The Role of Obesity in the Development of Polycystic Ovary Syndrome

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Abstract: Polycystic Ovary Syndrome (PCOS) is one of the common endocrine diseases that affects women in their reproductive age. PCOS has diverse clinical implications that include reproductive (infertility, hyperandrogenism, hirsutism), metabolic (insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular diseases) and psychological features (increased anxiety, depression and worsened quality of life). The exact patho-physiology of PCOS is complex and remains largely unclear. The prevalence of PCOS is estimated at 4-18%, depending on diverse factors discussed ahead. The phenotype varies widely depending on life stage, genotype, ethnicity and environmental factors including lifestyle and body weight. During the last decades, obesity and excess weight are major chronic diseases all around the word. Obesity increases some features of PCOS such as hyperandrogenism, hirsutism, infertility and pregnancy complications. Both obesity and insulin resistance increase diabetes mellitus type 2 and cardiovascular diseases. Moreover, obesity impairs insulin resistance and exacerbates reproductive and metabolic features of PCOS. It is well known that obesity is associated with anovulation, pregnancy loss and late pregnancy complications (pre-eclampsia, gestational diabetes). Obesity in PCOS is also linked to failure or delayed response to the various treatments including clomiphene citrate, gonadotropins and laparoscopic ovarian diathermy. It has been reported that, after losing as little as 5 % of initial body weight obese women with PCOS improved spontaneous ovulation rates and spontaneous pregnancy. Therefore, the weight loss prior to conception improves live birth rate in obese women with or without PCOS. The treatment of obesity may include lifestyle therapy (diet and exercise), pharmacological treatment and bariatric surgery. In summary, weight loss is considered the first-line therapy in obese women with PCOS. In the present review, the consequence and treatment of obesity in women with PCOS are discussed.

Keywords: Obesity, polycystic ovary syndrome, infertility, insulin resistance, leptin, adipokines, anti-mullerian hormone, cardiovascular risk, placenta, implantation.

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine diseases that affects women in their reproductive age [1]. The exact patho physiology of PCOS is complex and remains largely unclear. A hypothesis proposes that during gestation increased exposure to excess of androgen induces pubertal hyperandrogenism [2]. Post-pubertally, *in uterus* this early exposure to androgens produces abnormal secretion of LH and predisposes to the accumulation of central (abdominal) fat, exaggerates insulin resistance and compensatory hyperinsulinemia. These abnormalities induce reproductive, metabolic and long-term health implications Fig. (**1**). Obesity, through the production of adipokines (Tumor necrosis factor, leptin) and by decreasing the sex-hormone-binding globulin (SHBG), exacerbates the disorders of PCOS Fig. (**1**).

The heterogeneity of the syndrome makes it necessary to hild periodic scientific consensus for updating the diagnosis and treatments of PCOS. The expert conference sponsored by National Institute of Health (NIH) in 1990 [3] established that diagnosis criteria was represented by the combination of chronic oligo- or anovulation and clinical or biochemical signs of hyperandrogenism, with the exclusion of related disorders [4]. The inefficacy in using these criteria for diagnosis of all the PCOS-patients led to a more recent workshop in Rotterdam [5]. This consensus suggested the addition of a third criteria, the presence of polycystic ovaries, as well as the statement that any two of the three criteria were sufficient for the diagnosis of PCOS [5]. Later, the Androgen Excess Society (AES) stated that androgen excess is a central feature of the disease and that PCOS should be defined by the presence of hyperandrogenism (clinical and/or biochemical) in combination with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), with the exclusion of related disorders [1]. The PCOS phenotypes vary widely depending on the life stage, the genotype, the ethnicity and the environmental factors including lifestyle and body weight.

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During the last decades, obesity and excess of weight have been the major chronic diseases in all around the word. The increasing prevalence of obesity in women has implications for their reproductive outcome [6]. Obesity in PCOS increases hyperandrogenism, hirsutism, insulin resistance, infertility and pregnancy complications [7, 8]. Furthermore, women who are overweight or obese undergoing assisted reproduction have lower pregnancy rates and higher miscarriages [9]. During pregnancy, obesity increases pregnancy complications [10] and difficulties during labor [11]. Therefore, infants of obese women are at a greater risk of congenital abnormalities [12] and intrauterine demise [13], both of which contribute to an increased perinatal morbidity and mortality.

Obesity impairs insulin resistance and the consequent hyperinsulinemia increases diabetes mellitus type 2 and risk of cardiovascular diseases [14]. Consequently, these disturbances exacerbate the reproductive and metabolic disorders of PCOS. Hyperinsulinemia, then, contributes to anovulatory infertility by increased ovarian androgen secretion [15]. Insulin enhances intraovarian steroidogenesis by interacting with luteinizing hormone (LH) leading to inappropriate granulosa cell functions and the arrest of the follicular development [16].

The obesity treatment should be based on modifying lifestyle changes by diet, exercise and behavior modification [17]. It has been reported that, after losing as little as 5 % of the initial body weight obese women with PCOS improve spontaneous ovulation rates and spontaneous conception [18- 20]. Therefore, the weight loss prior to conception improves live birth rate in obese women with or without PCOS [14]. In summary, weight loss is considered the first-line therapy in obese women with PCOS. In the present review, the consequences and treatments of obesity in women with PCOS are discussed.

2. CHARACTERISTICS OF POLYCYSTIC OVARY SYNDROME IN OVERWEIGHT AND OBESE WOMEN

Obesity is one of the most important health threats throughout the world. Its prevalence has increased in all the countries as a consequence of dietary, stress and sedentary life. Although obesity is

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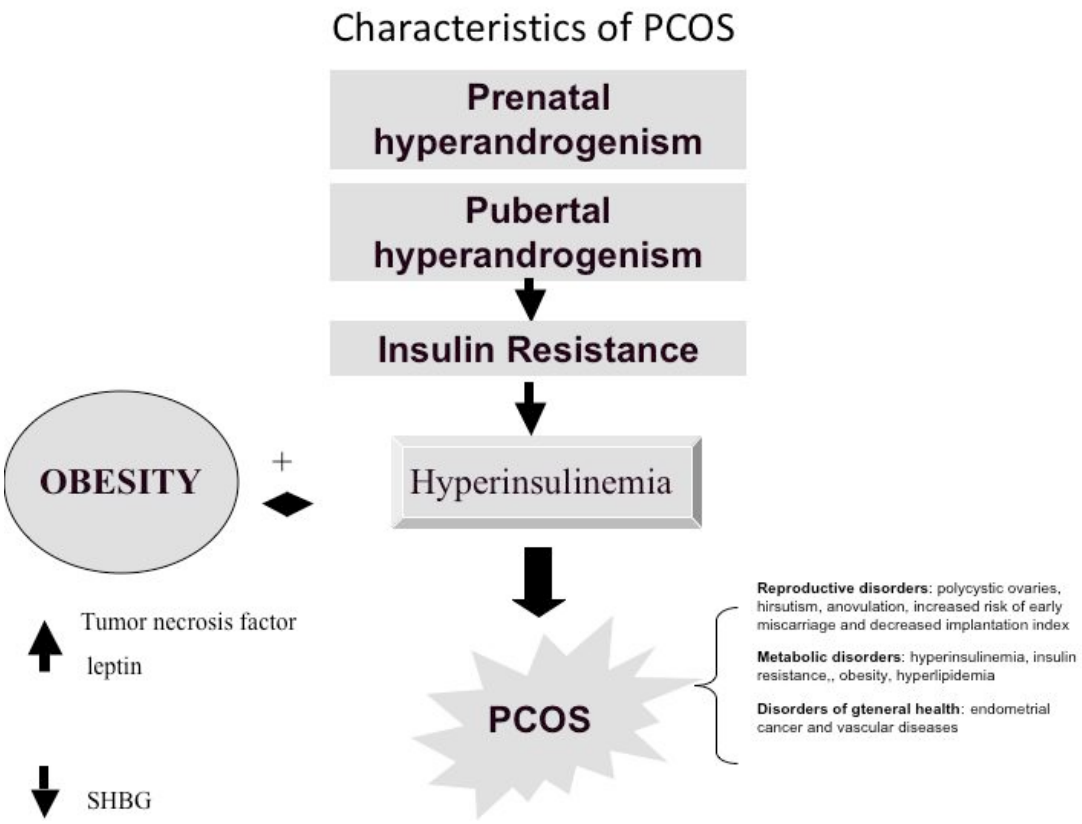

Fig. (1). Characteristics of PCOS.

frequently associated with PCOS, the study of the prevalence of PCOS in overweight and obese women is poor. Alvarez-Blasco *et al.* [21] by studying a total of 113 premenopausal overweight obese women found a 28.3 % prevalence of PCOS, as compared to 5.5 % prevalence of PCOS in lean women. The increased prevalence of PCOS observed in overweight and obese women was independent of the presence of the metabolic syndrome. These findings led the authors to suggest that obesity and insulin resistance are important contributors to the development of PCOS but are not the main etiologic defects of the syndrome. The authors consider that the primary defect in steroidogenesis would be the main factor which determines that overweight or obese women develop the syndrome. In contrast, in a case-control designed protocol by comparing a total of 385 sisters of women with PCOS, hyperandrogenic non-PCOS sisters and unaffected sisters Sam *et al.* [22] found that total cholesterol levels were higher in sisters with PCOS than unaffected sisters and control women. They also found that triglyceride levels were increased only in sisters of women with PCOS and that the prevalence of the metabolic syndrome was increased in sisters with PCOS and hyperandrogenic women when compared to unaffected sisters. The authors concluded that dyslipidemia and metabolic syndrome play a central role in the development of PCOS.

3. OBESITY, INSULIN RESISTANCE AND GENETIC REGULATION IN PCOS

It has been well established that there is a close relationship between obesity and insulin resistance in PCOS [23, 24]; however, the whole mechanisms are not fully understood. Multiple genetic studies have examined genes coding for enzymes of steroidogenesis, androgen receptor, insulin, and insulin receptor [25-27]. In contrast, there are few reports that identify genes related to obesity. Tan *et al.* [28] explored candidate genes markers for obesity and type 2 diabetes mellitus (T2DM) in 386 patients with PCOS and found an association with the genetic variation in intron 1 of obesity association gene *FTO*. In addition, they found that this association was characterized by metabolic aspects of PCOS, mainly with insulin resistance. In summary, the relationship between genes and obesity is limited while the relationship between genes and insulin resistance has been well established Fig. (**2**).

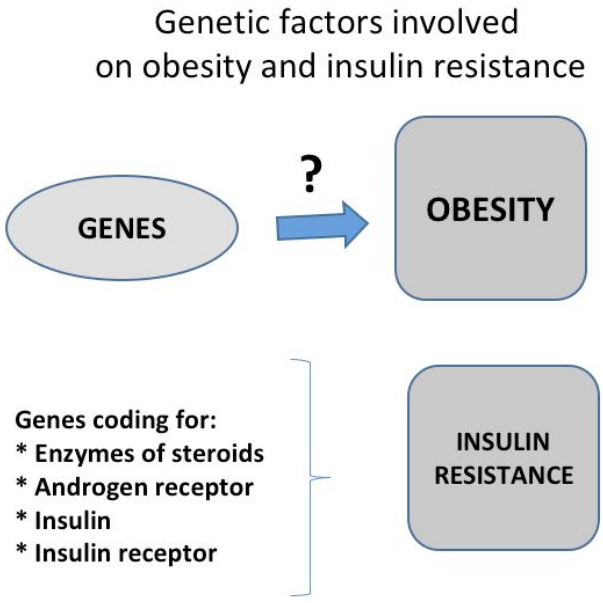

Fig. (2). Genetic factors of obesity and insulin resistance.

4. OBESITY AND LIPID METABOLISM ON CARDIOVASCULAR RISK IN PCOS

Epidemiological studies have reported that obesity is one of the main cardiovascular disease risk factor. Obesity is related to coronary heart disease, ventricular arrythmias, heart failure and arterial fibrillation. In addition, obesity is considered a causal factor in diabetes mellitus type 2, dyslipidemia, gastrointestinal reflux, obstructive sleep apnea (OSA), hypertension, non alcoholic fatty liver disease and many forms of cancer [29].

The serum high-sensitivity C-reactive protein (CRP) is considered a good marker of cardiovascular risk factor [30], low-grade chronic inflammation, myocardial infarction, ischemia stroke [31, 32] and diabetes [33, 34]. In addition, CRP is linked to insulin resistance and its associated features [33, 35]. The link between CRP and PCOS remains controversial. There is evidence that CRP is higher in PCOS women [36-40]; however, other authors failed to confirm a relationship between CRP and PCOS [41-44]. Most of these studies have reported a relationship between CRP levels and body weight [45, 46] focusing on the fact that since CRP is produced in the liver and it is modulated by adipocytokines, increased body fat might be responsible for the increased CRP in PCOS. However, some studies have reported increased levels of CRP in non-obese PCOS patients [47] and even when body fat is decreased [48]. Tosi *et al*. [49] investigated if CRP was an independent predictor of coronary disease in PCOS or to the contrary if CRP was a dependent predictor associated to insulin resistance, obesity and hyperandrogenism. The authors compared CRP levels of hyperandrogenic women, women with PCOS, women with idiopathic hyperandrogenism and healthy controls. They found that CRP was higher in women with PCOS than hyperandrogenic women and healthy controls. By multiple regression analyses the authors found that increased CRP was independently predicted by higher body fat and lower insulin sensitivity. Surprisingly, in lean women, the serum-free testosterone was a negative predictive variable. The authors suggest that androgen excess per se could play a protective role [49].

The adipose tissue secretes a variety of bioactive active substances including leptin, tumor necrosis alpha (TNF), interleukin 6 (IL-6), IL-18, plasminogen activator type 1 and adiponectin. These substances contribute to the modulation of both inflammation and metabolic diseases. Adiponectin has an insulin-sensitizing [51], antiatherogenic and anti-inflammatory property [52]. Adiponectin is inversely associated to CRP [53]. Cardiovascular risk factors in PCOS are represented by increased IL-6 [54, 55], TNF [56] and reduced adiponectin levels [57, 58] which have been reported in both obese and non-obese women with PCOS. The effect of weight loss on adiponectin, IL-6 and TNF has been poorly studied. Moran *et al* [59] found that a 4-5% weight loss improved lipid, glucose, and insulin profiles in women with and without PCOS; however, this degree of weight loss was not effective in lowering CRP in women with PCOS. These findings led the authors to suggest that greater weight loss is required in women with PCOS to achieve equivalent cardiovascular benefits equivalent to those of non-PCOS women [59].

It is unknown whether abnormalities in lipid metabolism are inherited in families of women with PCOS. There is evidence that family members of those women with PCOS have dyslipidemia [60]. One of the most important points to be established is which anthropometric parameters are more useful to evaluate central obesity in PCOS. Nowadays the waist circumference, the waist-to-hip ratio, the waist-to-height ratio, the conicity index and the body mass index are the most commonly used parameters to evaluate obesity. All of them are directed to evaluate visceral fat, which is related to insulin resistance, an important key in the development of PCOS [20]. It is important to point out that there is no doubt about the relationship between android obesity and increased cardiovascular risk [61]. However, lean women with PCOS showed a significantly higher amount of body fat and lower amount of lean body mass than the controls [62]. Therefore, the choices of adequate endocrine and anthropometric parameters in the monitoring of dyslipidemia in PCOS patients have to be monitored. In this context, the lipid accumulation product (LAP) index [63] which combines waist circumference and triglyceride concentration is considered as a useful marker. The LAP index is calculated using the formula [waist (cm) - 58] x triglyceride concentration (mmol/l) and is used in the screening for gestational glucose intolerance [64]. LAP is associated with homeostasis metabolic index (HOMA) and has been described as a reliable marker of cardiovascular risk in PCOS patients [65].

5. ANTI-MULLERIAN HORMONE, OBESITY AND PCOS

Women with PCOS show anovulation and menstrual irregularity characterized by excessive early follicular growth which yields larger numbers of primary and pre-antral follicles concomitantly with the lack of the development of a dominant follicle [66]. It has been proposed that an excessive production of local inhibitors such as anti-mullerian hormone (AMH) may lead to reduced sensitivity to FSH. For this reason a number of studies have demonstrated that AMH is a good marker of ovarian responsiveness, embryo number and assisted reproductive technology outcomes [67, 68]. It has been reported that AMH levels correlate with the menstrual cycle. In fact, AMH levels are higher in amenorrheic than oligomenorrheic women with PCOS [69]. Moreover, PCOS treatments which improve menstrual functions also reduce AMH levels [70, 71]. However, it has been reported that the treatment with metformin improves insulin resistance and polycystic ovary morphology even though levels of AMH remain unchanged.

The relationship between weight loss, AMH levels and metabolic changes is controversial [72-74]. No differences have been reported in PCOS patients who showed menstrual improvements after weight loss without changes in metabolic functions [75], insulin sensitivity [20, 76], LH levels [20], central fat [20] and estradiol levels [77]. However, on the other hand, Moran *et al*. [59] found that overweight women with PCOS that improve menstrual functions as a consequence of weight loss display lower AMH levels than those who are not able to improve menstrual functions after weight loss. In addition, the authors found that responders to weight loss programs have significantly greater reductions in surrogate measure of insulin sensitivity as fasting insulin and homeostasis model assessment. Some reports propose the improvements in reproductive functions even without changes in the AMH levels [59, 78].

6. OBESITY IN THE CONCEPTION AND IMPLANTATION PROCESS

In an early study, Rich-Edwards *et al* [79] compared 2527 married nulliparous women with anovulatory subfertility for 1 year with 46718 married muliparous women with no history of subfertility. They found a direct relationship between body mass index and impaired fertility; however, the mechanisms involved remained unknown. Other studies [80, 81] confirmed this affirmation and reported that a 0.1 unit increase in waist-hip ratio led to a 30% decrease in probability of conception [82]. The effects of obesity in fertility can be observed at hormonal, ovarian and endometrial level as it was discussed in the following sections.

6.1. Sex Hormone-binding Globulin (SHBG)

The menstrual cycle, ovulation and endometrial function are controlled by a complex network that involves different metabolites. Adipose tissue is a fundamental site of steroid production [83]. Adipose tissue also controls bioavailability, through transport proteins, and captures lipid-soluble steroid hormones [84]. Obese women have increased levels of steroid hormones and lower serum concentration of sex hormone-binding globulin (SHBG) when

compared with normal-weight controls [85]. The distribution of body fat modulates SHBG levels and central obesity induces greater reduction in serum SHBG concentration [84]. In fact, serum SHBG is inversely proportional to the waist circumference [84]. The role of insulin in regulating SHBG remains controversial. It has been reported that insulin decreases the hepatic production of SHBG [85] and that insulin, rather than sex steroids, is the regulator of SHBG production [86, 87]. However, Selva *et al*. [88] reported that monosaccharides regulate human SHBG gene expression by reducing hepatocyte nuclear factor-4alpha (HNF-4alpha), thus providing a mechanism that explains the relationship between plasma levels of SHBG and metabolic alterations.

The reduction of SHBG leads to increased levels of circulating sex steroids (testosterone, dihydrotestosterone and androstenediol) which in turn, increase the metabolic clearance of these hormones conducting to hyperandrogenism. This mechanism is more pronounced in those PCOS patients with central obesity, where the decrease in SHBG levels is prominent. In fact, the reduction in the visceral fat increases SHBG concentration and decreases androgen levels [89].

6.2. LH and Insulin

It has been demonstrated that hypersecretion of LH and increased ratio of LH: FSH impair folliculogenesis [89]. The relationship between weight loss and LH secretion in women with PCOS is controversial. It has been reported that weight loss decreases LH secretion [90] and has not effect on LH secretion [91, 92]. Lean women with PCOS show increased LH secretion and consequently hyperandrogenemia meanwhile it appears that in the obese women with PCOS the main factor responsible for hyperandrogenism is insulin resistance (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group) [93]. Insulin and insulin-like growth factor 1 (IGF-1) act on ovarian tissue and both receptors are present in granulosa, theca and ovarian stromal tissue. Insulin has three important functions; it stimulates ovarian steroidogenesis in both theca and granulosa cells [94], modulates the bioavailability of sex steroids (by modulating hepatic SHBG synthesis) and inhibits both hepatic and ovarian synthesis of IGF binding protein [84]. Obesity, particularly central obesity induces insulin resistance and hyperinsulinemia by mechanisms related to free fatty acids, leptin and tumor necrosis alpha [95].

Hyperinsulinemia, a consequence of systemic insulin resistance, leads to reduced SHBG concentration, hyperandrogenemia and alterations of the IGF system and both menstrual and ovulatory disturbances [95]. About 5% of weight loss in obese PCOS patients is able to decrease insulin levels and IGF secretion, and increases SHBG concentration thus improving menstrual cyclicity [95].

6.3. Leptin

Leptin, a 16 kDa protein secreted by adipocytes, increases after food intake and decreases during starvation [96]. Besides its role in energy storage, leptin also has metabolic and reproductive functions [83, 84, 97]. In the hypothalamus, leptin reduces appetite and increases energy expenditure [98]. When serum concentrations are normal leptin has stimulatory effects on the hypothalamus-pituitary-ovarian axis [97] while in obesity, the increased serum leptin levels have inhibitory effects on folliculogenesis [99]. Leptin levels vary during the menstrual cycle, increasing during folliculogenesis and during the luteal phase being highest with the LH surge [99]. Upon its receptors, found in the hypothalamus and pituitary, leptin controls gonadotropin secretion [84]. It has been reported that leptin treatment given to obese leptin-deficient mice restores hormonal alterations and fertility thus suggesting that leptin is involved in reproductive physiology [100].

Both the mRNA and protein expression of the leptin receptor have been found in theca and granulosa cells, oocytes, endometrial cells and pre-implantation embryos from rodents [101] and humans [102, 103].

Leptin suppresses IGF increased in LH-stimulated theca cells [102] and is able to interfere with the normal development of the dominant follicle, oocyte maturation and ovulation [104]. Reasonably, leptin levels are altered in PCOS patients. It has been reported that women with PCOS have increased serum leptin concentrations when compared with weight-matched controls [97, 99]. Women with normal menstrual cycles exhibit co-pulsatility of leptin and LH while PCOS patients show impaired pulse synchronicity [99, 105]. Leptin levels are linked to insulin resistance. It has been reported that insulin-sensitizing agents reduce leptin levels [106, 107]. Moreover, the alterations in the leptin system are higher in obese women with PCOS when compared with lean women with PCOS [108].

As a consequence of low-calorie diets, the weight loss decreases circulating leptin levels in obese women with or without PCOS [97, 109]. It has been reported that a 10% of reduction in body weight decreases 53% serum leptin concentration [110] and that the decrease in leptin levels precedes the weight loss [111].

6.4 Other Adipokines

Adipocytes are able to synthesize and release adipokines which participate in the metabolic regulation of insulin pathway. Adipokines are involved in reproductive functions [109], however, the direct effect of these adipokines on reproductive functions during obesity is not fully understood. Serum levels of adiponectin, a protein secreted by adipocytes, decrease in obese and insulin resistant patients [109] and increase after weight loss and bariatric surgery [109]. It has been proposed that in obese women, the decreased levels of circulating adiponectin are responsible for the decreased insulin sensitivity (The ESHRE Capri Workshop Group 2006) [112]. Adiponectin is present in the ovarian tissue and it is weakly expressed in granulosa cells [113]. Women with PCOS have lower levels of adiponectin than controls [114]. Moreover, obese anovulatory women with PCOS have lower adiponectin levels than ovulatory women with PCOS [36, 114]. Moreover, it has been proposed that the decrease in adiponectin levels in PCOS patients worsens insulin resistance and has negative effects on normal folliculogenesis [115].

One-third of circulating levels of Interleukin- 6 (IL6), an inflammatory cytokine, are derived from adipocytes. It has been reported that obesity increases IL6 levels and that weight loss and bariatric surgery decrease IL6 levels [109]. Increased levels of IL6 have been related to decreased insulin sensitivity and infertility [109], inhibition of LH secretion [116], prevention of LH-triggered ovulation, inhibition of LH-/FSH- induced estrogen synthesis and suppression of aromatase activity in granulosa cells [109]. PCOS patients have increased levels of IL6, being the highest in obese PCOS patients [108]. It has been demonstrated that the adverse effects of IL6 in both the hypothalamus-pituitary-ovarian axis and endometrial functions play an important role in the outcome of infertility [108, 109]. A direct association between IL6 and fertility has been also demonstrated in women with PCOS [117-119].

Plasminogen activator inhibitor (PAI) type-1, an adipokine produced by white and visceral fat, not only regulates fibrinolytic activity in the blood but also correlates with this metabolic syndrome [109]. In women with PCOS, PAI1 is associated with miscarriage through adverse effects on the implantation process and pregnancy development [109, 120]. It is known that reduced low-calorie diet and bariatric surgery decrease plasma PAI1 [108].

Tumor necrosis alpha (TNF), a cytokine produced by adipocytes [109] correlates to BMI and is increased during hyperinsulinemic states [121]. It has been demonstrated that TNF modulates insulin sensitivity [109]. Since TNF is involved in the main reproductive functions such as, gonadotropin secretion, ovulation, steroi-

dogenesis, corpus luteum regression and endometrial development [109, 116, 122], the increased levels of TNF contribute in PCOS patients to infertility.

6.5. Obesity and Pregnancy in Women with PCOS

The establishment and maintenance of pregnancy are associated with a Th2-dominant peripheral cytokine profile, while miscarriage is characterized by a Th1-dominant peripheral cytokine production [123]. It is known that the Th2/Th1 balance is controlled by sex hormones, in particular, progesterone, which promotes the development of a Th2 response. The biological effects of progesterone are mediated by a complex network of effectors, including a protein (glycodelin) called progesterone-induced blocking factor (PIBF). It has been reported that the PIBF synthesized by lymphocytes of healthy pregnant women in the presence of progesterone, inhibits arachidonic acid release and acts on the cytokine balance to control NK activity [124, 125]. Moreover, neutralization of endogenous PIBF results in altered cytokine production and pregnancy termination in mice [126] while low PIBF concentrations in the uteri of pregnant women suggest a risk for spontaneous pregnancy termination [127]. In addition, glycodelin secreted from the endometrial glands and decidual glandular epithelium, modulates immune and trophoblast cells [128]. Both *in vitro* [129] and *in vivo* studies [130] have shown that PIBF induces the Th2-biased cytokine production. It has been demonstrated that embryo resorption is characterized by increased central adiposity concomitantly with the dominant profile of pro-inflammatory cytokines and the lack of PIBF expression in the implantation sites of hyperandrogenized early pregnant mice [131]. The production of glycodelin is lower during the first trimestre of pregnant women with PCOS as compared with controls [132].

Obesity also impacts the inflammatory markers including prostaglandins and reactive oxygen species thus generating negative effects on implantation and embryonic development [131- 133].

Glucose transporters (GLUTs) are present at the endometrial levels [134, 135] however little is known about the metabolic functions of insulin on the endometrium. Mioni *et al*. [136] demonstrated that GLUT4 is present in the endometrium of healthy and PCOS women and that obesity has a negative effect on the expression of GLUT4 in PCOS. These findings reflect that insulin resistance also affects the endometrial development in obese PCOS women leading to infertility [137].

Controversial studies have reported the effect of obesity on embryo quality. In a prospective study of 247 women undergoing *in vitro* fertilization (IVF), it has been reported that obese women have poorer quality embryos than non-obese women [138]. Nevertheless, other studies have reported no differences in embryo quality compared with BMI [139, 140]. However, some authors have found a decrease in the overall quality of embryos created in an IVF cycle [133, 141].

6.6. Placental Function and PCOS

Adiponectin and adiponectin receptors are involved in the female reproductive tract; however, the mechanism by which adiponectin system regulates implantation and early pregnancy remains unknown. It has been recently reported that a failure on adiponectin system leads to a suboptimal uterine decidualization and pregnancy loss in obesity and PCOS [142].

Hyperandrogenemia in pregnancy is associated with subsequent development of pre-eclampsia [143]. Pre-eclampsia and the fetal growth restriction are consequences in part, by an impaired trophablast invasion that results in altered circulation in the uterine arteries [144]. The fact that metformin treatment of pregnant women with PCOS reduced pregnancy complications without modifying androgen levels [45] led Salvese *et al.* [146] to study the role of metformin in improving the uteroplacental circulation. The authors found that the treatment with metformin between 12 and 19 weeks of gestation reduced uterine artery impedance of pregnant women with PCOS.

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors that after activated act transcriptional factors. PPARs are expressed in the reproductive male and female tract (hypothalamus, pituitary, uterus, ovary and testis) and have important reproductive functions, especially in the ovary and during plancental development. Fuel sensors, such as glucose, leptin or insulin, regulate fertility at each level of the axis hypothalamo-pituitary-gonadal axis [94, 147]. PPAR gamma modulates those fuel sensors [148] even in reproductive tract. It has been reported that PPAR gamma is essential for the attachment of embryos to the endometrium and the placental function [149]. The inactivation of PPAR gamma leads to impaired vascularization [149] and PPAR beta/delta-null mice show placental malformations and embryo death during early pregnancy [150]. It has been reported that PPAR gamma is essential for the maturation of a functional placenta [151]. Hyperandrogenism alters PPAR gamma pathway in the uterine tissue impairing endometrial functions [152]. These abnormalities were prevented by the treatment with metformin [152]. These findings could explain, in part, the mechanisms by which the treatment of pregnant women with PCOS with insulin-sensitizing drugs increases pregnancy rates [153].

7. TREATMENT OF OBESITY

Data presented here show that obesity in PCOS aggravates insulin resistance and increases the prevalence of the syndrome. Obesity treatments involve lifestyle interventions (weight loss and physical exercise), pharmacological and psychological treatments and surgery. Lifestyle changes are the first line of treatment in the management of obesity in PCOS [76]. The 5% to 10% weight loss improves reproductive features such as menstrual cyclicity, ovulation and fertility [18-20]. Adequate standard diets are characterized by low fat (approximately 30% of energy and 10% satured fat), moderate protein (approximately 15%) higher carbohydrate intake (approximately 55%) and increased fiber-rich whole grain breads, cereals, fruits and vegetables and moderate regular physical exercise [154]. A moderate energy reduction in the diet (500 kcal/day) during a period of 6 to 12 months reduces the body weight around 7 to 10% [155]. The supplementation of omega-3 fatty acid in the diet decreases liver fat in PCOS patients [156]. A simple and moderate physical exercise (at least 30 min/day) increases weight loss and improves clinical features of PCOS [157].

There is no ideal medical PCOS therapy that fully reverses hormonal disturbances and clinical features of obesity in PCOS. Visceral Adipose tissue-derived Serine Protease INhibitor (VASPIN) is a novel adipokine that was recently identified in obese diabetic Otsuka Long-Evans Tokushima (OLETF) rats. VASPIN levels in the abdominal fat of OLETF rats are highest at 30 weeks concomitantly with serum insulin levels. However, VASPIN levels decline at 50 weeks of age, when these rats become diabetic. The link between VASPIN and PCOS remains controversial. Koiou *et al.* [158] found that serum vaspin levels are elevated in PCOS patients and that neither weight loss nor metformin affect VASPIN levels while, it has been reported that that metformin decreases VASPIN in overweight women with PCOS [159, 160].

With respect to pharmacological treatments, few safe and effective drugs are currently available for the treatment of obesity and although sibutramine and rimonabant [161, 162] are effective in inducing weight loss in women with PCOS, they both were withdrawn from some countries since they increased risk of psychiatric disorders and cardiovascular disease.

Orlistat is a lipase inhibitor that reduces fat absorption in the gut by approximately 30% [163]. In women with PCOS, a 4.69% weight reduction was reported with orlistat therapy with an associated improvement in total testosterone levels [164]. However, the use of orlistat is limited by its gastrointestinal side effects. Ap-

proximately, 15-30% of those taking orlistat experience oily stool, faecal urgency, or oily spotting, and 7% report faecal incontinence, particularly at the initiation of treatment [165]. Despite its side effects, orlistat is a useful treatment tool in the management of obese women with PCOS.

Metformin is commonly used in women with PCOS and is reported to improve insulin resistance, SHBG, hyperandrogenemia, and ovulation [166, 167]. However, metformin treatment on weight loss management remains controversial [168, 169].

2. CONCLUSIONS

Depending on the ethnic group and the environment, 35- 68% of women with PCOS are commonly overweight or obese, which leads to the expression of a more severe phenotype [1, 7, 170]. With respect to reproductive functions, it is known that obesity impairs disturbances of the menstrual cycle, although the complete mechanisms have not been elucidated [7]. It is accepted that insulin resistance, hyperandrogenism and central obesity are responsible for these adverse effects. Particularly, central obesity, through adipokines and the effect on SHBG plays a fundamental role in chronic oligo-anovulation [84, 170- 172]. In summary, abdominal obesity in women with PCOS induces insulin resistance and consequently, hyperinsulinemia. In turn, increased levels of insulin increase ovarian steroidogenesis and excessive production of androgen by theca cells [15]. The increased local androgen production induces premature follicular atresia and generates anovulation [15, 45, 94, 108, 170].

It has been demonstrated that central obesity alters insulin resistance, inflammatory mediators, coagulation and fibrinolysis. Obesity is associated with insulin sensitivity and hyperinsulinemia and increased levels of insulin. In addition, obesity mediates the decrease on glycodelin and reduces IGFBP1, both of them related to recurrent pregnancy loss [131, 173, 174]. Obese women with PCOS have increased levels of pro-inflammatory cytokines (including IL6, PAI1 and TNF) which exert negative effects on the implantation process and early embryonic development [109, 133, 174]. Adipokines not only affect reproductive functions but are also involved in cardiovascular diseases. It has been demonstrated that obese women with PCOS show increased cardiovascular risk comparing with non-obese PCOS patients [39, 59, 53].

There are few safe drugs to use in the treatment of obesity. Pharmacological treatments include orlistat [163, 164] and metformin [166- 169]. Finally, it appears that weight loss must be the first line of treatment of obese or overweight women with PCOS.

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