

Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet

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BACKGROUND: This prospective study evaluated the effect of weight reduction on anthropometric indices and ovarian morphology in anovulatory overweight patients with polycystic ovary syndrome (PCOS). **METHODS:** Thirty-three anovulatory overweight patients with PCOS were enrolled in the study. All had patent Fallopian tubes and chronic anovulation: 27 of them were oligo-amenorrhoeic. The partners were normospermic. Patients were prescribed a 1200 kcal/day diet, and physical exercise was recommended. Anthropometric indices and ovarian imaging parameters were assessed at baseline and after weight loss of 5 and 10%. **RESULTS:** Twenty-five patients (76%) lost at least 5% of their body weight. Eleven of these patients (33%) reached a 10% decrease in weight. Waist circumference at the umbilical level, hip circumference, four skin folds, body mass index and fatty mass ratio were significantly reduced after 5 and 10% weight loss. Ovarian morphology changed during the diet: we observed a significant reduction in ovarian volume and in the number of microfollicles per ovary. Among the 27 patients with oligo-amenorrhoea, 18 had a resumption of regular cycles and 15 experienced spontaneous ovulation; 10 spontaneous pregnancies occurred in patients who lost at least 5% of their weight. **CONCLUSIONS:** Weight loss through a controlled low-calorie diet improves anthropometric indices in obese PCOS patients, reduces ovarian volume and microfollicle number and can restore ovulatory cycles, allowing spontaneous pregnancy.

Key words: diet/fertility/ovarian morphology/PCOS

Introduction

Irregular menstrual cycles, reduced spontaneous and assisted fertility and an increased risk of miscarriage are risks associated with obesity that are often overlooked (Grodstein *et al.*, 1994; Barbieri, 2001). Excessive weight and central distribution of body fat are both related to an increased risk of normogonadotrophic anovulation (Zaadstra *et al.*, 1991). The mechanism through which weight impairs fertility is largely unknown, but these patients have a lower concentration of sex hormone-binding globulin (SHBG) (Kiddy *et al.*, 1990) and increased androgens, insulin secretion and insulin resistance (Barbieri *et al.*, 1988). It is of note that a positive significant correlation has been reported between ovarian volume and body mass index (BMI) in patients with polycystic ovary syndrome (PCOS) (Balen *et al.*, 1995).

Weight loss in obese PCOS patients reduces circulating androgens and raises SHBG (Kiddy *et al.*, 1990; Hollmann *et al.*, 1996), enhances insulin sensitivity (Guzick *et al.*, 1994; Andersen *et al.*, 1995; Holte *et al.*, 1995; Huber-Buchholz *et al.*, 1999) and regularly improves menstrual cyclicity and fertility rates (Bates and Whitworth, 1982; Franks *et al.*, 1991; Pasquali

et al., 1997). On clinical grounds, weight loss can re-establish ovulation in obese anovulatory patients or improve their response to ovulation induction (Clark *et al.*, 1995, 1998; Crosignani *et al.*, 1999, 2002). No data are available on ovarian morphology systematically checked during weight loss.

The aim of this study was to correlate weight reduction and anthropometric indices, ovarian morphology, menstrual cyclicity and spontaneous fertility in overweight PCOS patients following a diet combined with a programme of physical exercise.

Materials and methods

Between June 1998 and June 2000, overweight patients with primary infertility associated with chronic anovulation, polycystic ovaries and obesity were recruited by the Infertility Unit of the Department of Obstetrics and Gynecology of the University of Milan. Inclusion criteria were as follows: (i) BMI >25 kg/m²; (ii) duration of infertility at least 6 months; (iii) chronic anovulation demonstrated by oligo-amenorrhoea or after transvaginal ultrasound monitoring of follicular growth in one cycle and plasma progesterone concentration <6 ng/ml in the midluteal phase, according to a protocol described elsewhere

Table I. Characteristics of the 33 patients enrolled in the study

Characteristics	Mean \pm SD
Age (years)	30.7 \pm 3.9
Height (cm)	160.1 \pm 6.4
Weight (kg)	82.1 \pm 10.1
BMI (kg/m ²)	32.1 \pm 4.2
Duration of infertility (months) ^a	24 (6–168)
Regular menstrual cycles ^b	6 (18%)

^aMedian (range).

^bNumber (%). Regular menstrual cycles are defined as regular cycles with mean length <35 days.

(Guermendi *et al.*, 2001); (iv) polycystic ovaries diagnosed according to Adams *et al.* (1985, 1986) by transvaginal ultrasound scan; (v) no other obvious causes of infertility; (vi) no previous ovarian stimulation; (vii) no other endocrinological abnormalities such as hyperprolactinaemia, hypothyroidism or congenital adrenal hyperplasia which were excluded by prolactin, TSH and 17-OH-progesterone serum dosages; and (viii) informed consent. A detailed personal history was collected after recruitment, before starting the diet.

Characteristics of the patients are reported in Table I. The study design is presented in Figure 1. Patients were prescribed a 1200 kcal/day diet (20% protein, 25% lipids, 55% carbohydrates plus 30 g of fibre/week); we did not directly ascertain if the prescribed diet was followed: compliance with diet treatment was ascertained indirectly by evidence of weight reduction. Aerobic exercise was recommended. No particular exercises were specified, with no specific duration or frequency. Patients were simply advised to do some swimming or aerobics at least once or twice a week. They were prescribed regular controls and weight assessment every 6–8 weeks. The maximum time to 5% body weight reduction response was 6 months: non-responders after 6 months dropped out and underwent ovulation induction. Similarly, patients who achieved a 5 or 10% reduction in body weight and subsequently did not respond in terms of resumption of ovulatory cycles within 6 months also dropped out to undergo ovulation induction.

An echographic and anthropological evaluation was done at study entry and when patients reached 5 and 10% body weight loss. At study entry, all women were asked to record the date of their menses for the entire study period and were prescribed serial serum progesterone assessments in mid-luteal phase if regular menstrual cycles resumed. Regular menstrual cycles were defined as an interval of <35 days between two successive menses in at least two consecutive cycles. Cycles were considered ovulatory when at least two serum progesterone assessments in mid-luteal phase were >6.0 ng/ml and/or a pregnancy occurred. Pregnancy was defined as the presence of a gestational sac detected by ultrasound at 6–7 weeks gestation.

Ovarian volume and the number of microfollicles were evaluated by transvaginal ultrasonography (Ansaldo 580 system and a transvaginal 6.5 MHz probe). Ovarian volume was calculated as $4/3\pi$ (1/2 diameter)³, where the diameter was taken as the mean of the height, width and depth of the ovary, in the absence of a dominant follicle (Conway *et al.*, 1989). Microfollicles were counted by progressive ultrasound scan of the entire ovary. All ultrasonographic examinations were done on days 3–5 of a spontaneous or progestin-stimulated cycle by the same operator (M.C.) who was blinded to the study design. Intra-observer variation assessed in a preliminary series of 10 overweight patients with polycystic ovaries was <5%.

Body height and weight were measured, respectively, without shoes and without clothes. Waist circumference was recorded as the smallest measurement between the iliac crest and the lateral costal margin; hip

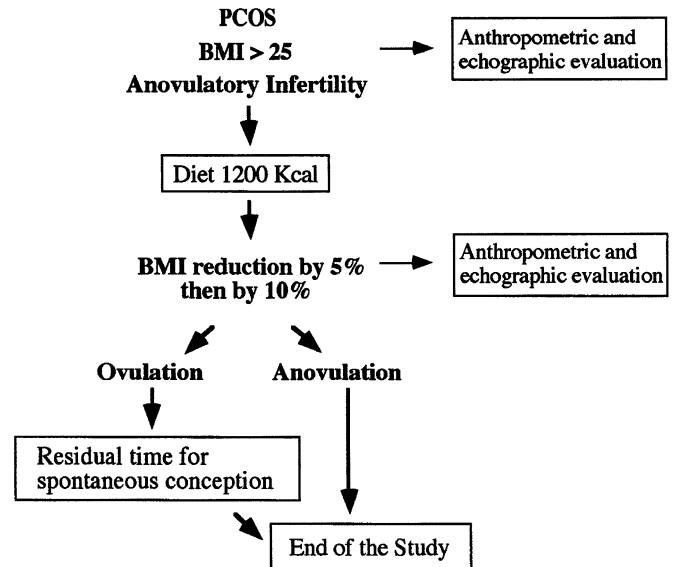


Figure 1. Protocol of the study. Infertile patients with anovulation due to PCOS, BMI >25 kg/m² and no other known causes of infertility were enrolled. Subjects were prescribed a 120 kcal/day diet (20% protein, 25% lipids, 55% carbohydrates plus 30 g of fibre/week) and physical exercise was recommended. A complete evaluation was done at study entry and when patients reached 5 and 10% body weight loss. During the study, patients were not included in any other pro-fertility protocols. The study period was limited to 12 months from recruitment.

circumference was the largest measurement over the buttocks, using a 1 cm wide metal measuring tape (World Health Organization, 1997). Subscapularis, tricipital, bicipital and suprailiac folds were measured using a Holtain–Tanner/Whitehouse plicometer (Holtain Ltd, UK). Body composition was analysed by whole body bioelectrical impedance analysis (BIA). Bioelectric impedance is a relatively new method to assess body fat composition by calculating total body fluid (Goodpaster *et al.*, 2002; Jinno *et al.*, 2000). The BIA was performed using a Multifrequency Human-Im Scan (Dietosystem, Milan, Italy) which analyses bioelectric behaviour over a range of 256 frequency values from 300 Hz to 100 KHz. The test was completely non-invasive and used electrodes in an adhesive gel which were applied in pairs (source electrodes and sensor electrodes) to the right hand (third metacarpal joint) and to the right foot (second metatarsal joint, on the dorsal side) of patients lying down on an examination table in a supine position with the legs slightly apart. The surface area of the electrodes was at least 5 cm². The standard supplied software includes, out of many available parameters, weight and percentage lean and fat mass. The fat mass ratio (fat mass/total body mass) was calculated directly by the software (Trovato *et al.*, 1996).

All anthropometric measurements were made by the same operator (A.G.) who was blinded to the study design. Intra-observer variation, assessed in a preliminary series in 10 overweight patients with polycystic ovaries, was <5%.

Data were analysed using the Statistics Package for Social Sciences (SPSS, Chicago, IL, USA). Baseline characteristics of patients who did and did not lose weight were compared using categorical, unpaired non-parametric rank tests and analysis of variance (ANOVA) using *post hoc* tests. Paired analyses were performed to evaluate anthropometric and ultrasonographic modifications in patients who achieved weight loss. Specifically, paired non-parametric rank test or paired Student *t*-test adjusting for multiple comparisons were

Table II. Anthropometric data in patients at study entry and after weight loss

	Basal (<i>n</i> = 33)	5% weight loss (<i>n</i> = 25)	10% weight loss (<i>n</i> = 11)	<i>P</i>
Waist circumference (cm)	100 ± 8	94 ± 9	86 ± 7	0.005
Hip circumference (cm)	111 ± 8	106 ± 7	101 ± 7	0.001
Waist/hip ratio ^a	0.90 (0.79–1.05)	0.88 (0.78–0.99)	0.86 (0.78–0.98)	NS
Tricipital fold (mm)	29 ± 5	27 ± 6	24 ± 6	0.05
Bicipital fold (mm)	22 ± 6	19 ± 6	16 ± 5	0.02
Subscapularis fold (mm)	33 ± 4	32 ± 5	28 ± 6	0.01
Suprailiac fold (mm)	27 ± 6	24 ± 7	19 ± 6	0.01
Fatty mass ratio ^a	0.42 (0.36–0.52)	0.38 (0.25–0.51)	0.36 (0.24–0.42)	0.02

The only variable which did not significantly decrease during weight loss was the waist/hip ratio. For all the other variables, all three comparisons were statistically significant, and the levels of significance adjusted for multiple comparisons were at least below the reported value.

Data are expressed as mean ± SD, unless specified otherwise.

^aData are expressed as median (range). NS: not significant.

employed, as appropriate. *P*-values of <0.05 were considered significant.

Results

Twenty-five of the 33 patients (76%) lost at least 5% weight, with the remaining eight (24%) failing to lose weight. Moreover, 11 patients (33%) achieved a 10% decrease of body weight. The median (range) time to reach the 5 and 10% reduction in weight was 42 (21–77) and 122.5 (70–273) days respectively. More specifically, the median (range) of the percentage reduction at 5 and 10% was 5.6% (5.1–8.2) and 10.3% (10.0–11.0) respectively. None of the women who managed to lose weight was found to have gained weight during successive visits.

Anthropometric modifications are shown in Table II. A parallel reduction in ovarian volume and in the number of follicles was observed in patients who lost weight (Figure 2). Ovarian volume was reduced by 18% [95% confidence interval (CI) 7–29] in women who lost 5%, and by 27% (95% CI 10–41) in those who reached 10% weight loss. Similarly, the number of microfollicles per ovary decreased from 23.5 ± 11.5 to 19.9 ± 9.9 with 5% weight loss and to 18.3 ± 7.5 with 10% weight loss.

In order to identify factors that may predict weight loss, we compared baseline characteristics of patients who did and did not lose weight. The only anthropometric variable significantly associated with the probability of losing weight was the fatty mass ratio: indeed, the lower the basal ratio, the higher the probability of losing weight. The median (range) basal fatty mass ratios in patients who did not lose weight, patients who lost 5% and patients who lost 10% were, respectively, 0.44 (0.40–0.51), 0.42 (0.36–0.52) and 0.40 (0.36–0.47) (*P* = 0.02).

Resumption of regular menstrual cycles was reported by 18 patients (72% of the compliant subjects). In addition, 15 had ovulatory cycles during the study period (Figure 3). Ten (30%) of the 33 women enrolled became pregnant spontaneously within 12 months (Figure 3) and eight delivered singleton healthy newborns at term. Two patients were lost to follow-up after echographic assessment of a viable pregnancy at 7 and 8 weeks gestation. The pregnancy rate and percentage of women with ovulatory cycles increased to 40 and 60% respectively, when only patients who reached at least a 5% reduction in body

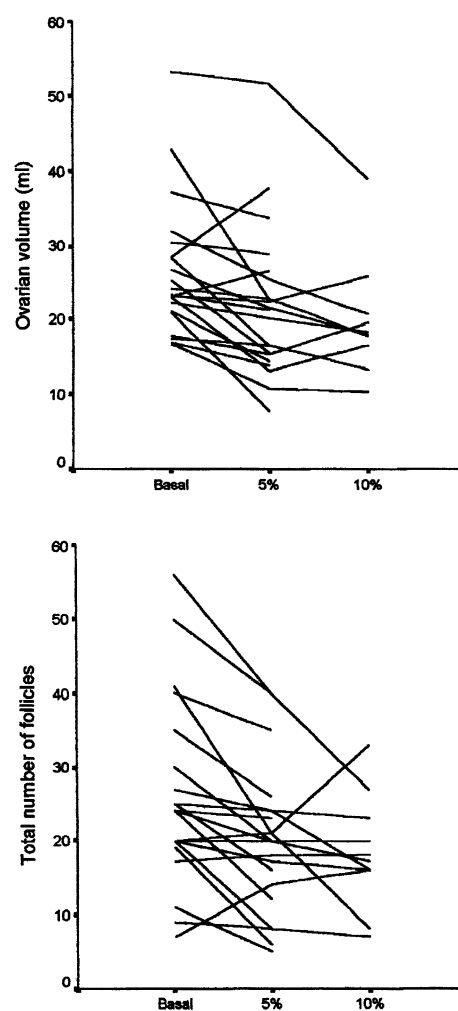


Figure 2. Ovarian volume (upper panel) and number of follicles (lower panel) in relation to body weight loss. Paired analysis was done. Data were available for, respectively, 33, 25 and 11 patients at study entry, at 5% weight loss and at 10% weight loss. Ovarian volume: *P* = 0.01 basal versus 5% weight loss, *P* = 0.02 basal versus 10% weight loss. Number of follicles: *P* = 0.001 basal versus 5% weight loss, *P* = 0.09 basal versus 10% weight loss.

weight were analysed. The eight patients who did not lose weight had no improvement in menstrual cyclicity or in their ovulatory values of progesterone, and no pregnancies occurred.

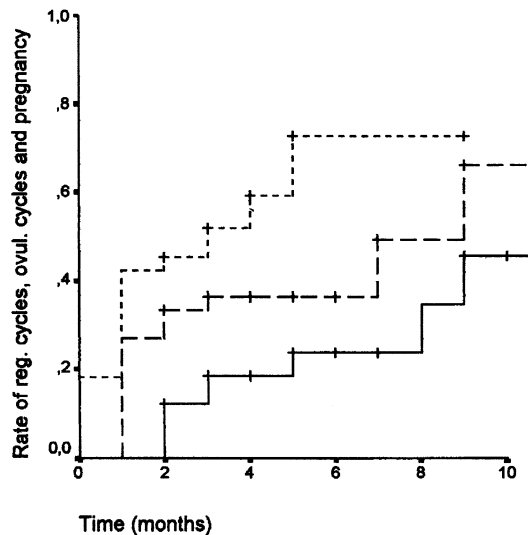


Figure 3. Cumulative rate of pregnancy (solid line) of patients with ovulatory cycles (dashed line) and of patients with regular menstrual cycles (dotted line) among the 33 women in the study. Overall, the rates of patients who became pregnant, who had ovulatory cycles and who had regular menstrual cycles were, respectively, 30% (10/33), 45% (15/33) and 55% (18/33). Vertical marks indicate censored observations due to pregnancy occurring or patients dropping out (patients who did not respond in terms of resumption of ovulatory cycles within 6 months).

Discussion

A negative effect of obesity on fertility was first noted 2500 years ago by Hippocrates, and obesity is now known to be associated with menstrual irregularities, chronic anovulation, PCOS and infertility (Reid and Van Vugt, 1987; Grodstein *et al.*, 1994; American Society of Reproductive Medicine, 2001).

According to Zaadstra *et al.* (1991), the central distribution of fat is more important than body weight in reducing fecundity. In addition, obesity is associated with an increased rate of miscarriage in women with PCOS or normal ovarian morphology (Pettigrew and Hamilton-Fairley, 1997). Obesity lowers the success rate of assisted reproduction technique (ART) cycles (Homburg *et al.*, 1989; Hamilton-Fairley *et al.*, 1992; Crosignani *et al.*, 1994; Imani *et al.*, 1998; Fedorcsak *et al.*, 2000). Overweight and obesity have a positive relationship with the risk of spontaneous abortion in women who become pregnant after assisted reproductive technology treatment (Wang *et al.*, 2002).

Insulin stimulates androgen secretion and, together with androgens, influences the pattern of body fat distribution in overweight women (Pasquali *et al.*, 1991; Sharp *et al.*, 1991; Ditkoff *et al.*, 1995). In obese women, weight loss after gastroplasty quickly restores normal insulin secretion, clearance and action on glucose metabolism (Letiexhe *et al.*, 1995).

In other studies, weight loss resulted in a significant reduction in blood glucose, insulin and androgen concentrations in obese, non-PCOS women (Hollmann *et al.*, 1996), and more consistently in obese PCOS patients (Lefebvre *et al.*, 1997; Pasquali *et al.*, 1997, 2000). In these patients, the raised production of SHBG induced by weight loss further reduces circulating free androgen (Kiddy *et al.*, 1990) and, in addition,

in PCOS patients, weight reduction enhances insulin sensitivity (Guzick *et al.*, 1994; Andersen *et al.*, 1995; Holte *et al.*, 1995; Huber-Buchholz *et al.*, 1999).

This study found a prompt improvement in the indices of body fat and its distribution, and rapid reduction of ovarian volume and microfollicle number. A possible controversy in our study may be related to the study design since our trial was not randomized. In particular, the lack of controls does not allow us to rule out that the observed effects could not be period or observer related. However, in light of current available literature on this topic that clearly demonstrates the benefits of diet (Bates and Whitworth, 1982; Franks *et al.*, 1991; Clark *et al.*, 1995, 1998; Pasquali *et al.*, 1997), we believe that a randomized trial is no more ethically tenable and practically feasible than our study. Overall, although we are unable to assess the importance of this aspect, it seems highly unlikely that our study design could play an important role in explaining the relevant modifications detected in our study population.

The mechanism through which body weight reduction modifies ovarian morphology can only be guessed: it might involve a more favourable endocrine environment after a rise in SHBG and a reduction in free androgens, and improved insulin sensitivity. The decrease in volume might be due to the reductions in microfollicles and ovarian stroma. The amount of ovarian stroma is correlated with overproduction of theca-derived steroids, particularly androstenedione (Kyei-Mensah *et al.*, 1998), in PCOS patients: a reduction in ovarian volume and in the number of microfollicles could therefore be involved in lowering circulating androstenedione and improving the clinical picture of these patients during diet treatment.

Interestingly, Falsetti *et al.* (2000) recently reported a comparable improvement in ovarian morphology with long-term pharmacological inhibition of ovarian function in 140 PCOS patients under oral contraceptive treatment. Our data show comparable and quicker changes in this easy-to-check parameter after only moderate body weight reduction; to the best of our knowledge, this is an important and original observation.

At the same time, weight loss improves menstrual cyclicity, ovulation and fertility. Clark *et al.* (1998) found that weight loss re-established ovulation in obese anovulatory patients or improved their response to ovulation induction: in a series of 67 anovulatory women, 90% resumed ovulation after weight loss and 78% conceived (Clark *et al.*, 1998). The same group confirmed these findings in a larger series (Clark *et al.*, 2000), and similar results were obtained in preliminary observations by our group (Crosignani *et al.*, 1999, 2002). In our series, among the 27 out of 33 patients with irregular menstrual cycles who lost weight, 18 re-established regular cycles. A total of 60% had ovulatory levels of plasma progesterone after weight loss. In a year of observation, 10 spontaneous pregnancies occurred in the 25 patients who lost weight (40% pregnancy rate). Neither menstrual cycle improvement, ovulatory values of progesterone nor pregnancies occurred in the eight patients who did not lose weight. In contrast, it should be noted that we obtained resumption of ovulatory cycles and pregnancy even after a slight (5%) reduction of baseline body weight.

In conclusion, weight loss is an effective treatment and should be considered the first-line approach for infertile overweight PCOS patients.

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