

# Obesity in Polycystic Ovary Syndrome

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## 1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine and metabolic heterogeneous disorder, with a likely genetic origin, influenced by environmental factors such as nutrition and physical activity. The main clinical features of PCOS are related to hyperandrogenism, such as hirsutism, acne and menstrual disorders (Moran et al., 1994; Azziz, et al., 2004; Carmina et al., 2006). PCOS is also associated with overweight or obesity (Azziz, et al., 2004), mainly abdominal adiposity (Moran et al., 1999). The etiology of PCOS is unknown. The genetic origin is based on the observation that PCOS is more frequent among the sisters and mothers of these patients (Lunde et al., 1989; Govind et al., 1999). Moreover, in a study done with twins, a higher correlation in the presence of PCOS is observed more in monozygotic than in dizygotic (Vink et al., 2006). Multiple genes related to the production of androgen, the function of the gonadotropin, the action of insulin and the regulation of energy have been evaluated. Although associations of some genes with clinical disorders of PCOS have been found, in specific regions and determined polymorphisms, the findings of studies and in different populations have not been consistent (Wood et al., 2003).

The hypothesis of the origin of PCOS by environmental factors is based on the beneficial results observed by weight loss, and the worsening with increasing weight in these patients. The interaction of environmental factors of PCOS in women affected starts from their prenatal and postnatal life (Abbott et al., 2002). Food habits and lifestyle are also factors in the presentation and the development of PCOS. The influence of the environmental component of PCOS and its interaction with the genetic component has been less studied. Obesity plays an important role in the pathogenesis of PCOS, and the majority of patients with PCOS are overweight or obese; however, these disorders are not considered as diagnostic criteria for PCOS, since not all obese women present hyperandrogenism.

## 2. Diagnosis

The major criteria of PCOS, proposed in the consensus of the National Institutes of Health in Bethesda, M.D., were (in order of importance): a) hyperandrogenism and/or hyperandrogenemia, b) oligoovulation, c) exclusion of other known disorders, and d) possibly

the characteristic morphology of polycystic ovaries on ultrasound (Zawadzki & Dunaif, 1992). At the Rotterdam consensus, the presence of two out of the three following criteria was considered as diagnostic for PCOS: a) oligoovulation or anovulation, b) clinical and/or biochemical signs of hyperandrogenism, and c) polycystic ovaries by ultrasound, after exclusion of other related disturbances (ESHRE/ASRM-Sponsored PCOS Consensus, 2004). The Androgen Excess and PCOS Society considers as PCOS: hyperandrogenism (hirsutism and/or hyperandrogenemia), ovarian dysfunction (oligo-anovulation and/or polycystic ovaries), and the exclusion of other androgen excess or related disorders (Azziz, et al., 2006).

### 3. Phenotypes

Overweight and obesity are not considered for PCOS phenotypes (Azziz, et al., 2006). Phenotypes of PCOS patients can be classified as follows: A) hyperandrogenism, oligo-anovulation and polycystic ovaries by ultrasound; B) hyperandrogenism and oligo-anovulation (and normal appearance of the ovaries by ultrasound); C) hyperandrogenism and polycystic ovaries by ultrasound (with regular ovulatory menstrual cycles); and D) oligo-anovulation and polycystic ovaries by ultrasound (without hyperandrogenism). The National Institutes of Health criteria recognizes A and B phenotypes. The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group accepts all these phenotypes. The AE-PCOS Society admits A, B and C phenotypes (Table 1). However, each one of the phenotypes can be subdivided considering the presence of obesity, when body mass index is (BMI)  $\geq 27$ .

Features	A1	A2	B1	B2	C1	C2
	Obese	Non obese	Obese	Non obese	Obese	Non obese
Hyperandrogenism	Yes	Yes	Yes	Yes	Yes	Yes
Oligo-anovulation	Yes	Yes	Yes	Yes	No	No
Polycystic ovaries	Yes	Yes	No	No	Yes	Yes
No.	83	28	39	17	3	2
%	48.3	16.3	22.7	9.9	1.7	1.2

Table 1. Phenotype classification in 172 patients with polycystic ovary syndrome taking into account obesity (body mass index  $\geq 27$ ) to subdivide each group. The frequencies of different phenotypes are unpublished data yet, Moran C, 2011.

### 4. Prevalence of PCOS and/or obesity

Polycystic ovary syndrome (PCOS) affects 4-7% of women in reproductive age (Knochenhauer et al., 1998; Diamanti-Kandarakis et al., 1999; Asuncion et al., 2000; Moran et al., 2010). It is considered one of the most frequent endocrine disorders in women of reproductive age (Moran et al., 2010). It is noteworthy that PCOS affects 60-80% of the patients with hyperandrogenism (Table 2) (Moran et al., 1994; Azziz et al., 2004, Carmina et al., 2006). Overweight or obesity affects approximately 60-80% of PCOS patients (Azziz et al., 2004).

Diagnosis	Mexico <sup>1</sup> (n = 250) %	USA <sup>2</sup> (n = 873) %	Italy <sup>3</sup> (n = 950) %
Polycystic ovary syndrome	53.6	82.0	56.6
Idiopathic hirsutism/hyperandrogenism	24.8	4.5	7.6/15.8
Overweight or obesity*	18.0	---	---
Hyperandrogenism and ovulation	---	6.7	15.5
Classic/Non classic CAH	2.0	0.7/2.1	4.3
Androgen secreting tumors	0.8	0.2	0.2
HAIKAN syndrome	---	3.8	---
Cushing's syndrome	0.4	---	---
Iatrogenic hirsutism	0.4	---	---

Table 2. Classification of hyperandrogenism in women. PCOS: polycystic ovary syndrome, CAH: Congenital adrenal hyperplasia, HAIKAN: Hyperandrogenism, insulin resistance and acanthosis *nigricans*. \*Hyperandrogenic overweight or obese patients with regular menstrual cycles. Taken from <sup>1</sup>Moran et al., *Archives of Medical Research*, 1994; <sup>2</sup>Azziz et al., *The Journal of Clinical Endocrinology & Metabolism*, 2004; <sup>3</sup>Carmina et al., *The Journal of Clinical Endocrinology & Metabolism*, 2006.

## 5. Clinical presentation in obese and nonobese PCOS patients

It has been reported that obese PCOS patients have a greater prevalence of some clinical manifestations, such as hirsutism and menstrual disorders (Kiddy et al., 1990); however, other studies have not found differences (Singh et al., 1994). The discrepancies between these studies may be the result of different diagnostic criteria used to classify obesity and PCOS.

## 6. Role of obesity in the pathophysiology of PCOS

### 6.1 Gonadotropic dysfunction

The main pathophysiological components of PCOS are gonadotropic dysfunction and insulin resistance (Dale et al., 1992; Fulghesu et al., 1999; Moran et al., 2003). It has been found that both of these components are related to BMI.

Dissociation of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) higher in PCOS patients with normal weight than in obese PCOS patients has been observed in some studies (Dale et al., 1992); although this observation has not been found in other studies (Fulghesu et al., 1999; Moran et al., 2003) (Table 3).

### 6.2 Insulin resistance

PCOS is associated to metabolic disorders like insulin resistance (Matteini et al., 1982; Chang et al., 1983; Shoupe et al., 1983; Pasquali, et al., 1983), becoming a risk factor for development

of carbohydrate intolerance and type 2 diabetes *mellitus* (Legro et al., 1999; Ehrmann et al., 1999). Insulin resistance appears in women with PCOS with suitable weight (Chang et al., 1983), and overweight or obesity (Moran et al., 2003), but is more frequent and of greater magnitude when there is obesity (Dunaif et al., 1989; Moran et al., 2003). The insulin resistance is approximately two-fold that of non obese PCOS patients (Table 3) (Moran et al., 2003). The magnitude of overweight and obesity is directly related to insulin resistance in PCOS patients (Figure 1) (Moran et al., 2003).

Disorder	PCOS with obesity %	PCOS without obesity %	Total %
Gonadotropic dysfunction LH/FSH $\geq 2$	19	25	22
Insulin resistance Insulin/Glucose $\geq 28.6$ (pmol/mmol)	63*	31*	47

Table 3. Frequency of pathophysiologic components of polycystic ovary syndrome (PCOS). All the determinations were performed in one sample in fasting conditions. \*Statistically significant difference ( $P < 0.01$ ). From Moran et al, *Fertility and Sterility*, 2003.

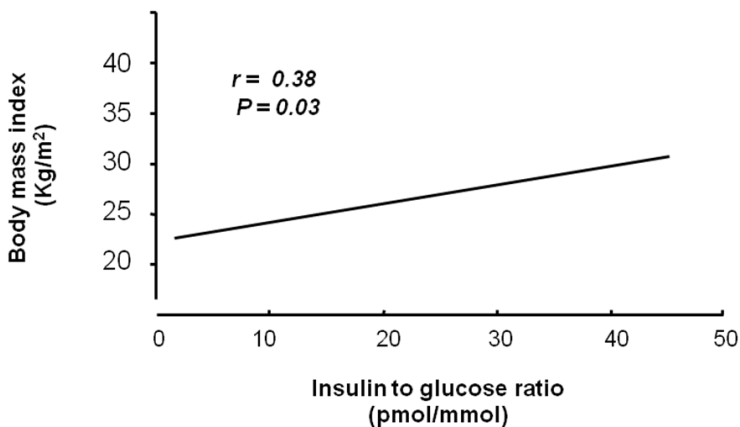


Fig. 1. Relationship between body mass and insulin resistance in patients with polycystic ovary syndrome. Modified from Moran et al, *Fertility and Sterility*, 2003.

### 6.3 Body fat distribution

Obesity is associated mainly to abdominal adiposity in PCOS patients (Moran et al., 2003). It is important to recognize the presence of obesity and its upper body distribution or abdominal adiposity, which changes in accordance to race and geographical distribution (ESHRE/ASRM-Sponsored PCOS Consensus, 2004). The upper body adiposity is related to insulin resistance in PCOS patients (Figure 2) (Moran et al., 2003). To this matter, upper body adiposity has been found to be associated with a higher percentage of anovulation in comparison to lower body adiposity (83% vs. 65%, respectively) (Moran et al., 1999).

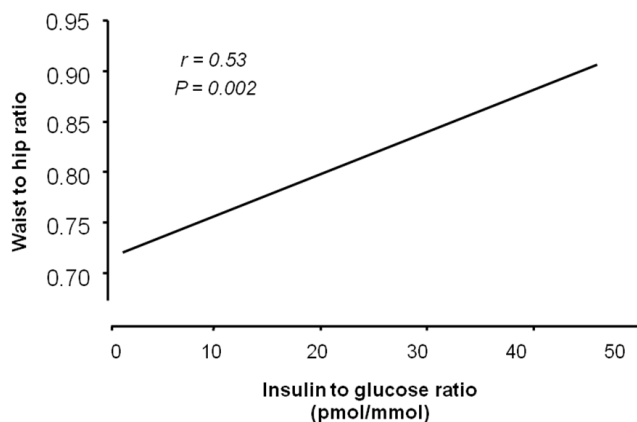


Fig. 2. Relationship between body fat distribution and insulin resistance in patients with polycystic ovary syndrome. Modified from Moran et al, *Fertility and Sterility*, 2003.

#### 6.4 Ovarian morphology of polycystic ovaries

There is some evidence indicating the relationship of anthropometric and hormonal measures with the characteristic polycystic ovarian morphology. On analyzing the anthropometric variables of PCOS patients, BMI is significantly greater in PCOS patients with a characteristic polycystic ovary image than in those without it; also, it has been found that the hip perimeter is significantly greater in PCOS patients with characteristic image of polycystic ovary than in those without this ultrasonographic morphology (Tena et al., 2011). In addition, PCOS patients with the polycystic ovarian morphology by ultrasound present greater levels of testosterone than patients without it.

#### 6.5 Adipocytokines

Patients with PCOS-in comparison to control women-present lower serum levels of adiponectin but not of leptin. A decrease was observed in the expression of the ribonucleic acid (RNA) messenger of adiponectin in the subcutaneous and visceral adipose tissue, while that of leptin has been found significantly less only in the subcutaneous adipose tissue. Also, it has been observed an inverse relationship among adiponectin and leptin expression and the measurement of subcutaneous and visceral adipose tissue by ultrasound (Carmina et al., 2008). Other authors have reported that obese PCOS but not normal weight PCOS patients have significantly lower adiponectin levels than control women (Olszanecka-Glinianowicz et al., 2011).

#### 6.6 Metabolic syndrome

The prevalence of metabolic syndrome is higher in PCOS patients than in control women (47% vs. 4%, respectively) (Dokras et al., 2005). Free fatty acids, total cholesterol and low density lipoprotein cholesterol are higher in obese PCOS patients than in non obese PCOS patients (Holte et al., 1994). Both PCOS and obesity are associated with dyslipidemia and endothelial dysfunction that increase the cardiovascular risk. Although metabolic disorders prevail in the climacteric period, the risk of metabolic syndrome is high even at reproductive age.

Both PCOS and obesity induce an increase in serum inflammatory cardiovascular risk markers (Samy et al., 2009). Increased C-reactive protein, interleukin-6 and tumor necrosis factor alpha have been reported in obese PCOS patients with respect to control women; in addition, these markers have correlated with BMI and insulin resistance (Samy et al., 2009). Fatty liver has been reported present until 40% of PCOS patients associated to higher BMI, abdominal obesity and worse lipid profile (Ma et al., 2011). The pathogenetic relation among PCOS, obesity, metabolic and cardiovascular disease is controversial. A low-grade chronic inflammation has been proposed as the potential cause of the long-term complications of PCOS (Repaci et al., 2011).

## **7. Androgen production in obese and non obese PCOS patients**

In normal women, androstenedione and testosterone are produced mainly in the ovaries, while dehydroepiandrosterone and dehydroepiandrosterone sulfate are secreted predominantly in the adrenals (Parker, 2006). The ovaries produce approximately 50% of testosterone and androstenedione while the adrenals 70% of dehydroepiandrosterone and almost all dehydroepiandrosterone sulfate (Longcope, 1986). Dehydroepiandrosterone is the main precursor of androgens and estrogens, and it is sulfated by the enzyme *SULT2A1* in adrenals (Miller et al., 2006).

Controversy exists about the effect of obesity on serum androgen concentrations in PCOS. Some investigators have reported that testosterone and androstenedione levels are similar in obese and non obese PCOS patients (Dale et al., 1992; Dos Reis et al., 1995). However, it is well known that obesity generates a decrease in the sexual hormone-binding globulin (SHBG), and therefore an increase in the free androgens (Kiddy et al., 1990; Holte et al., 1994). Other studies have found that obesity generates an increase of testosterone levels in PCOS patients (Figure 3) (Holte et al., 1994; Acien et al., 1999, Moran et al., 2008). In contrast, dynamic studies have shown a decrease in androstenedione levels in obese PCOS patients (Dunaif et al., 1988; Moran et al., 2008).

Hyperandrogenism may be of ovarian or adrenal origin (Rosenfield et al., 1972). Participation in PCOS by the increment of dehydroepiandrosterone sulfate is found in 22-25% of PCOS patients (Moran et al., 1999). However, some studies have found frequencies of hyperandrogenism due to dehydroepiandrosterone sulfate of 48-52% in different populations (Carmina et al., 1992). Hyperandrogenic patients with higher adrenal androgen excess have been informed to be leaner, younger and present more hirsutism than patients with lower levels of these steroids (Moran et al., 1999).

## **8. Obesity in pregnant PCOS patients**

Due to obesity and PCOS determine independently a deleterious effect on pregnancy and reproductive outcome, their impact of both conditions together are expectedly adverse in pregnant women and their fetuses. Obese patients with PCOS are characterized by a more severe hyperandrogenic and metabolic state, more irregular menses, less ovulatory cycles and lower pregnancy rates, compared with normal weight PCOS patients; the importance of obesity in the pathogenesis of PCOS is evidenced by the efficacy of weight loss to improve metabolic alterations, to decrease hyperandrogenism, to increase ovulatory menstrual cycles

and to improve fertility (Pasquali et al., 2006). The information with respect to the impact of obesity in hormonal and metabolic factors during intrauterine life is scarce yet.

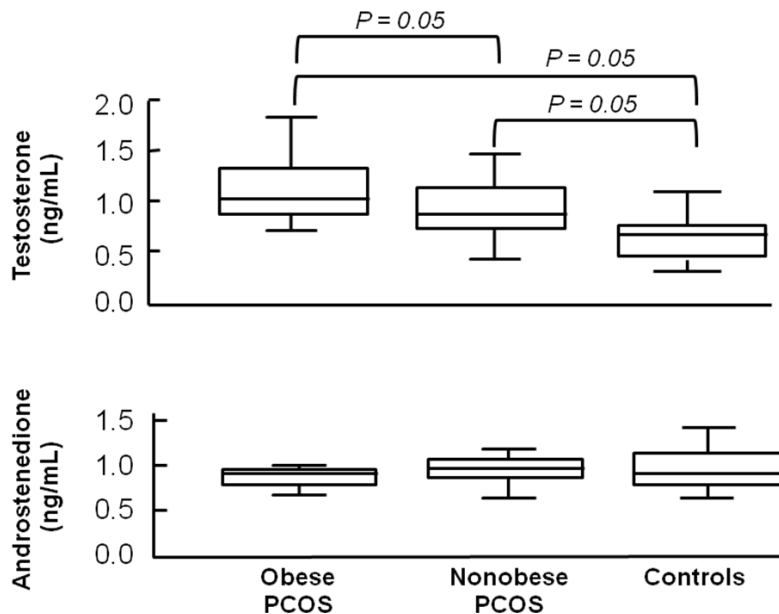


Fig. 3. Values of total testosterone and androstenedione in obese and nonobese patients with PCOS and in control women. Box-and-whiskers plots of basal levels of androgens. The line within each box represents the median. Upper and lower boundaries of each box indicate 75<sup>th</sup> and 25<sup>th</sup> percentiles, respectively. The whiskers (above and below) show the upper and lower adjacent values, respectively. The levels of testosterone were significantly greater in the obese patients with PCOS compared with non obese PCOS patients and controls. Also, the testosterone levels were significantly greater in non obese PCOS patients than in control women. There were no significant differences in the levels of androstenedione. Modified from Moran et al, *Fertility and Sterility*, 2008.

## 9. Treatment of obesity and metabolic abnormalities in PCOS patients

The current management of PCOS has to attend to the clinical, hormonal and metabolic abnormalities. The change in PCOS concept of the treatment is that it is not considered only a reproductive problem but also an endocrine and metabolic disorder that requires a long term follow-up. Furthermore, the treatment must address specific problems that affect PCOS patients, such as hirsutism, acne, overweight or obesity, menstrual disorders and infertility (Moran et al., 1994; Azziz et al., 2004, Carmina et al., 2006).

### 9.1 Modifications in life style

Weight loss is the principal recommendation as the first line of treatment in obese women with PCOS. The treatment of obesity in PCOS must include nutritional counselling in food habits and lifestyle (Kiddy et al., 1992; L.J. Moran et al., 2003). The weight loss partially

ameliorates hirsutism (Pasquali et al., 1989; Kiddy et al., 1992), regularizes menstrual cycles and ovulation, as well as improves the endocrine and metabolic abnormalities (Pasquali et al., 1989; Kiddy et al., 1992; Guzick et al., 1994; Holte et al., 1995).

### **9.1.1 Food habit**

There is a known beneficial effect of the decrease of body weight and a worsening with the increase of excess weight in PCOS patients. It has been observed that some patients with PCOS can present menstrual cycles and ovulation after having reduced at least 5 % of her body weight (Kiddy et al., 1992). The studies on food habits in patients with PCOS have shown that the most important thing is caloric restriction, achieving a reduction of about 7% body weight, and that there is no difference in the metabolic results changing the composition of the diet (L.J. Moran et al., 2003). However, it has been reported that low glycemic index diet improved insulin sensitivity and menstrual periodicity more than the conventional healthy diet in PCOS patients (Marsh, 2010).

### **9.1.2 Exercise**

Physical activity has been shown lower in PCOS patients than in control women (Write et al., 2004). The changes in lifestyle that incorporate an increase of physical activity and limited caloric intake have been beneficial in some studies. Regular physical activity is an important component to support the reduction of long-term weight; the results are minimal with exercise alone (Hoeger, 2008). An increase in physical activity is recommended for women with obesity and PCOS, as long as cardiovascular and orthopaedic limitations are considered (Moran et al., 2006).

## **9.2 Insulin sensitizer agents**

### **9.2.1 Metformin**

The temporary use of metformin is considered, as a coadjutant of diet and exercise to control insulin resistance, especially in patients with obesity and glucose intolerance (Velazquez et al., 1994; ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008). Nevertheless, the duration of this therapy is unknown yet. The metformin diminishes the hepatic glucose synthesis, inhibiting the gluconeogenesis; it also increases the glucose use by the striated muscle (Kirpichnikow et al., 2002).

Administration of metformin to obese PCOS patients reduces the levels of circulating insulin, the activity of the complex P450c17 $\alpha$  and the ovarian secretion of androgens (Nestler & Jakubowicz, 1996). Metformin can reduce the circulating androgen levels, may normalize the menstrual cycles and improve ovulation (Velazquez et al., 1994). The combined use of metformin and clomiphene has been recommended for PCOS patients with overweight or obesity who present more insulin resistance, especially in those refractory to the clomiphene (ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008).

Metformin has contraindications and some side effects (Lord et al., 2003). It must not be used in patients with renal insufficiency, hepatic malfunction, congestive heart failure and those with a history of alcoholism. It is important to take into account that metformin in rare cases can produce lactic acidosis; it is necessary to evaluate renal function before and



periodically during its administration, even though this complication is extremely rare. The gastrointestinal adverse effects, mainly nausea and diarrhoea, affect 10 to 25% of the patients taking metformin. The undesirable effects are transitory; however, in a minority of patients these can cause discontinuation of the treatment. To minimize adverse effects, metformin must be administered gradually. Metformin can induce bad absorption of vitamin B12 in patients who use it for long periods of time, even though this effect is very rare. In patients who wish to use contraception, it is necessary to add an oral contraceptive while still taking metformin. In those cases of hirsutism it is possible to add antiandrogens, oral contraceptives or both.

### **9.2.2 Thiazolidindiones**

Among thiazolidindiones are troglitazone, rosiglitazone and pioglitazone, which improve the sensitivity of the insulin in the liver, striated muscle and adipose tissue; they also reduce the concentrations of insulin and circulating androgens (Lord et al., 2003). The use of troglitazone was ceased in research protocols conducted in PCOS patients because of hepatotoxicity reports. Although rosiglitazone and pioglitazone are as effective as metformin to treat insulin resistance in PCOS patients, it appears they are less effective to lower BMI than metformin. These drugs have been used less due to the concern of their use during pregnancy.

### **9.3 Drugs for obesity and dyslipidemia**

Drugs to control obesity have been used in obese patients with PCOS, although few studies exist to support this therapeutic approach. It is known that orlistat blocks the absorption of intestinal fat (Jayagopa et al., 2005), and sibutramine suppresses the appetite (Sabunku et al., 2003); both favor weight loss independently from the androgen excess and insulin resistance. It is important to take into account that these treatments must not be considered first line treatments for obesity in patients with PCOS.

There are little evidences that statins, apart from specific action on lipid profile decreasing total cholesterol and low density lipoprotein cholesterol, can reduce serum androgens, inflammatory markers and insulin resistance (Banaszewska et al., 2009; Sathyapalan et al., 2009, Raja-Khan et al., 2011). However, statins and bezafibrate (Hara et al., 2010) should only be used in women with PCOS who meet current indications for those treatments.

### **9.4 Bariatric surgery**

Few studies exist on the impact of bariatric weight loss surgery on manifestations of PCOS in patients with morbid obesity. The initial results of bariatric surgery in patients with morbid obesity and PCOS seem encouraging, since aside from the weight reduction there is a decrease of hyperandrogenemia, hirsutism, insulin resistance and restoration of menstrual cycles and ovulation (Escobar-Morreale et al., 2005).

## **10. Research of obesity and PCOS for the future**

The differences in the hormonal and metabolic profile, as well as the different response to treatment of obese and non obese PCOS patients suggest that obesity has to be considered as a secondary characteristic for the PCOS phenotype classification in prospective trials.

The intrauterine milieu in pregnancy and the reproduction outcome of PCOS patients with overweight or obesity are important topics for research in prospective studies.

PCOS and obesity induce an increase in serum inflammatory cardiovascular risk markers. The precise mechanisms underlying these associations require additional studies, to determine the relative contribution of different factors on cardiovascular disease.

## 11. Summary

PCOS is associated with overweight or obesity, mainly abdominal adiposity; approximately 80% of patients with PCOS are either overweight or obese. The insulin resistance, present in most of patients with obesity and/or PCOS, is a risk factor to develop carbohydrate intolerance and type 2 diabetes *mellitus*. Insulin resistance is higher and of greater magnitude in obese than non obese PCOS patients. A decrease in the synthesis of SHBG has been found, and therefore an increase in the free androgens in obese PCOS patients. It has been observed in some studies that obese PCOS patients present an increase of testosterone levels and a decrease in androstenedione. Weight loss is the main recommendation in obese PCOS patients. The treatment of obesity in PCOS must include nutritional counselling in food habits and life style. An increase in physical activity is recommended for PCOS patients. The temporary use of metformin may be useful, in conjunction with diet and exercise, to control insulin resistance, especially in PCOS patients with obesity and glucose intolerance. The combined use of metformin and clomiphene for ovulation induction has been suggested mainly in patients with overweight or obesity, who present more insulin resistance, refractory to the clomiphene alone. Drugs used to control obesity, as orlistat or sibutramine, must not be considered as the first choice for obesity in patients with PCOS. The initial results of bariatric surgery in patients with morbid obesity and PCOS seem encouraging, since aside from the weight reduction, a decrease of hyperandrogenemia, insulin resistance, hirsutism, and the restoration of menstrual cycles and ovulation have been observed. Obesity decreases or delays the results of several treatments for infertility such as the administration of clomiphene, gonadotropins and ovarian drilling. The differences in the hormonal and metabolic profile, as well as the different response to treatment between obese and non obese PCOS patients suggest that obesity has to be considered as a secondary characteristic for the determination of PCOS phenotypes.

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