Introduction

Adipose tissue is currently recognized as an endocrine organ because of its capacity to secrete adipokines, proteins that act as mediators of hormone action. Adipokines are involved in the regulation of glucose and fat metabolism, energy expenditure, inflammatory response, immunity, cardiovascular function, and reproduction **(Hausman and Barb, 2010).**

In women, the progressive increase in adiposity that occurs with age seems to decrease serum adiponectin levels with body fat mass **(Lecke et al., 2011b).**

Adiponectin is a newly discovered hormone secreted by adipocyte, which constitute a link between intraabdominal fat mass and the metabolic and cardiovascular complication of obesity. There is growing evidence that this protein is an important regulator of insulin sensitivity. Adiponectin suppress hepatic glucose production **(Combs et al., 2001).**

Adiponectin increases fatty acid oxidation in adipose tissue, liver and muscle, enhancing insulin sensitivity, and inhibits inflammatory mediators and the

expression of adhesion molecules within the vascular wall, lowering atherogenic risk **(Michalakis and Segars, 2010).**

In humans, adiponectin levels were found paradoxically to be decreased in obese, compared with normal individuals **(Arita et al., 1999),** making it the only known adipocyte specific hormone that is down-regulated in obesity. Moreover, decreased adiponectin levels are associated with coronary artery disease and increase significantly after weight reduction **(Hotta et al., 2000),** adiponectin concentrations in plasma were found to be independently associated with reduced risk of type 2 diabetes in apparently healthy individuals **(Spranger et al., 2003).**

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disorder in women of reproductive age, affecting 5 to 10% of women worldwide. It is characterized by hyperandrogenism and ovarian dysfunction, including oligo-anovulation and/or polycystic ovaries in the absence of other diseases affecting the pituitary and/or adrenal glands. PCOS is also a metabolic disorder, manifested by obesity, insulin resistance, dyslipidemia, and hypertension. These factors are associated with higher risk of type 2 diabetes and probably cardiovascular disease in PCOS

patients. In fact, obesity, predominantly abdominal, is recognized as an important determinant of metabolic risk in these patients **(Spritzer and Wiltgen, 2007).**

In PCOS, adiponectin levels have been reported to be decreased **(Carmina et al., 2009)** or unchanged **(Gulcelik et al., 2006).**

Women with PCOS are under an increased risk of cardiovascular disease is still being debated. Cardiovascular risk factors including dyslipidemia, hyperandrogenemia and markers of inflammation in women with PCOS were demonstrated. As to dyslipidemia, a lower serum level of high-density lipoprotein cholesterol (HDL-C)in women with PCOS compared to those without PCOS was documented. HDL-C is the best potential lipoprotein predictor of morbidity and mortality in patients with cardiovascular disease **(Chang et al., 2012).**

Metformin, increasingly used for treatment of PCOS, is found to be effective in reducing insulin resistance in obese patients with PCOS, inducing ovulation **(Ortega et al., 2005).**

Aim of the Work

The aim of the study is to investigate the effect of Metformin on adiponectin levels in over weight women with PCOS.

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome is one of the most common endocrine disorders affecting women of reproductive age **(Sieminska et al., 2004).**

Polycystic ovarian syndrome is characterized by menstrual disturbances, chronic anovulation and increased ovarian androgen production **(Sieminska et al., 2004)**. It is associated with obesity, hyperinsulinemia, elevated luteinizing hormone levels, elevated androgen levels, hirsutism, follicular atresia, ovarian growth and cyst formation, anovulation and amenorrhea. Insulin resistance or hyperinsulinemia is associated with excess abdominal fat, glucose intolerance, hypertension and dyslipidemia **(Norman et al., 2004).**

Although for many years the interest in PCOS has been focused on the cutaneous and reproductive manifestations of this disorder, the recent evidence suggests that metabolic and cardiovascular risk factors cluster in these patients. This evidence has renewed research efforts on hyperandrogenism and PCOS, including those directed toward the identification of the genetic and environmental

factors invloved in the pathogenesis of these prevalent conditions **(Hector et al., 2005).**

Definition:

In 1935, Stein and Leventhal first described the polycystic ovary as a frequent cause of irregular ovulation in women seeking treatment for subfertility. They published their report of seven women with amenorrhea, hirsutism, obesity, and enlarged polycystic appearing ovaries. Since then, much has been learned about this complex disorder **(Chang, 2004).** Defining the polycystic ovary syndrome has generated a lot of original studies and reviews, and it keeps stimulating passionate debates, particularly intense after an ASRM/ESHRE-sponsored consensus conference was held in Rotterdam, The Netherlands **(Rotterdam ESHRE/ASRM, 2003).** By adding the ultrasound criteria for polycystic ovaries to the items of the former so-called National Institutes of Health (NIH) definition i.e. hyperandrogenism (HA) and oligoanovulation (OA), and by requiring a minimum of two items of three, the so-called Rotterdam definition has extended the frame of PCOS. By giving more flexibility, this definition recognizes four PCOS phenotypes: HA+OA+PCO (full-blown syndrome), HA+OA (former

NIH definition), HA+PCO (so-called ovulatory PCOS), and OA+PCO. The absence of a label for the last phenotype is symptomatic of the perplexity that it induces **(Dewailly et al., 2006).**

Polycystic ovaries, as defined by ultrasonography (the presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter, and/or ovarian volume > 10 mL) should also be considered as one of the possible diagnostic criteria for PCOS **(Ehrmann, 2005).**

Prevalence:

The overall prevalence among women of reproductive age is between 4% and 8% **(Chang, 2004).** The use of different diagnostic criteria for PCOS have undermined attempts to derive an accurate, population-based prevalence for this condition. The incidental finding of polycystic ovaries at time of ultrasound examination is relatively frequent, occurring in up to 33% of women, although most studies report an incidence around 22% in an unselected population **(Hart et al., 2004)**.

In a study of 173 symptomatic women, the ultrasonographic appearance of polycystic ovaries was found in 92% of women with hirsutism with regular menstrual cycles, 87% of women with oligomenorrhoea.

Interestingly, of those women with the sonographic appearance consistent with polycystic ovaries, up to 25% will be asymptomatic. A farther study of women who had regular menstrual cycles but were anovulatory demonstrated polycystic ovaries in 91% of cases **(Hart et al., 2004).**

Aetiology:

To a great extent, PCOS seems to be a congenital disorder that is first diagnosable at puberty. Accumulating evidence suggests that PCOS arises as a complex trait with contributions from heritable and non-heritable factors. A genetic basis for the disorder has been suggested by familial clustering of cases. Nearly half of sisters of women with PCOS were found to have an elevated plasma testosterone level. Only half of these sisters, however, had symptoms such as menstrual irregularity. Polycystic ovaries appear to occur as a dominant trait, with a suggestion of a counterpart malephenotype of premature male pattern baldness **(Adams et al., 2004).**

The underlying cause for the androgen excess is unclear. Various subclinical steroidogenic defects have been reported to be risk factors for the syndrome. Recently, theca cells were found to retain their capacity for excessive

steroidogenesis through many doublings in culture, supporting an intrinsic mechanism. The excessive androgen secretion is caused by over expression of several steroidogenic enzymes. Thus, Some as yet undiscovered, more fundmnental disorder, such as a malfunctioning coregulator system, could account for these multiple abnonnalities. Another possibility is excessive serine phosphorylation of the steroidogenic enzyme P450c17 and the insulin receptor, which would explain the combination of hyperandrogenism and insulin resistance. Recently, evidence has shown a developmental basis for the syndrome. Either prenatal androgen excess or perinatal insults that cause intrauterine growth retardation may predispose to obesity, insulin resistance, and androgen excess in later life **(Eisner et al., 2003).**

Pathogenesis:

Despite being one of the most common endocrinopathies, a comprehensive explanation of pathophysiology is still lacking. The heterogeneity of polycystic ovarian syndrome may well reflect multiple pathophysiological mechanisms, but the definition of each contributing mechanism has been slow to emerge. Traditionally, it has been useful to consider the polycystic

ovarian syndrome as the result of a 'vicious cycle', which can be initiated at any one of many entry points. Altered function at any point in the cycle leads to the same result: ovarian androgen excess and an ovulation **(Tsilchorozidou et al., 2004).**

LH Secretion

LH hypersecretion is a characteristic hallmark of PCOS, LH is secreted in a pulsatile manner. Women with PCOS have an increase in both the LH pulse frequency and amplitude, resulting in increased 24-hour secretion. This increase in LH secretion is thought to occur as a result of increased frequency of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. Increased LH, in turn, leads to an increase in androgen production by the theca cells within the ovary **(Ehrmann, 2005).**

Hyperinsulinemia, Insulin Resistance & Androgen Excess

The increase in LH, together with hyperinsulinemia, leads to an increase in androgen production by ovarian theca cells **(Tsilchorozidou et al., 2004).** The most likely primary factor driving the increase in testosterone secretion in PCOS is an increase in ovarian enzymatic activity

involved in the synthesis of testosterone precursors **(Hill, 2003).**

Genetics

A familial pattern in some cases suggests a genetic component, but the candidate genes have yet to be identified **(Tsilchorozidou et al., 2004)**. The literature to date provides a strong basis for arguing that PCOS clusters in families, supporting an underlying genetic cause of the disorder. The risk of developing PCOS appears to be governed to a large degree by family history, as about 35% of mothers and 40% of sisters of PCOS patients are affected by the disorder. However, the mode of inheritance of PCOS is still uncertain, although the majority of studies are consistent with an autosomal dominant pattern, modified perhaps by enviromnental factors. Although a number of candidate genes involved in the androgen biosynthetic pathway or metabolic pathways involved in insulin action have been proposed, the putative PCOS gene(s) has yet to be identified. This is not surprising considering the diversity of the syndrome and the controversial diagnosis to date **(Michael and Costello, 2005).**

Diagnostic Approach

PCOS can be a challenge to diagnose because the disorder presents with a wide range of signs and symptoms that can easily be missed **(Azziz, 2004)**. Widely accepted criteria for diagnosis of PCOS in adolescent patients are based on standards that were established at the 1990 Consensus Conference of the National Institute on Child Health and Human Development **(Kent and Legro, 2002).** These criteria include chronic anovulation and hyperandrogenism in the absence of other endocrine disorders. The presence of polycystic ovaries is not a criterion for diagnosis in adolescents as it is with young adults and middle age women as determined by the Rotterdam Criteria.

History:

The history should first focus on several aspects regarding menstruation such as age at menarche, length of time between periods, quantity of menstrual flow, and presence of dysmenorrhea **(Markle, 2001)**. The clinician should have a high degree of suspicion when a woman presents with complaints of infrequent menstrual cycles since menarche, hirsutism, and infertility. Occasionally, the menstrual irregularity may not begin until the woman is in

her late teens or early twenties. It is important to remember that some women with PCOS continue to menstruate regularly even though they are anovulatory **(Carmina, 2003).** Obtaining information regarding the development of secondary sexual characteristics is also an important component of the history **(Goolsby, 2001)**. Research has indicated that adolescent girls diagnosed with PCOS had a history of precocious pubarche **(Ibanez et al., 2004).**

The most distinctive clinical feature is hirsutism, the degree of which can vary from mild to severe. The rate of hair growth is important. Generally, in women with PCOS, the hair growth is gradual and progressive. Rapid onset, specifically if associated with signs of virilization (e.g. deepening of the voice, clitoromegaly, temporal hair loss, and balding) is suggestive of an ovarian or adrenal androgen-secreting tumor. A medication history is also important because many drugs may cause hirsutism. A history of oily skin and acne are also subtle signs of androgen excess and may be present in women with PCOS **(Hunter et al., 2003).**

Physical Examination

The physical examination should include an assessment of the body mass index and the blood pressure.

An elevated blood pressure may suggest androgen excess related to congenital adrenal hyperplasia. Note the amount of excess hair as well as the distribution. The Feriman-Gallwey scoring system has been used for evaluation of hirsutism but is limited by subjective variability and is thought by many experts to be of little clinical use. Note skin changes, such as acne, acanthosis nigricans, and striae, which may be a clinical feature of Cushing's syndrome. Other signs and symptoms of Cushing's syndrome include truncal obesity, moon facies, hypertension, spontaneous ecchymosis, buffalo hump, and muscle weakness. A thorough abdominal and pelvic examination should be performed to exclude any masses **(Hill, 2003)**. It is also important to check for the presence of galactorrhea by compressing the areola from its outer perimeter toward the nipple **(King et al., 2006).**

Laboratory Data:

At present, recommendations for testing should include free testosterone, dehydroepiandrosterone-sulfate (DHEA-S), androstenedione, prolactin, thyroid stimulating hormone (TSH), 17-hydroxyprogesterone (17-OHP), and a pregnancy test **(Sheehan, 2004)**. To rule out nonclasssical congenital adrenal hyperplasia, obtain a blood sample for 17-hydroxyprogesterone. If the result is <2 ng/mL,

nonclassical adrenal hyperplasia is safely excluded; if the result is >2 ng/mL, refer the patient to an endocrinologist for further evaluation **(Guzick et al., 2004).**

Menstrual dysfunction that presents with irregular menses, oligomenorrhea, or amenorrhea is highly suggestive of an ovulation. Tests for ovulatory function include basal body temperature evaluation, serum progesterone concentrations, or endometrial biopsy. A secretory endometrium is an indication that ovulation has occurred.

Because of the connection between insulin resistance and PCOS, the recommendation is that all adolescents who are suspected of having the disorder be screened by drawing fasting blood glucose levels. If fasting blood glucose levels are elevated, the next step is to order a 2 hour 75 g glucose tolerance test (GTT) to confirm glucose intolerance or type 2 diabetes **(Meisler, 2002).**

Because women with PCOS are at increased risk for impaired glucose tolerance, type 2 diabetes, and cardiovascular disease, it is imperative that the patient be evaluated for these problems. Obese women with PCOS should be screened for metabolic syndrome **(Apridonidze et al., 2005)**. This includes a lipid panel and testing for