ***(March et al., 2010)***.

Etiology and Pathogenesis:

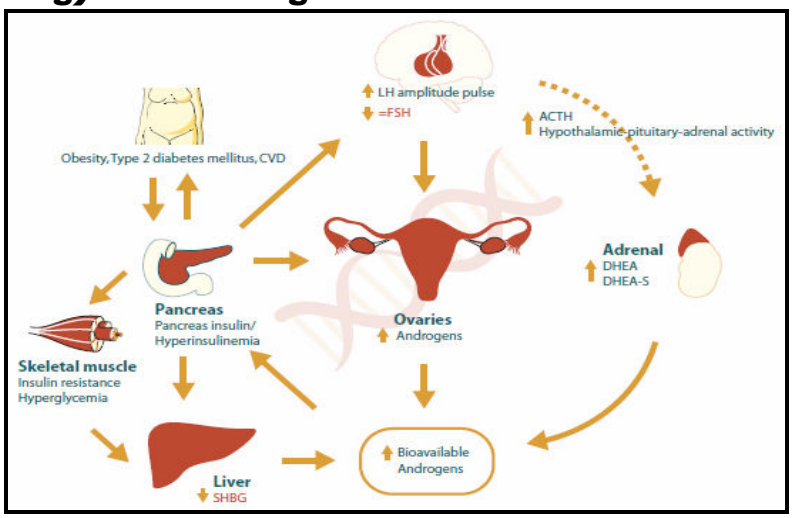

Figure (1): Simplified illustration of some of the different organ-specific aberrations and their interactions in the pathophysiology of PCOS ***(Schmidt, 2011).***

Genetics and Environmental Factors

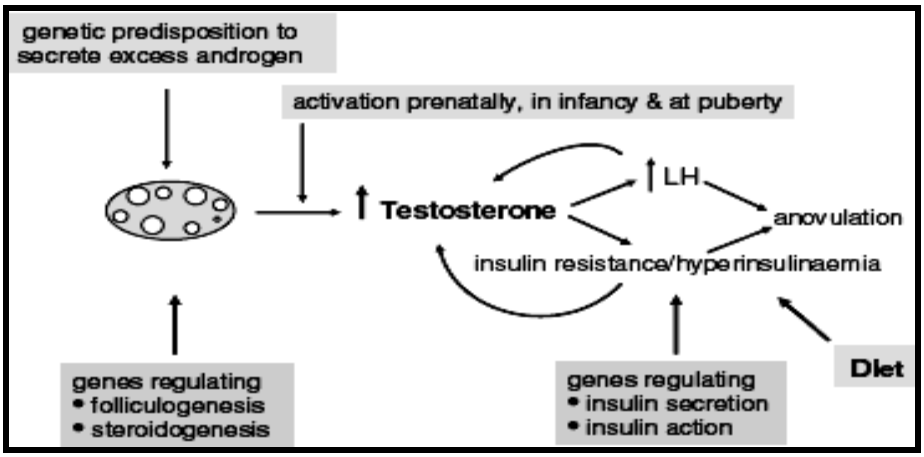

Figure (2): Proposed developmental aetiology of polycystic ovary syndrome (PCOS). We suggest that the ovary is genetically predisposed to hypersecrete androgens, perhaps as early as intrauterine life but certainly during the activation of the hypothalamic–pituitary–ovarian axis that occurs transiently in infancy and in a sustained manner at puberty. Higher than normal circulating levels of testosterone 'programme' the hypothalamic– pituitary unit to produce high tonic levels of luteinizing hormone (LH), and also amplify the physiological insulin resistance of puberty. Higher than normal concentrations of LH and insulin further enhance ovarian androgen production and may contribute to the mechanism of anovulation ***(McCarthy et al., 2006).***

Several lines of evidence suggest that PCOS is heriditable ***(Kashar et al., 2001)***, and various approaches have been initiated to attempt to define a specific genetic cause ***(Wood et al., 2003)***. In rare instances, single gene mutations can give rise to the phenotype of the syndrome ***(Draper et al., 2003)***.

PCOS appears to be inherited as an autosomal dominant trait. Insulin resistance, which has a heritable component, may be fundamentally related to PCOS since thgere is evidence that polycystic ovaries are related to paternal metabolic syndrome ***(Rosenfield, 2008)***.

Hyperandrogenism

Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic pituitary ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrensic abnormality in the hypothalamic GnRH pulse generator, favoring the production of LH over follicle stimulating hormone (FSH) in patients with the polycystic ovary syndrome ***(Ehrmann, 2005)***.

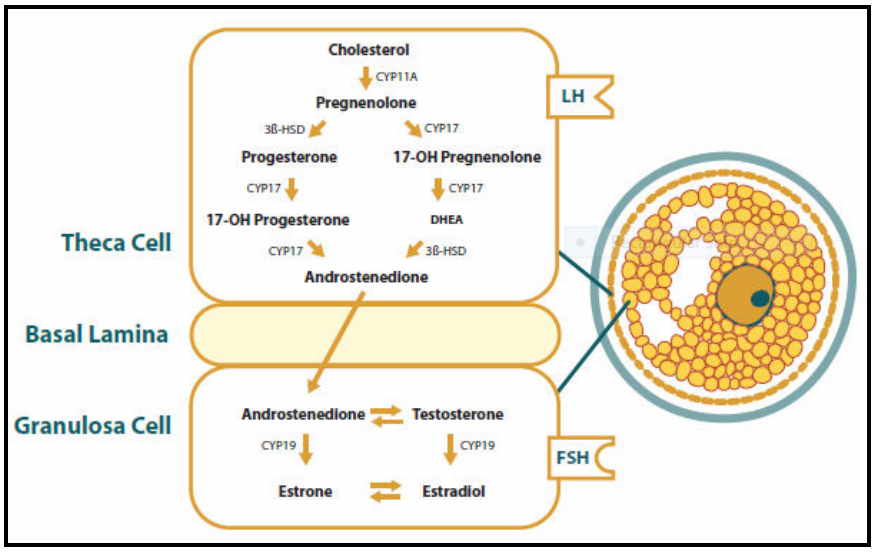

Figure (3): The steroidogenesis in the theca and granulose cells of the ovary. LH stimulates the theca cells after receptor binding, which, by second messenger activation involving cyclic adenosine monophosphate, leads to increased expression of cholesterol side chain cleavage cytochrome P450 (CYP11A),17αhydroxylase/C17,20 Lyase cytochrome P450 (CYP17),and 3β-hydroxysteroid dehydrogenase (3β-HSD). The theca cell is then able to synthesize androstenedione from cholesterol. Androstenedione diffuses across the basal lamina into the granulose cells and in normal ovaries, the major part of androstenedione is converted into estrone by aromatase cytochrome P450 (CYP19) and then to estradiol by 17β-hydroxysteroid dehydrogenase (17β-HSD). However, in PCOS ovaries, testosterone is produced (by conversion by 17β-HSD) to a larger degree from androstenedione ***(Schmidt, 2011).***

By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione which is converted by 17β-hydroxysteroid dehydrogenase (17β-HSD) to form testosterone or aromatised by the aromatase enzyme to

form estrone. Within the granulosa cells, estrone is converted into estradiol by 17β-HSD. Numerous autocrine, paracrine, and endorine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of the theca cells; insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone-binding globulin, the key circulating protein that binds to testosterone and thus increase the proportion of testosterone that circulates in the unbound, biologically available, or free state. Testosterone inhibits and estogen stimulates hepatic synthesis of sex hormone binding globulin ***(Ehrmann, 2005)***.

Insulin Resistance:

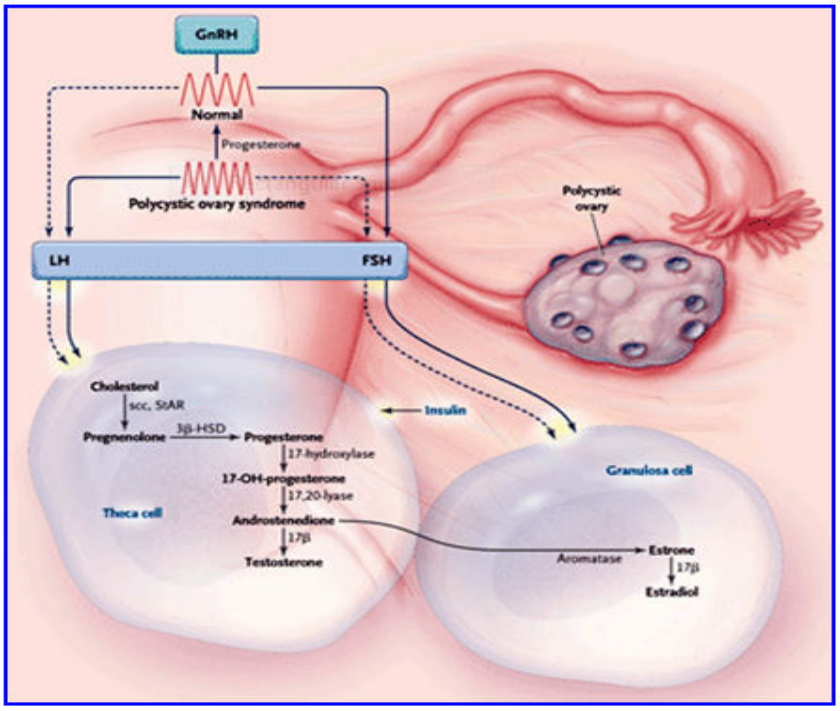

Figure (4): Hypothalamic-pituitary ovarian axis and the role of insulin in PCOS. The increased frequency of hypothalamic gonadotrophin releasing hormone (GnRH) pulses leads to increased frequency of luteinizing hormone pulses which ultimately result in increased production of androgens by the ovary theca cells. Insulin acts synergistically with LH to enhance androgen production. SCC: Side chain cleavage enzyme, STAR: steroidogenic acute regulatory protein and 3β-HSD: 3β hydroxy steroid dehydrogenase. Solid arrows denote higher degree of stimulation than dashed arrows ***(Dasgupta and Reddy, 2008).***

In normal women, the menopausal transition increases the prevalence of components of metabolic syndrome ***(Pai and Manson, 2013)***. This has been associated with a decrease in ovarian function, leading to a decrease in estrogen synthesis

and a redistribution of fat to the abdominal depot ***(Lizcano and Guzman, 2014)***. In PCOS women, metabolic abnormalities begin early in life and are worsened by the presence of hyperandrogenism. However, the evolution of MS components with advanced age has not been thoroughly explored ***(Alemzadeh et al., 2010)***.

A family history of type 2 diebetes is also more widely met among PCOS women with IGT or type 2 DM compared with those with normal glucose tolerance ***(Ehrmann, 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)***.

Clinical Picture:

PCOS produces symptoms in approximately 5% to 10% of women of reproductive age. It is thought to be one of the leading causes of female subferitlity and the most frequent endocrine problem in women of reproductive age ***(Goldenberg and Glueck, 2008)***.

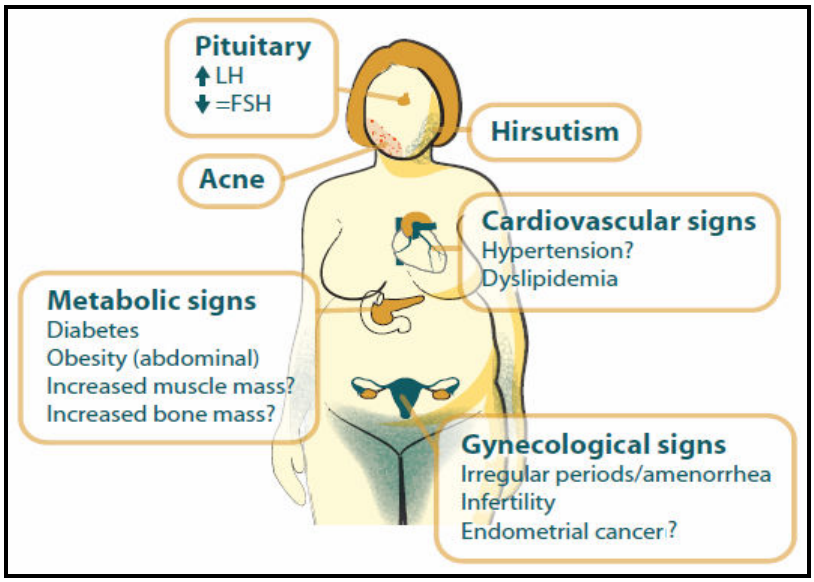

Figure (5): Illustration of the characteristic clinical features of PCOS in women of fertile age and the possible long-term consequences ***(Schmidt, 2011).***

Common symptoms of PCOS include:

Menstrual disorders

This is typically chronic dating since menarche. Oligomenorrhea (50-90%), fewer than eight episodes of menstrual bleeding per year or menses that occur at intervals more than 35 days ***(Norman et al., 2007)***, amenorrhea (26-51%) (absence of menstrual bleeding for more than six months) or dysfunctional uterine bleeding (29%) secondary to chronic anovulation or oligo-ovulation can occur ***(Lujan et al., 2008)***.

The Practice Committee of the American Society for Reproductive Medicine in ***2006 (ASRM)*** stated that menstrual irregularity in women with PCOS is primarily the consequence

of anovulation. Ovulatory dysfunction may be present in women with PCOS who report regular menstrual cycles. For these reasons, menstrual history alone is insufficient for defining PCOS phenotypes in women who describe having regular cycles ***(Lujan et al., 2013)***.

Hyperandrogenism:

Clinical manifestations of hyperandrogenism include:

Hirsutism:

It is the most common clinical manifestation of hyperandrogenism in women ***(Rosenfield, 2005)***. Approximately 60 to 70% of women with PCOS have hirsutism ***(Azziz, 2006)***. Hirsutism is defined as excessive terminal hair growth that takes on a male pattern distribution ***(Marla et al., 2008)***.

Acne:

One third of women with PCOS, particularly younger women, demonstrate acne. Scoring systems that classify and/or grade severity of acne are reliable and widely used in dermatology to facilitate therapeutic decisions and assess response to treatment ***(Strauss et al., 2007)***.

Alopecia:

Women may have a diffuse pattern of thinning of hair over the vertex of the scalp with the frontal hair line commonly preserved. It is a poor predictor of biochemical hyperandrogenemia. And low serum iron levels and aging are more common causes of hair loss in women ***(Barth et al., 2007)***.

Obesity:

It has been widely proved that 50-60% of women with PCOS have a body fat distribution of the android type irrespective of their BMI ***(Barber et al., 2007)*** and that patients with PCOS have a central fat excess independent of total fat mass ***(Lambrinoudaki, 2011)***.

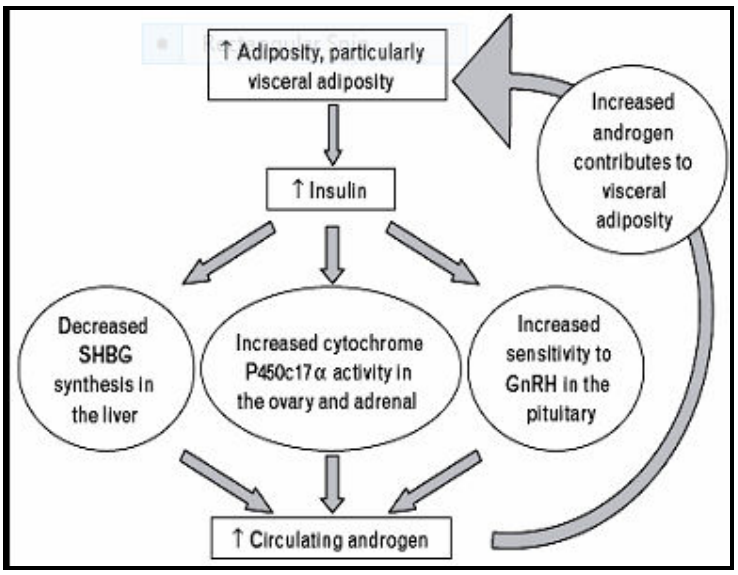

Figure (6): Insulin acts on the liver, adrenal, ovary, and pituitary to increase circulating free androgen. Increased free androgen, in turn, may increase visceral adiposity ***(Takara and Madhusmita, 2008)***.