Outlook

Role of changes in dietary habits in polycystic ovary syndrome

Renato Pasquali is the Director of the Endocrinology Division, Department of Internal Medicine, S Orsola Hospital, University of Bologna, Italy. He is also the Director of the School of Specialization of Endocrinology and Metabolism, University of Bologna. Dr Pasquali is a member of several international and national scientific societies and several editorial boards, and reviewer for many journals. His scientific activity pertains to the pathophysiology of the polycystic ovary syndrome and endocrinology of obesity and the metabolic syndrome. He is the author of 114 full papers in international journals.

Dr Renato Pasquali

Renato Pasquali, Alessandra Gambineri
Endocrinology Unit, Department of Internal Medicine, S Orsola-Malpighi Hospital, University Alma Mater Studiorum, Bologna, Italy
Correspondence: U. O. di Endocrinologia, Dipartimento di Medicina Interna, Policlinico S. Orsola-Malpighi, Via Massarenti 9, 40138, Bologna, Italy. Tel/Fax: +39 51 6364147; e-mail: renato.pasquali@unibo.it

Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous clinical condition. In most women, especially in the obese, all features of the metabolic syndrome, particularly insulin resistance and associated hyperinsulinemia, are present. Insulin is a physiological hormone regulating ovarian function, specifically ovarian steroidogenesis and androgen blood transport and/or activity in the target tissues. Hyperinsulinemia may therefore play a pivotal role in favouring the hyperandrogenic state and related clinical and metabolic alterations. The abdominal obesity phenotype is common, affecting more than half of PCOS women. Menstrual cycles and fertility rate are negatively affected by the presence of insulin resistance, hyperinsulinemia and obesity. PCOS women with obesity and insulin resistance are the obvious target for lifestyle intervention, such as changes in dietary habits and increased physical activity. Weight loss should therefore represent the first-line approach in the treatment of obese PCOS women, since it significantly improves hormonal and metabolic abnormalities and may favour spontaneous ovulation and improve fertility rate in the majority of patients. Individualized pharmacological support aimed at favouring weight loss and maintenance and improving insulin resistance may play a complementary role to lifestyle intervention.

Keywords: diet, obesity, polycystic ovary syndrome, weight loss

Introduction

The polycystic ovary syndrome (PCOS) is a complex disorder, affecting approximately 5–10% of reproductive-age women (Franks, 1995). Over the years, since the first description, this syndrome has been defined in a number of different ways. According to a recent workshop consensus held in Rotterdam, the Netherlands, the diagnostic criteria for PCOS should be based on the cardinal presence of hyperandrogenism associated with chronic oligoovulation, with the exclusion of other causes of hyperandrogenism such as adult-onset congenital adrenal hyperplasia, hyperprolactinaemia and androgen-secreting neoplasms; in addition, polycystic ovary appearance at ultrasound examination has been recently included in the list of criteria to define PCOS (Rotterdam EHSRE/ASMR sponsored PCOS Consensus Workshop, 2003). This last feature was not included in the previous workshop aimed at defining diagnostic criteria of PCOS, which took place in 1990 at the National Institutes of Health, United States (Zawadszki and Dunaif, 1992). However, the definition still appears to be incomplete, since it does not consider characteristics frequently present in PCOS, particularly insulin resistance, hyperinsulinemia and obesity, the key features of the metabolic syndrome (Dunaif, 1997). At a physiological level, insulin acts as a true gonadotrophic hormone, synergizing with LH to stimulate ovarian steroidogenesis. Insulin resistance and associated hyperinsulinemia are now recognized as important pathogenetic factors in determining hyperandrogenism in the majority of PCOS women, particularly when obesity is present (Dunaif, 1997; Poretsky et al., 1999). On the other hand, obesity by itself may favour ovarian hyperandrogenism in a subset of PCOS women, by mechanisms that may be partly independent of the primary role of excess circulating insulin.
Outlook - Effects of dietary changes on PCOS - R Pasquali & A G gambineri

(Pasquali and Casimirri, 1993; Gambineri et al., 2002), providing that genetic or other still undefined factors are present (Legro, 2000). In most PCOS patients, however, obesity probably represents a secondary additional pathogenetic condition, capable of amplifying primary factors leading to exaggerated ovarian androgen secretion, such as an increased LH stimulation (Soule, 1996; Dunaif, 1997; Poretsky et al., 1999).

Regardless of their causative factors, there is no doubt that the phenotype of a woman affected by PCOS is fundamentally related to two main factors, the hyperandrogenic and the insulin resistant–hyperinsulinic state (Table 1). These factors can be strongly influenced by the presence of obesity, although they should also be considered as important factors involved in the development of obesity itself, particularly its abdominal phenotype (Pasquali et al., 2004). Before entering into the core of this article, which is how to manage obese PCOS with lifestyle intervention (such as changes in dietary habits and increased physical activity), the main mechanisms responsible for insulin resistance and hyperandrogenemia in PCOS will be briefly discussed, focusing in particular on the role of obesity.

PCOS, insulin resistance, and the metabolic syndrome

The metabolic syndrome is a consistent feature of the majority of obese women with PCOS and can also be detected in many normal-weight affected women (Dunaif, 1997; Poretsky et al., 1999). Obese women with PCOS, particularly those with the abdominal obesity phenotype, are usually more insulin resistant and more hyperinsulinemic than their normal-weight counterpart (Pasquali and Casimirri, 1993; Dunaif, 1997) (Figure 1). Both fasting and glucose-stimulated insulin concentrations are in fact significantly higher in obese than in non-obese PCOS subgroups. Accordingly, studies examining insulin sensitivity by using different methods, such as the euglycaemic hyperinsulinaemic clamp technique, the frequent sample intravenous glucose test and the insulin test, further demonstrated that obese PCOS women had significantly lower insulin sensitivity than their non-obese PCOS counterparts, and therefore a more severe insulin-resistant state (see extensive revision in Pasquali and Casimirri, 1993; Dunaif, 1997; Gambineri et al., 2002).

There are several mechanisms by which obesity may induce an insulin-resistance state. An important role appears to be played by several metabolites [i.e. free fatty acids (FFA) and lactate] (Holte, 1996; Poretsky et al., 1999; Vetter et al., 2000) as well as tumour necrosis factor α (TNFα) and leptin (Gambineri et al., 2002). In addition, several molecular mechanisms that have been described in PCOS women appear to be involved in the pathogenesis of insulin resistance, particularly in obese affected patients. These include excess serine phosphorylation of the insulin receptor (Dunaif, 1997), mutations of the insulin-receptor gene or insulin-receptor substrate-1 (IRS-1), particularly in the muscle cells (Dunaif et al., 2001), adenosine depletion in human adipocytes (Ciaraldi et al., 1997), alteration of the peroxisomal proliferator activated receptor γ (PPARγ) (Lambe et al., 1996), and finally, defects in the adipocyte glucose transporter GLUT4 (Rosebaum et al., 1993). The role of FFA has been recently emphasized by some studies even to explain insulin resistance in normal-weight PCOS women. In fact, it has been demonstrated that the visceral adipocytes of these women appear to have an abnormal sensitivity at the post-receptor level to catecholamines, because of a defect in protein-kinase A-dependent hormone-sensitive lipase (Ek et al., 2002). Interestingly, this defect appears to be different from that observed in adipocytes of non-PCOS women with the metabolic syndrome, who are characterized, according to another study, by an alteration of the balance between the lipolytic β3-adrenoreceptors and the antilipolytic α2-adrenoreceptors (Hoffstedt et al., 1996). However, it still remains to be defined whether this defect is primary or secondary to other factors, for example an excess of androgens.

In the last few years, a considerable effort has been made to define the potential genetic background of insulin resistance in PCOS. This disorder frequently clusters in the same family, and several studies have found a strong association between the presence of insulin resistance and features of a PCOS status, particularly mild hyperandrogenism, in first-degree relatives of women with PCOS (Legro et al., 2002). Numerous genes have been tested for their potential involvement in regulating insulin secretion or tissue insulin sensitivity (Urbanek et al., 1999), but only for a few of them did linkage studies or studies of familiar clusters yield some significant results. Studies performed in familiar clusters have described an association between PCOS status and polymorphism of the VNTR (variable number tandem repeats), a gene involved in the regulation of the insulin gene, and therefore affecting insulin secretion (Waterworth et al., 1997). Two different studies have demonstrated a significant association between the insulin resistance state and polymorphisms of genes encoding for both IRS-1 or IRS-2 (El Mkadem et al., 2001; Ehrmann et al., 2002), and other studies have found a significant association with mutations of the insulin receptor gene (Moller and Flier, 1988; Sorbara et al., 1994; Talbot et al., 1996).

Glucose intolerance is present in as many as 30–40% of obese PCOS women in the United States (Dunaif, 1997) and probably to a lower extent in those living in Europe, whilst it is uncommon in their normal-weight counterparts (Dunaif, 1997; Gambineri et al., unpublished data). In any case, the prevalence rate for impaired glucose tolerance in the population of obese PCOS subjects appears to be higher than that reported in population-based studies on the incidence of glucose intolerance in women of a similar age (Harris et al., 1987), although epidemiological studies are lacking. These findings indicate that obesity may contribute to determine the insulin-resistant state and may impair glucose tolerance in PCOS. Although insulin resistance seems to play a determining role in the development of diabetes, the presence of insulin resistance does not immediately imply a concomitant alteration of glucose tolerance. In fact, most obese insulin-resistant PCOS women still have normal glucose tolerance. On the other hand, it has recently been found that PCOS women with impaired glucose tolerance or type 2 diabetes were significantly more insulin resistant and hyperinsulinemic than those with normal glucose tolerance (Gambineri et al., unpublished data) (Figure 2). In the same study, it was also found that the development of states of glucose intolerance could be predicted to a certain extent, the former being characterized by a significantly lower birth weight and early menarche with respect to the latter. These data are in accordance with the repeated finding that low birth weight is associated with susceptibility to develop insulin resistance and...
type 2 diabetes in the general population (Phillips, 1996; Hofman et al., 1997). In a previous prospective study in a small group of PCOS women followed up for approximately 10 years, it was also found that insulin resistance tended to worsen with time together with a further increase of the insulin and C-peptide response to an oral glucose challenge, and that in several cases glucose tolerance tended to became impaired (Pasquali et al., 1999). Taken together, these findings strongly support the role of insulin resistance in the development of the altered glucose tolerance, which can, however, develop even in the presence of increased β-cell function.

On the other hand, there are studies examining the entity of insulin secretion in relation to insulin sensitivity, which have demonstrated that a β-cell dysfunction may co-exist with insulin resistance in obese PCOS women. In particular, when expressed in relation to the degree of insulin resistance, defective early phase β-cell insulin secretion and reduced insulin secretory response, either to boluses or graded infusions of glucose administered intravenously, have been reported in these women (Ehrmann et al., 1995; Dunaif and Finegood, 1996). Notably, these findings have been demonstrated only in Hispanic–American insulin-resistant PCOS women with obesity, but not in studies performed in PCOS women living in Europe or in Mediterranean areas (Holte et al., 1995). It is therefore possible that several environmental factors, such as habitual diet or other lifestyle behaviour, may explain this difference.

**Table 1. Hyperandrogenism and the insulin resistance–hyperinsulinaemia state represent the main factors determining the PCOS phenotype.**

**Hyperandrogenism**
- Responsible for:
  - Signs/symptoms of androgen excess, including anovulation
  - Reduced sex hormone-binding globulin (SHBG)
  - Abdominal fatness
  - Insulin insensitivity (?)
  - Lipid abnormalities

**Hyperinsulinaemia and insulin resistance**
- Responsible for:
  - Metabolic syndrome
  - Abdominal fatness
- Co-factor favouring:
  - Androgen excess
  - Reduced SHBG
  - Chronic anovulation

**Figure 1.** The insulin-mediated glucose disposal rate (estimated by the euglycaemic–hyperinsulinaemic clamp technique) is reduced by approximately 35–40% in women with PCOS, either obese or normal-weight; this defect is similar to that observed in women with type 2 diabetes but without PCOS. From Dunaif (1997), with permission of the editor. NIDDM = non-insulin dependent diabetes mellitus or type 2 diabetes; NL = normal–lean.

**Figure 2.** Fasting insulin (a), insulin_{AUC-OGTT} (b), and HOMA_{OGTT} (c) in obese PCOS women with impaired glucose tolerance or type 2 diabetes (black bars), obese PCOS women with normal glucose tolerance (white bars), and normal-weight PCOS women with normal glucose tolerance (grey bars). OGTT = oral glucose tolerance test; AUC = area under the curve (given as µU/ml × min); HOMA = homeostasis model assessment.
PCOS women, particularly if they are obese, may also present with a more atherogenic lipoprotein pattern profile, which is characteristic of the metabolic syndrome and is strongly associated with the presence of insulin resistance. A greater reduction of HDL-cholesterol, together with a higher increase of both triglycerides and total and LDL-cholesterol concentrations, was observed in obese with respect to normal-weight PCOS women, particularly when the abdominal obesity phenotype is present (reviewed in Gambineri et al., 2002).

Hyperandrogenism and obesity in PCOS women

Although comparisons of the hormonal status between obese and non-obese women with PCOS have yielded conflicting results, there are numerous studies indicating that obese PCOS women may also have more severe hyperandrogenism and lower SHBG concentrations with respect to their non-obese counterparts (Pasquali and Casimirri, 1993). In particular, obese PCOS women may present higher total and free testosterone concentrations with respect to non-obese PCOS. The abdominal obesity phenotype may also further exacerbate the hyperandrogenic state in PCOS women (Pasquali and Casimirri, 1993). There may be various mechanisms by which obesity influences hyperandrogenism in women with PCOS. As discussed in a recent review (Gambineri et al., 2002), candidate factors may be insulin, insulin-like growth factors, oestrogens and the hypothalamic–pituitary–adrenal axis. In addition, obesity, particularly the abdominal phenotype, is characterized by a condition of so-called ‘functional hyperandrogenism’, since production rates of major androgens are increased as is the delivery of free androgen fraction to target tissues, due to the reduction of SHBG synthesis in the liver. The role of leptin in the hyperandrogenism of obese PCOS women is still under debate. In fact, leptin appears to directly stimulate ovarian 17α-hydroxylase activity, which is involved in both ovarian and adrenal steroidogenesis (Zamorano et al., 1997). However, whether leptin excess could play a role in the development of hyperandrogenism in obese PCOS women remains to be further elucidated. A novel peptide hormone, ghrelin, primarily expressed in the stomach and intestine and in many other organs and tissues, including theca and granulosa in the ovaries, may also be involved in the regulation of synthesis and/or secretion of steroids. A recent study has in fact shown that ghrelin affects testosterone secretion induced by both choric gonadotrophin and cAMP in rat testis by inhibiting key enzymes of steroidogenesis (Tena-Sempere et al., 2002). This intriguing contiguity between ghrelin and steroid biosynthesis is highlighted by recent data demonstrating that sex hormones are important and probably direct regulators of ghrelin concentrations (Pagotto et al., 2002; Gambineri et al., 2003; Pagotto et al., 2003). Available data therefore support the concept that ghrelin may be another factor involved in the regulation of ovarian steroidogenesis, but also that sex hormones are involved in the regulation of ghrelin secretion and, probably, action.

Androgens per se may play a non-secondary role in determining insulin resistance in PCOS, through the activation of the lipolytic cascade that leads to an increase in FFA release and the modification of the muscle histological structure (Bjorntorp, 1996). The direct effect of testosterone at the level of muscle structure was first described in female rats (Holmäng et al., 1992) and subsequently confirmed in biopsies derived from women affected by hyperandrogenism and severe insulin resistance state (Bjorntorp, 1996).

Dietary habits: an unexplored factor linked to the development of PCOS?

There are theoretical possibilities that the quality of diet may interfere with the metabolic and endocrine abnormalities of PCOS, although very few studies have addressed this issue (Pasquali and Casimirri, 1993; Gambineri et al., 2002; Pasquali and Gambineri, 2002). There is in fact a complex interrelationship between different nutritional factors and endocrine status. It is known that diet plays an important role in the regulation of the metabolism of sex steroids and LH secretion. High fibre diet reduces serum oestrogen concentrations in premenopausal women, and it is supposed that a low fibre–high lipid diet may increase circulating oestrogen and androgen concentrations. Moreover, a very high lipid intake has been found to decrease sex hormone-binding globulin (SHBG) concentrations, with a consequent increase in both androgen and oestrogen availability to target tissues (Gambineri et al., 2002).

The mechanisms by which high lipid intake decreases SHBG concentrations are still unknown, although a role of high insulin concentrations has been suggested. In addition, fibre intake was significantly positively correlated with serum SHBG concentrations, whereas protein intake showed a clear negative association with SHBG serum concentrations (Longcope et al., 2000). There is also evidence that dietary fibre may play a key role in the regulation of circulating insulin concentrations. Fibre reduces insulin secretion by slowing the rate of nutrient absorption following a meal (Jenkins and Jenkins, 1985). Moreover, various studies show that insulin sensitivity increases (Fukagawa et al., 1990) and body weight decreases in individuals on high fibre diets (Stevens, 1988). In contrast, experimental evidence has indicated that the typical western diet, which is high in fat and refined carbohydrate and low in fibre, induces insulin resistance and may favour obesity (Abbasi et al., 2000). Finally, the combination of carbohydrate-rich and protein-rich food in the same meals increases the post-prandial insulin response (Spiller et al., 1987). The quality of diet also seems to influence serum concentrations of insulin-like growth factors (IGF). In particular, a high protein intake increases IGF-I (Thissen et al., 1994). In addition to the amount of protein ingested, the proportion of essential amino acids making up protein is also important. In fact, refeeding an essential amino acid diet after a fasting period causes a greater increase in serum IGF-I than refeeding a diet rich in non-essential amino acids (Thissen et al., 1994). Both low fibre and high lipid intake appear to favour the onset and development of obesity.

To support this assumption, it has been demonstrated that the modification of the type of food consumed, specifically fat, even without restrictions on amounts, induces weight loss in both obese and non-obese individuals (Lissner et al., 1987). In some reports, PCOS women were found to have a higher intake of saturated lipids and a lower intake of fibres when compared with control groups (Wild et al., 1985) and this fits...
very well with personal experience in a large cohort of obese and non-obese women (unpublished data). These findings increase the possibility that diet may be partly involved in the pathogenesis of PCOS, by favouring insulin resistance, hyperinsulinaemia and hyperandrogenism and by increasing body weight. Obviously, an excess lipid and low fibre intake does not represent a universal way of becoming obese. The possibility that other factors, including excess calories or other still undefined nutritional factors, may be involved should therefore be taken into account. In fact, despite the limited availability of nationally representative data (particularly secular trend data), evidence is now emerging to suggest that the prevalence of overweight and obesity is increasing worldwide at an alarming rate and that nutritional factors, other than other lifestyles, may have a dominant aetiological responsibility (WHO Document, 1997). Both developed and developing countries are affected.

Epidemiological surveys on the prevalence of PCOS in different areas of the world are lacking. On the other hand, due to the link between obesity and PCOS, it could be expected that this disorder may be as frequent as expected, based on available scarce epidemiological data obtained in Europe and North America (Dunaif, 1997; Poriesky et al., 1999). The search for other potential nutritional factors possibly involved in the development and pathophysiology of PCOS should therefore be encouraged worldwide. This is, however, also an attractive challenge.

Lifestyle interventions in PCOS: the lesson from studies in obesity

The importance of obesity in the pathogenesis of PCOS and the implications that metabolic alterations frequently associated with the obesity state have on long-term health have induced many investigators to evaluate strategies to control weight disorders in PCOS. Obese women with PCOS often report extreme difficulty in losing weight and maintaining weight loss. Nevertheless, when studied, the resting metabolic rate and post-prandial thermogenesis do not differ in obese women with PCOS and weight-matched control subjects, suggesting that the same need for caloric restriction relative to energy expenditure is necessary for weight loss in both groups (Segal and Dunaif, 1990). Moreover, no differences in hormonal responses to physical exercises were found between PCOS and weight-matched control women (Jaatinen et al., 1993).

The best therapeutic strategy for favouring weight loss in obese PCOS women has not yet been investigated. However, lifestyle interventions, particularly with hypocaloric diet with or without associated increased physical activity, have proved their efficacy (Pasquali et al., 1997; Pasquali and Gambineri, 2002). Physical exercise can have an important impact on insulin resistance. In the context of overall glucose homeostasis, a single period of exercise can markedly increase rates of whole-body glucose disposal (Richter et al., 1989) and increase the sensitivity of skeletal muscle glucose uptake to insulin (Mikines et al., 2001). These effects can last for several hours after completion of exercise. Moreover, regular physical activity is required in order to have a lasting effect on insulin responsiveness (Marshall, 2001). Physical activity is also an important long-term modulator of serum IGF-I, even if the duration, type and intensity of exercise as well as the subject’s level of physical training are important regulators of the decline in IGF-I that accompanies exercise. Only one study evaluated the impact of regular physical activity in adolescent women with PCOS, and a significant decrease was described in the frequency of self-reported acne, dysmenorrhea and menstrual irregularities in those engaging in more than 8 h of sports activity per week (Van Hooff et al., 2000). All other studies (see next paragraph) investigated the impact of only caloric restriction or modification of the composition of the diet on hormonal and metabolic abnormalities of obese PCOS women and on the main clinical features, including menstrual abnormalities, chronic anovulation and infertility.

Effects of dietary-induced weight loss

Because obesity affects many women with PCOS and may independently affect the adverse health consequences of PCOS, the role of weight reduction in the management of PCOS should be encouraged. Although published literature on the effect of weight loss in obese women is not abundant, nonetheless all studies demonstrate that weight loss improves both endocrine and metabolic abnormalities and that ovulation and fertility may be significantly restored (Pasquali and Gambineri, 2002) (Table 2).

Several studies have demonstrated a beneficial impact of weight loss on insulin resistance and hyperinsulinaemia in PCOS. In a first non-controlled study (Pasquali et al., 1989), 20 obese anovulatory women were evaluated, 14 with PCOS and 6 with the hyperandrogenism–insulin resistance–acanthosis nigricans syndrome, before and after an average of 8 months on a hypocaloric dietary regimen. After a mean weight loss of 9.7 kg (from 85.9 ± 13.1 to 76.1 ± 14.1), glucose-stimulated insulin concentrations significantly decreased, consistent with an improvement in insulin sensitivity. The beneficial effect of diet-induced weight loss on fasting and glucose-stimulated insulin concentrations was subsequently confirmed by other controlled and non-

**Table 2. Summary of the beneficial effects of weight loss in obese women with PCOS (modified from Pasquali et al., 1997, with permission of the editor).**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total and visceral body fat</td>
<td>Reduced</td>
</tr>
<tr>
<td>Hirsutism score</td>
<td>Improved</td>
</tr>
<tr>
<td>Menstrual cycles (no.)</td>
<td>Improved</td>
</tr>
<tr>
<td>Ovulation rate</td>
<td>Improved</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>Improved</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>Improved</td>
</tr>
<tr>
<td>Acne (?)</td>
<td>Improved</td>
</tr>
<tr>
<td>Androgens (testosterone)</td>
<td>Reduced</td>
</tr>
<tr>
<td>Insulin</td>
<td>Reduced</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Reduced</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Improved</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>Improved</td>
</tr>
<tr>
<td>SHBG</td>
<td>Unchanged/increased</td>
</tr>
<tr>
<td>LH</td>
<td>Unchanged/decreased</td>
</tr>
</tbody>
</table>
Dietary-induced weight loss also has important beneficial effects on androgen concentrations and related clinical features. Harlass and coworkers (Harlass, 1984) first reported an increase in SHBG along with a decrease in total and free testosterone in a small group of obese anovulatory women after weight loss of 4.8–18% (initial 103.4 kg; final 92.1 kg). In subsequent larger non-controlled studies that have been recently reviewed (Pasquali and Gambineri, 2002), a significant reduction of total and free testosterone concentrations after dietary induced weight loss was confirmed. Several other studies have obtained similar findings. In contrast, Andersen and co-workers (1995) reported the results of a 24-week hypocaloric diet in which no significant change in testosterone concentrations was noted. All the studies mentioned above involved significant caloric restriction. On the other hand, in another study in which a lifestyle modification programme that did not involve significant caloric restriction resulted in 2–5% weight loss, the free testosterone index fell by 21% (Huber-Buchholz et al., 1999). In most studies, an increase in SHBG concentrations has been repeatedly reported, which implies an impact on the free testosterone concentrations or bioavailable hormone reaching the target tissues. Diet-induced reduction of body weight has been demonstrated to decrease the activity of P450c17α, a key enzyme involved in the ovarian androgen production (Jakubowicz and Nestler, 1997). The key factors responsible for these effects appear to be the reduction of insulin concentrations associated with an improvement in the insulin-resistant state. Notably, weight loss does not alter androgen concentrations in non-PCOS obese women (Jakubowicz and Nestler, 1997), therefore confirming that the over-stimulation of ovarian steroidogenesis by inappropriately high circulating insulin is a specific feature of PCOS. The reduction of leptin concentrations after weight loss may represent an additional mechanism favouring the reduction of ovarian steroid secretion in obese PCOS women, leptin being involved in the regulation of endocrine ovarian function (Gambineri et al., 2002). Hirsutism tends to significantly decrease in most obese PCOS women after weight loss (Gambineri et al., 2002). Since this effect can be further significantly increased by the administration of antiandrogens, particularly flutamide, this combined treatment should be taken into account while planning therapeutic strategies in obese PCOS women presenting with severe hirsutism.

As reported in a recent review, weight reduction also has a potential benefit on lipid abnormalities, such as an increase in HDL-cholesterol and a decrease in triglyceride concentrations (Pasquali et al., 1997). However, data are insufficient and long-term results are not available.

Chronic anovulation is a common feature of PCOS patients, and the restoration of normal menstrual cycles and of ovulatory function represents the primary goal to be achieved for many women with PCOS. Evidence exists that dietary-induced weight loss may improve both menses abnormalities and spontaneous ovulation in the majority of affected women (Harlass et al., 1984; Clark et al., 1995; Hollman et al., 1996; Crosgnani et al., 2002). On the other hand, it should be noted that available data on the consequences of weight loss on menses and ovulatory abnormalities among obese women with PCOS were obtained in uncontrolled prospective studies, or in studies including a control group who failed to complete the study programme.

In the last decade, insulin sensitizers, such as metformin, have been widely used in the treatment of anovulation and infertility in PCOS women, Velasquez and coworkers (1994) were the first to demonstrate that metformin administration in obese PCOS women was not only able to significantly improve insulin concentrations, but also to decrease LH and testosterone concentrations, regardless of changes in body weight, with a significant improvement of menses abnormalities in most patients. The finding of the beneficial effect of long-term metformin treatment on fertility has been confirmed by many other studies. Recently, several reviews have focused on the clinical efficacy of metformin in the treatment of hyperandrogenism, and anovulation or infertility in PCOS women (Ehrmann, 1999; Kim et al., 2000; De Leo et al., 2003; Lord et al., 2003; Oberfield, 2003). In the majority of the reviewed studies, however, metformin was given alone, without energy restriction. Some years ago, a 6-month double-blind controlled study was performed, in order to investigate the effects of a combined metformin administration (500 mg twice daily) and hypocaloric diet on insulin, androgens and fat distribution in a group of abdominally obese women with and without PCOS (Pasquali et al., 2000). A greater reduction of body weight and abdominal fat was found, particularly the visceral depots, and a more consistent decrease of serum insulin and testosterone concentrations after metformin administration in PCOS obese women when compared with placebo; these changes were also associated with a significant improvement in hirsutism and menstrual abnormalities. The effects of metformin were confirmed to be additive to those of the hypocaloric dietary treatment, most of the benefits also being present in the dieting group treated with placebo. These same conclusions were achieved in another more recent study...
investigating the effect of metformin and flutamide, a pure antiandrogen, given alone or in combination, added to a hypocaloric diet in obese women with PCOS (Gambineri et al., 2004). It is suggested that, at least in women with PCOS and obesity, insulin sensitizers should be administered together with dietary advice, rather than alone.

The mechanisms responsible for the beneficial effect of weight loss on menses alterations and fertility definitely depend on the co-existent reduction of both hyperinsulinaemia and hyperandrogenism. This is further confirmed by studies using insulin sensitizers, such as metformin and tiazolidinediones, in PCOS women with insulin resistance, demonstrating that by improving insulin resistance and associated hyperinsulinaemia, androgen concentrations may decline, menstrual abnormalities may improve and ovulation may be restored in most women, regardless of weight loss and even after just a few weeks of pharmacological treatment. On the other hand, insulin seems to be involved in the interruption of the normal follicle maturation, favouring the formation of atretic follicles (Dunaif, 1997). The granulosa cell maturation arrest and the resulting deficient aromatase activity of atretic follicles may, in turn, be directly responsible for the increased ovarian androgen secretion. Further factors involved in the regulation of ovarian function are IGF and the IGF-binding protein (IGFBP) family. High concentrations of expression of IGF and low concentrations of expression of inhibitory IGFBP in healthy follicles, and the reverse in atretic follicles, indicate that the concentration of bioavailable IGF may play an additional role in regulating follicular growth and steroid synthesis and metabolism (Poretsky et al., 1999). Whether dietary modifications and weight loss may influence this system in PCOS women is, however, unknown, nor are data obtained in experimental animal models available.

To conclude, it is believed that weight loss using dietary or behavioural interventions should be used as a first-line therapy in all obese insulin-resistant PCOS women, prior to any pharmacological treatment aimed at improving menses cyclicity and ovulation. In such cases, even a reduction of less than 5% in body weight often leads to the restoration of normal cycles, especially if a sustainable programme of dietary changes and exercise is implemented. This suggests that the effects of calorie restriction may be more important than weight loss by itself, although this remains to be proven. Moreover, even if a patient’s ovulatory dysfunction persists after weight loss, it can also be expected that a favourable response to clomiphene citrate (Shepard et al., 1979; Imani et al., 1998) or injectable gonadotrophin treatment will be more likely (Franks and Hamilton-Fairley, 1996).

One problem is represented by the categorization and selection of women responding to weight loss before starting the therapeutic programme. One group (Pasquali et al., 1989) attempted to define the clinical and laboratory characteristics of those obese anovulatory women who responded to weight reduction in terms of amelioration of menstrual function and those who did not. However, no significant differences were found in the clinical and laboratory data between those women who had significant improvement in menstrual cyclicity compared with those who did not. Similarly, there were no obvious differences between those who conceived and those who did not.

Which diet is best? A role for different nutrient composition?

In search of the best diet to improve fertility and hormonal alterations in obese PCOS women, Moran et al. (2003) carried out a short-term study to investigate the effectiveness of a moderately energy restricted low protein–high carbohydrate (15 and 55% respectively) versus a high protein–low carbohydrate (25 and 40% respectively) diet. The authors found that both diets had a similar effect on body weight loss, glucose and insulin response to a standard meal test, with marginal differences in androgen concentrations in favour of the low protein–high carbohydrate diet. No other studies have investigated the efficacy of other different diets or of a selected manipulation of the macronutrient without energy restriction. Moreover, there are no studies on the potential benefit of short-term versus long-term lifestyle manipulation, or on the effect of mild-to-moderate weight loss versus sustained weight loss. Issues for which more detailed data are needed also include the effect of lifestyle intervention in normal-weight PCOS women, whether some differences may exist according to ethnic variability, the effect of previous dietary habits, the effects of dietary manipulation on acne and hirsutism, pregnancy and neonatal outcomes, and, finally, long-term effects on diabetes and cardiovascular diseases.

Conclusions

To summarize, weight loss reduces androgen and insulin concentrations, improves insulin sensitivity and lipid profile, and restores normal menses cycles, ovulation and fertility in a large number of obese PCOS women. In addition, a moderate weight loss has been described to achieve the same effects as a more sustained weight loss. This has an important impact on clinical practice, in consideration of the difficulty worldwide in losing weight and in maintaining long-term weight loss in the majority of obese patients. Unfortunately, not all women respond positively to weight loss and at present the identification of responder versus non-responder patients cannot be based on scientific support. Therefore, besides obesity, insulin resistance should represent the key prerequisite for interventional therapeutic programmes. The quality of diet should also be taken into account in interpretation of the results or to achieve a therapeutic goal. It is uncertain whether it is merely caloric restriction or the composition of the diet that is important in reducing insulin and androgen concentrations. Long-term trials investigating the effects of weight maintenance over several years are also needed. Moreover, whether hypocaloric dieting combined with chronic treatments with insulin sensitizers may be more effective than diet alone is still under debate. At the present time, it is believed that any treatment of women with obesity and PCOS should firstly include a long-term low-calorie diet schedule, possibly in association with physical exercise, in order to achieve weight loss and related benefits on hormonal and metabolic abnormalities and menses and ovulation dysfunction. This therapeutic schedule might be applied even in conjunction with other pharmacological procedures aimed at improving hirsutism, ovulation and fertility rates.
Outlook - Effects of dietary changes on PCOS - R Pasquali & A Gamberini

References


Oberfield SE 2003 Metabolic lessons from the study of young adolescents with polycystic ovary syndrome – is insulin, indeed, the culprit? Journal of Clinical Endocrinology and Metabolism 85, 3520–3525.
Pasquali R, Casimirri F, Vicenati F 1997 The beneficial effect on fertility in women with obesity and polycystic ovary syndrome. Human Reproduction 12 (suppl. 1), 82–87.
Urbanek M, Legro RS, Driccall DA et al. 1999 Thirty-seven candidate genes for polycystic ovary syndrome: strongest evidence for linkage is with follistatin. Proceedings of the National Academy of Science USA 96, 8573–8578.


Received 7 January 2004; refereed 23 January 2004; accepted 5 February 2004.