Weight control and its beneficial effect on fertility in women with obesity and polycystic ovary syndrome

R.Pasquali¹, F.Casimirri and V.Vicennati

Endocrine Section, Department of Internal Medicine and Gastroenterology, St. Orsola-Malpighi Hospital, Alma Mater University, Via Massarenti 9, 40138 Bologna, Italy

¹To whom correspondence should be addressed

Obesity may be an important pathogenetic factor involved in the development of hyperandrogenism in women with polycystic ovary syndrome (PCOS). Among several other mechanisms, hyperinsulinaemia plays a fundamental role, due to its gonadotrophic function, which has been demonstrated both in vitro and in vivo. Therefore, not surprisingly, weight loss may be expected to have several beneficial effects upon clinical, endocrinological and metabolic features of obese women presenting with PCOS. In particular, weight loss appears to be associated with a significant improvement in menses abnormalities, ovulation and fertility rates, and with a reduction of hyperandrogenism, hyperinsulinaemia, and altered gonadotrophin pulsatile secretion. The central role of improved insulin concentrations and insulin-resistant state is emphasized by the fact that similar effects can be achieved by both short- and long-term administration of metformin, an insulin-lowering drug which ameliorates peripheral insulin action in non-diabetic insulin resistant states. We therefore recommend weight loss as a first-line therapeutic option in all women with obesity and PCOS.

Key words: fertility/obesity/polycystic ovary syndrome/weight loss

Obesity, polycystic ovary syndrome and infertility.

A great number of women with polycystic ovary syndrome (PCOS) are overweight or obese. This association has aroused a great deal of interest in recent years, particularly since the discovery that PCOS women are often hyperinsulinaemic and that the degree of hyperandrogenism may be positively and significantly correlated with that of hyperinsulinaemia (Burghen et al., 1980; Poretsky and Kalin, 1987). The association between obesity and menstrual disorders, hyperandrogenism and polycystic ovaries was firstly described by Stein and Leventhal (1935) and subsequently confirmed by many other authors (Roger and Mitchell, 1952; Franks, 1989). Usually there is a close relationship between the onset of menstrual disorders and hirsutism and that of overweight, particularly at the time of menarche and during puberty (Pasquali et al., 1985). Several lines of evidence suggest that the onset of obesity in this period of life could play a crucial role in the subsequent development of PCOS (Yen, 1980). Although comparisons of the hormonal status between obese and non-obese women with PCOS have yielded conflicting results (for review, see Pasquali and Casimirri, 1993), there are numerous studies indicating that obese PCOS women may have more severe hyperandrogenism and lower sex hormone-binding globulin (SHBG) concentrations with respect to their non-obese counterparts. Obese PCOS women may also have more severe hirsutism (Franks, 1989; Pasquali and Casimirri, 1993) and menstrual irregularities and they often present with acanthosis nigricans (Franks, 1989; Pasquali and Casimirri, 1993). Moreover, they are frequently hyperinsulinaemic and insulin resistant, both disorders which can only be partially explained by the degree of overweight and excess body fat (Poretsky and Kalin, 1987; Pasquali and Casimirri, 1993). The relative prevalence of visceral fat distribution seems to partially
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Figure 1. Schematic representation on hormonal, metabolic, and nutritional factors theoretically involved in the pathophysiology of polycystic ovary syndrome (Pasquali and Casimirri, 1993).

explain both insulin resistance and hyperinsulinemia in PCOS, regardless of whether they are obese or non-obese. In fact, we have recently demonstrated that the pattern of body fat distribution may have significantly different effects not only on hormones and metabolism, but also on the clinical features of women with PCOS (Pasquali et al., 1994). We examined a large group of 97 consecutive hyperandrogenic women with PCOS and we divided them into three groups, based on their waist-to-hip ratio values, which can be adequately used to define abdominal versus peripheral body fat distribution. Compared with the group with peripheral fat prevalence and after adjusting for body mass index and age, PCOS women with abdominal body fat distribution had higher luteinizing hormone (LH), oestrone and androstenedione concentrations, higher concentrations of both fasting and glucose-stimulated insulin, a greater prevalence of hirsutism, acanthosis nigricans and obesity, and a more atherogenic lipid profile (Pasquali et al., 1994).

Pathophysiological aspects of the obesity-related hyperandrogenism in women with PCOS

There may be various mechanisms by which obesity may influence hyperandrogenism in pre-menopausal women with PCOS. As we have discussed in a previous review (Pasquali and Casimirri, 1993), candidate factors may be oestrogens, insulin and the insulin growth factor system, the opioid system, and diet (Figure 1). It is well known
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that obesity, particularly the abdomino-visceral (central) phenotype, is associated with supranormal oestrogen production, due to increased activity of the aromatase system. Moreover, several authors have reported that PCOS women with central adiposity may have higher oestrone concentrations compared with women with a peripheral fat distribution (Pasquali et al., 1994; Morales et al., 1996). In addition, reduced SHBG values, which usually accompany obesity, may favour greater amounts of free oestradiol to be delivered to target tissues, including fat tissue. Obese women are also characterized by reduced formation of inactivated oestrogen metabolites (i.e. oestradiol metabolites hydroxylated in the C2 position and oxidized at the 17 position), and by greater availability of oestrone sulphate in the target tissues (for revision, see Pasquali and Casimirri, 1993). All these conditions concur in favouring a hyperoestrogenic state in obese women. Since oestrogens exert a positive feed-back regulation upon gonadotrophin release, Yen (1980) suggested that increased ovarian androgen production in obese PCOS women could be partly favoured by increased LH secretion secondary to prevailing hyperoestrogenaemia.

Hyperinsulinaemia, which represents a genuine feature of both obesity and PCOS, appears to play a pivotal role in favouring the development of hyperandrogenaemia in obese women with PCOS. Its role was first suggested on the basis of the significant positive correlation observed between the degree of hyperandrogenism and that of hyperinsulinaemia in women with PCOS (Burghen, 1980). In-vitro studies have subsequently demonstrated that insulin is capable of stimulating androgen secretion by the ovaries, reducing aromatase activity in peripheral tissues and, finally, reducing SHBG synthesis in the liver. There are several recent excellent reviews on this topic (Poretsky and Kalin, 1987; Poretsky et al., 1991; Nestler et al., 1992). In vivo, numerous studies have demonstrated that both acute and chronic hyperinsulinaemia can stimulate testosterone production and that suppression of insulin concentrations can conversely decrease androgen concentrations (Nestler et al., 1992). The fact that hyperinsulinaemia and insulin resistance are invariably associated with obesity and, particularly, abdominal-visceral obesity (Kissebah and Peiris, 1989), represents the basis for the hypothesis supporting its role in the development of hyperandrogenism in PCOS women. Preliminary data exist demonstrating that suppression of insulin concentrations by diet (Pasquali et al., 1989; Kiddy et al., 1990) or chronic metformin administration (Velazquez et al., 1994; Nestler and Jabukowicz, 1996) can improve not only the hyperandrogenic state but also the degree of hirsutism and the fertility rate. These data obviously add further emphasis to the role of obesity-related hyperinsulinaemia as a co-factor responsible for increased androgen production in obese PCOS women.

Obesity, as well as PCOS, is also characterized by increased opioid system activity, and studies in vitro and in vivo have shown that β-endorphin is able to stimulate insulin secretion (Feldman et al., 1983). Moreover, there are data suggesting that the administration of β-endorphin can determine a reduction of LH release at the hypophyseal level in normal but not PCOS women (Reid et al., 1981). The possibility that increased opioid activity may favour the development of hyperinsulinaemia and, in turn, of hyperandrogenism, is further supported by the finding that both acute and chronic administration of opioid antagonists, such as naloxone and naltrexone, suppresses both basal and glucose-stimulated insulin blood concentrations in a small group of obese women with PCOS and acanthosis nigricans (Givens et al., 1987).

Finally, there are theoretical possibilities that diet may play some role in the development of the obesity–PCO syndrome, although very few studies have addressed this issue. However, there are data suggesting that women eating vegetarian-rich and fibre-rich diets may have lowered androgen blood concentrations with respect to those following typical Western diets (Hill et al., 1980). Moreover, a very high lipid intake has been described in PCOS women by some authors (Wild et al., 1985) and there are studies reporting a significant negative correlation between lipid intake and SHBG values (Wild et al., 1985). As both low fibre and high lipid intake represent risk factors for the development of obesity, we believe that the possibility that diet may also partly favour hyperandrogenism in susceptible individuals is an attractive hypothesis, which merits further investigation.
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Table I. Effects of weight loss on hormones, metabolism, and clinical features in obese women with polycystic ovary syndrome

<table>
<thead>
<tr>
<th>Effect Parameters</th>
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<tbody>
<tr>
<td>Reduced Total and visceral body fat</td>
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<tr>
<td>Improved Hirsutism score</td>
</tr>
<tr>
<td>Reduced Menstrual cycles (no.)</td>
</tr>
<tr>
<td>Improved Fertility rate&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reduced Acanthosis nigricans</td>
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<tr>
<td>Improved Testosterone</td>
</tr>
<tr>
<td>Reduced Androstenedione</td>
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<tr>
<td>Improved Insulin</td>
</tr>
<tr>
<td>Unchanged/unchanged Sex hormone binding globulin</td>
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<tr>
<td>Unchanged/reduced Luteinizing hormone</td>
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<sup>a</sup>Includes ovulation and pregnancy rate.

Beneficial effect of weight loss on clinical features, hormones and metabolism in women with obesity and PCOS

The effects of weight loss on the clinical course of women with obesity and PCOS has been partly neglected, whereas impressive clinical efforts have been made in the pharmacological management of the syndrome. Nevertheless, there is long-standing clinical evidence concerning the efficacy of weight reduction upon both clinical and endocrinological features of obese women presenting with PCOS (Table I). As previously reported by others, we have demonstrated that weight loss may improve menstruation abnormalities and, most importantly, both ovulation and fertility rate (Pasquali et al., 1989). Moreover, in two separate studies we found that hirsutism significantly improved in most of the patients, as did acanthosis nigricans (Pasquali et al., 1985b, 1989). Reduction of hyperandrogenaemia appears to be the key factor responsible for these effects. In fact, peripheral testosterone, androstenedione and dehydroepiandrosterone sulphate values were significantly reduced after weight loss in obese PCOS women (Pasquali et al., 1989). These findings were subsequently confirmed by Kiddy et al. (1990) in women who had obtained even only moderate weight loss (>5 kg) after long-term low calorie regimen. Moreover, the same authors found that weight loss was associated with a significant increase of SHBG and a reduction of the free-testosterone values. Conversely no significant benefit was observed in women who lost <5 kg, maintained their excess body weight or increased it. Interestingly, there are studies demonstrating that weight loss may decrease LH pulse amplitude (Halass et al., 1984) which, in turn, can be followed by reduced androgen production.

An important beneficial effect of weight reduction is the reduction of the degree of hyperinsulinaemia. This fact obviously improves the insulin resistant state. Changes in testosterone and insulin (both basal and glucose-stimulated) concentrations may be significantly correlated, regardless of body weight variations (Pasquali et al., 1989; Kiddy et al., 1990). Recent studies have suggested that hyperinsulinaemia may be responsible for increased activity of the activity of the ovarian cytochrome P450c17 system, which has been suggested as playing a key role in determining ovarian hyperandrogenism in many PCOS women (Ehrmann et al., 1992). Reduction of insulin concentrations by metformin (Nestler and Jabukowicz, 1996) and diet (D.Jabukowicz and J.E.Nestler, personal communication) has been demonstrated to reduce this enzyme activity and, consequently, ovarian androgen production. Recently we found that obese PCOS women undergoing hypocaloric dietary treatment coupled with antiandrogen (cyproterone acetate plus ethynylestradiol) or metabolic drugs (such as metformin or dexfenfluramine) had a similar degree of weight loss and also a similar reduction of testosterone serum concentrations (unpublished data). Therefore, improving peripheral sensitivity by both diet and drugs may be as effective as diet and antiandrogen therapy in reducing the degree of hyperandrogenism in women with obesity and PCOS.

To summarize, the principal effects of weight loss on both clinical and endocrinological features in women with obesity and PCOS include not only the reduction of total and particularly visceral fat, but also improve menstrual cycles and fertility rate, reduce androgen and insulin concentrations, and improve insulin sensitivity. The effects of dietary-induced weight loss on androgens seem to be peculiar to obese hyperandrogenic women, since they have not been reported in non-PCOS obese women (Grenmann et al., 1986).

Conclusions and perspectives

We have briefly reviewed the main data supporting the idea that obesity may represent a pathogenetic
factor in susceptible individuals in developing hyperandrogenism and PCOS and we have presented the data demonstrating the effects of weight loss on clinical features, and hormonal and metabolic abnormalities of women with obesity and PCOS. Future research will be directed towards: (i) characterization of the cluster of PCOS women in whom obesity may play a key role in determining the syndrome, by also defining their genetic background; (ii) defining the role of different dietary manipulations to manage these patients, particularly with regard to insulin-lowering regimens; (iii) defining the role of new antiandrogenic drugs, such as flutamide and finasteride, and that of metabolic drugs, such as metformin, dexamfetamine and troglitazone.

At the present time, however, we believe that any treatment of women with obesity and PCOS should firstly include a 3–6 month low-calorie diet schedule in order to obtain weight loss and related benefit with regard to both clinical and endocrinological features of the patients. This therapeutic schedule might be applied even in conjunction with other pharmacological procedures aimed at achieving pregnancies, since weight loss has been demonstrated to favour ovulation and improve fertility in obese women with PCOS.

References
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