

## Endocrine abnormalities in ovulatory women with polycystic ovaries on ultrasound

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**Polycystic-appearing ovaries (PAO) on ultrasound have been described in a variety of endocrinopathies and also occur in ovulatory women. By some investigators this is merely referred to as 'PCO' (polycystic ovaries). Although there is controversy in this regard, we do not consider women with PAO/PCO who have no known endocrine disturbance to have polycystic ovary syndrome (PCOS) and therefore prefer not to use the term 'PCO' which is often equated with PCOS. We studied 15 ovulatory women with normal-appearing (NAO) ovaries on ultrasound and 15 matched ovulatory women with PAO/PCO. Compared to ovulatory women, 25 other women were studied who were considered to have PCOS. Of these, 15 were overweight and 10 were of normal weight. All the PCOS women had serum concentrations of luteinizing hormone (LH), testosterone, unbound testosterone, androstenedione and dihydroepiandrosterone sulphate (DHEAS) which were significantly higher ( $P < 0.01$ ) than values in the normal women, regardless of ovarian morphology. These values were similar in the two groups of ovulatory women with NAO and PAO/PCO. Fasting insulin was elevated in women with PCOS with increased body weight ( $P < 0.01$ ) and was higher than in ovulatory women with NAO and PAO/PCO and than in women of normal weight with PCOS. Serum insulin-like growth factor (IGF)-I and binding protein (BP)-3 were similar in all groups but serum IGFBP-1 was significantly ( $P < 0.01$ ) lower in those women with PCOS with increased body weight, compared to all other groups. Compared to values in ovulatory women with NAO, serum IGFBP-1 was also significantly ( $P < 0.05$ ) lower in women with PAO/PCO and those women with PCOS of normal weight. These lower values were similar in women with PAO/PCO and in normal weight women with PCOS. On an individual basis, an elevation of at least one serum androgen value was found in 33% of women with PAO/PCO. These data confirm that increased body weight accentuates the metabolic alterations in PCOS, but suggest that subtle endocrine disturbances, similar to those that are found in PCOS, may be uncovered in up to a third of ovulatory women with PAO/PCO. It appears that a**

**disturbance of the IGF/IGFBP-1 axis is common and apparently closely associated with alterations in ovarian morphology.**

*Key words:* androgens/IGFBP-1/polycystic ovary syndrome

### Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder which is characterized by the findings of hyperandrogenism and chronic anovulation (Yen, 1991; Lobo, 1991, 1995). However, there is controversy in this diagnosis, and others have considered the syndrome to occur as long as women have the ultrasound findings of polycystic ovaries (PCO) (Balen *et al.*, 1995; Homburg, 1996). It is known, nevertheless, that polycystic ovaries occur in other disorders as well, whether or not androgen excess is present (Abdel-Gadir *et al.*, 1992; Shoham *et al.*, 1992; Carmina, 1995). Indeed PCO have been found in 16–25% of 'normal' ovulatory women (Polson *et al.*, 1988; Clayton *et al.*, 1992). We have made a distinction between women with only the ultrasound findings and no disorder, and PCOS which we view to be an endocrinopathy, which requires the existence of both hyperandrogenism and anovulation. Although we are aware that a spectrum of abnormalities exists and no clear line demarcates women with PCOS from normal women, here we will attempt to describe differences and/or similarities between normal ovulatory women with polycystic ovaries on ultrasound and those women with characteristic features of PCOS who are either of normal body weight or who are overweight. While we prefer to refer to ovulatory women with merely the classic ultrasound appearance of PCO as having PAO (polycystic-appearing ovaries), to avoid confusion we will describe these patients as 'PAO/PCO'. However, we do not wish to equate these patients (PAO/PCO) with those having PCOS and our data have been collected to address the potential similarities and differences.

Recently we have studied normal ovulatory women undergoing ovarian stimulation for oocyte donation (Wong *et al.*, 1995). Although ovarian responses to gonadotrophins were exaggerated in these normal women with PAO/PCO, fertilization and other fertility criteria were similar to those of women with normal appearing ovaries (NAO). However, it remains unclear whether women with PAO/PCO only have altered ovarian morphology and no endocrine disturbance or in fact represent a cryptic or unexpressed form of the syndrome, PCOS. Accordingly we postulated that by studying androgen and growth factor parameters characteristic of PCOS (Suikkari *et al.*, 1989; Lobo, 1991; Carmina *et al.*, 1995) in normal

women with PAO/PCO, we might gain insight into alterations in ovarian morphology and the pathophysiology of PCOS.

## Materials and methods

### Subjects

A total of 55 women was studied of whom 15 were ovulatory (mean age  $28 \pm 1$  years) and had proven fertility, no hirsutism or menstrual disturbances and were found to have sonographic evidence of polycystic-appearing ovaries (Adams *et al.*, 1986). We used the following standard criteria for the ultrasound diagnosis of PAO/PCO and PCOS. Each woman had to have findings on both ovaries of  $\geq 10$  peripherally oriented cysts ( $< 8$  mm) on a sonographic plane, increased ovarian volume and increased stromal density. This diagnosis should not be confused with the normal-sized multifollicular ovary or a morphologically normal ovary during any stage of follicular development. These women were volunteers in the donor oocyte programme at the University of Southern California.

In addition, 15 ovulatory control women (mean age  $28 \pm 1$  years) with normal-appearing ovaries on ultrasound (NAO), who were also enrolled in the donor oocyte programme, were studied. The ovulatory groups (NAO and PAO/PCO) had completely normal, cyclic menstrual function and consistently elevated luteal phase progesterone concentrations.

Twenty-five women with PCOS (mean age  $25 \pm 1$  years) were studied, all of whom had hyperandrogenism and chronic anovulation. In addition, these women all had PCO which met the ultrasound criteria listed above (Adams *et al.*, 1986). PAO/PCO and NAO subjects had normal body weight (mean BMI  $21.1 \pm 0.6$  and  $20.7 \pm 0.3$  respectively) whereas women with PCOS were divided into two groups: 10 had normal body weight (mean BMI  $22.6 \pm 0.6$ ) and 15 had increased body weight (mean BMI  $27 \pm 2$ ).

### Protocol

PCO were defined by the presence of 10 or more cysts, in one ultrasonographic plane, each 2–8 mm in diameter, arranged around a dense stroma (Adams *et al.*, 1986). These criteria were applied to the inclusion of both ovulatory women and those with PCOS for this study. During the midfollicular phase (days 5–8), after an overnight fast, blood samples were obtained for luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone, androstenedione, unbound testosterone, dihydroepiandrosterone sulphate (DHEAS),

insulin-like growth factor-I (IGF-I), insulin-like growth factor binding protein-1 (IGFBP-1), IGFBP-3 and insulin.

PAO/PCO and control women underwent ovarian stimulation preceded by pituitary down-regulation with a gonadotrophin releasing hormone agonist (GnRHa) (Lupron; TAP, Deerfield, IL, USA). The GnRHa was begun during the midluteal phase and once down-regulation was reached (serum oestradiol  $< 30$  pg/ml) ovarian stimulation using human menopausal gonadotrophins (HMG) (Pergonal; Serono, Aubonne, Switzerland) was initiated with three ampoules (225 IU) given daily i.m. Human chorionic gonadotrophin (HCG) 10 000 IU was given i.m. as soon as five or more follicles  $> 18$  mm in diameter were present or oestradiol concentrations reached 5000 pg/ml. Blood samples for serum testosterone and androstenedione were obtained 12 h before and 36 h after HCG administration.

### Assays

Serum LH, FSH, testosterone, non-sex hormone-binding globulin bound testosterone (unbound testosterone), androstenedione and DHEAS were measured by well-established radioimmunoassay methods which were validated previously in our laboratory (Mishell *et al.*, 1971; Goebelsmann *et al.*, 1974; Lobo *et al.*, 1980).

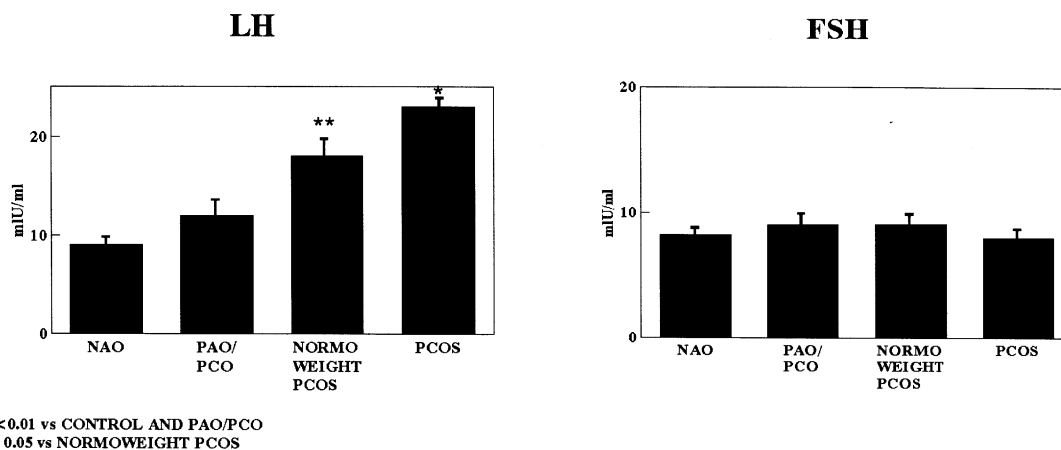
Steroid assays included extraction and celite chromatography. In the LH and FSH assays, the standard used was LER 907, which was referenced to the Second International Reference Preparation.

An acid ethanol extraction step was used to extract IGF-I which was then quantified by radioimmunoassay using a commercial kit from Nichols Institute (San Juan, Capistrano, CA, USA). Both IGFBP-1 and IGFBP-3 were quantified by immunoradiometric assay and direct radioimmunoassay methods, respectively, using kits obtained from Diagnostic Systems Laboratories (Webster, TX, USA). Insulin was quantified by use of a direct radioimmunoassay kit (Diagnostic Systems Laboratories).

In all assays, intra-assay and interassay coefficients of variation did not exceed 6 and 13% respectively.

### Statistics

All data are expressed as the mean  $\pm$  SE. Statistical differences between groups were determined by analysis of variance. Correlations were analysed using the Pearson product moment correlation.  $P < 0.05$  was considered significant.



**Figure 1.** Serum values (mean  $\pm$  SE) of luteinizing hormone (LH), follicle stimulating hormone (FSH), in women with normal-appearing ovaries (NAO) and in women with polycystic-appearing ovaries (PAO/PCO), and in polycystic ovarian syndrome (PCOS) patients of both normal and increased body weight.

## Results

PAO/PCO women had values of serum LH, FSH, testosterone, unbound testosterone, androstenedione and DHEAS which were similar to those of NAO women (Figure 1 and Table I). Both groups of ovulatory women had values of LH, testosterone, unbound testosterone, androstenedione and DHEAS which were significantly ( $P < 0.01$ ) lower than those of PCOS (Figure 1 and Table I). This was the case for both subgroups of women with PCOS (normal and increased body weight). An increased individual value level of a hormonal parameter was defined as one which exceeded 2SD from the mean value of normal women with normal ovaries (NAO). These upper limits for values in our patients with NAO were 1.46 nmol/l for testosterone, 9.0 nmol/l for androstenedione and 22.2 pmol/l for unbound testosterone. Only two PAO/PCO women had an elevation of all ovarian androgens (testosterone, unbound testosterone and androstenedione). These values were 2.07 and 1.85 nmol/l for testosterone, 14.0 and 11.2 nmol/l for androstenedione, and 26 and 24.6 pmol/l for unbound testosterone. Two other PAO/PCO women had an elevation only of androstenedione at values of 11.1 and 11.9 nmol/l; and one PAO/PCO woman had an increase only of unbound testosterone (22.9 pmol/l). No PAO/PCO woman showed an increase of serum DHEAS. After ovarian stimulation, testosterone and androstenedione responses as a group were similar in PAO/PCO and NAO women (Figure 2). The upper limits in NAO after ovarian stimulation were 2.17 nmol/l for testosterone, and 20.3 nmol/l for androstenedione. Only the two PAO/PCO women with an increase of all ovarian androgens

had an exaggerated rise of both testosterone and androstenedione (to 5.3 and 5.76 nmol/l for testosterone and 46.1 and 26.2 nmol/l for androstene-dione).

In all groups, IGF-1 and IGFBP-3 were similar while fasting insulin was significantly ( $P < 0.01$ ) higher in women with PCOS who had increased weight compared to PAO, women with NAO and normal weight women with PCOS (Figure 3). Insulin concentrations were similar in the ovulatory groups and normal weight PCOS (Figure 3). Serum IGFBP-1 was significantly lower in the overweight PCOS group compared to all other groups including the normal weight women with PCOS ( $P < 0.05$ ; Figure 3). However, serum IGFBP-1 was also significantly ( $P < 0.05$ ) lower in the PAO group and normal weight women with PCOS compared to the NAO group (Figure 3). No differences in serum IGFBP-1 were found between PAO/PCO and normal weight women with PCOS. No correlation was found between serum values of insulin and IGFBP-1 in NAO or PAO/PCO ( $r = 0.15$ , NS) ( $r = 0.25$ , NS), or in normal weight women with PCOS ( $r = 0.31$ , NS). A negative correlation between insulin and IGFBP-1 ( $r = 0.67$ ,  $P < 0.01$ ) was present in overweight women with PCOS.

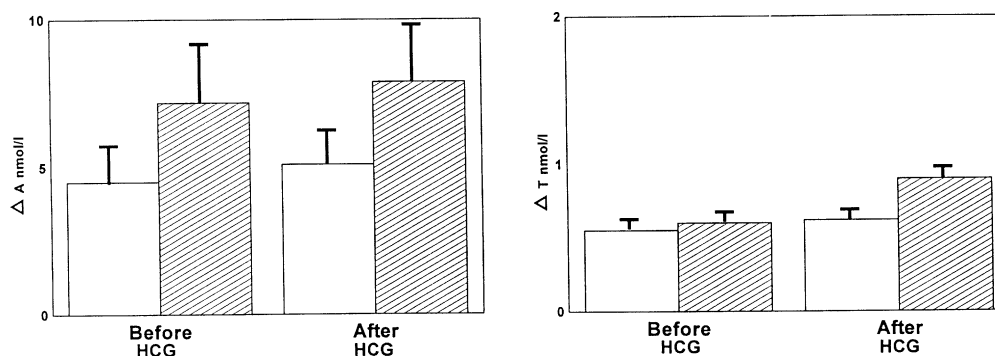
Calculated IGF-I:IGFBP-3 ratios were similar in all groups but the IGF-I:IGFBP-1 ratio was significantly ( $P < 0.01$ ) higher in overweight women with PCOS compared with PAO and NAO women and normal weight women with PCOS. PAO/PCO and normal weight women with PCOS had significantly ( $P < 0.01$ ) higher IGF-I:IGFBP-1 ratios when compared with the NAO group which served as the true control group.

**Table I.** Serum androgens (mean  $\pm$  SE) in ovulatory NAO (normal-appearing ovaries) and PAO (polycystic-appearing ovaries)/PCO (polycystic ovaries) women, in obese polycystic ovarian syndrome (PCOS) and in normal weight PCOS patients

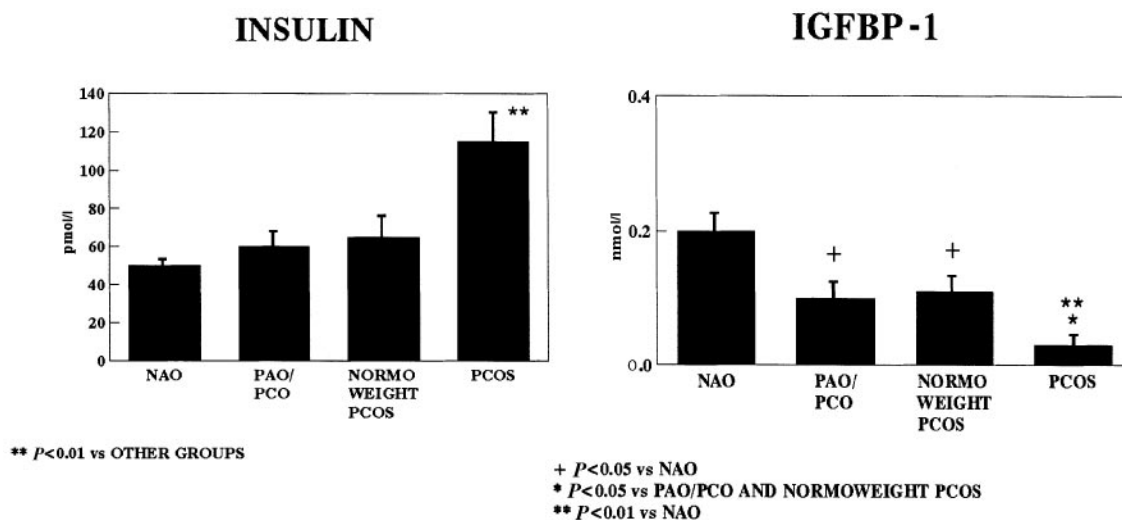
	Testosterone (nmol/l)	Unbound testosterone (pmol/l)	Androstenedione (nmol/l)	DHEAS ( $\mu$ mol/l)
NAO	1 $\pm$ 0.1	11.8 $\pm$ 1.4	6 $\pm$ 0.3	4.7 $\pm$ 0.5
PAO/PCO	1.2 $\pm$ 0.1	15.9 $\pm$ 3.5	7.7 $\pm$ 0.7	4.7 $\pm$ 0.4
Overweight PCOS	3.2 $\pm$ 1.3 <sup>a</sup>	39.4 $\pm$ 5 <sup>a</sup>	12.9 $\pm$ 1 <sup>a</sup>	8.7 $\pm$ 0.9 <sup>a</sup>
Normal weight PCOS	2.8 $\pm$ 0.8 <sup>a</sup>	35 $\pm$ 5 <sup>a</sup>	11.8 $\pm$ 1 <sup>a</sup>	10 $\pm$ 1.1 <sup>a</sup>

DHEAS = dihydroepiandrosterone sulphate.

<sup>a</sup> $P < 0.01$  versus NAO and PAO/PCO women.



**Figure 2.** Testosterone and androstenedione increases after ovarian stimulation in ovulatory NAO (clear bars) and PAO/PCO (striped bars) women. HCG = human chorionic gonadotrophin. For other abbreviations see Figure 1.



**Figure 3.** Serum concentrations (mean  $\pm$  SE) of insulin and insulin-like growth factor binding protein-1 (IGFBP-1) in ovulatory NAO and PAO/PCO women and in PCOS patients of normal and increased body weight. For abbreviations see Figure 1.

## Discussion

There has been controversy regarding the definition of PCOS. Although this diagnosis is often based solely on the ultrasonographic appearance of the ovaries, we have only used this diagnosis in women who exhibit endocrine features of the disorder, namely anovulation and hyperandrogenism. Polycystic ovaries have been identified in patients having disorders with apparently normal androgen status, as well as in normal ovulatory women (Polson *et al.*, 1988; Clayton *et al.*, 1992; Abdel Gadir *et al.*, 1992). Although it has been suggested that these patients have some endocrine abnormalities similar to those found in classic PCOS (Polson *et al.*, 1988; Pache *et al.*, 1993), no definitive studies have been performed to our knowledge in women who are completely normal, apart from this ovarian morphological alteration.

In this study, we had the opportunity to evaluate 15 normal ovulatory women with PAO/PCO. These women, while normal participants in an oocyte donation programme, were selected for evaluation to assess whether the morphological appearance of PAO/PCO may be associated with PCOS. We found that cryptic hyperandrogenism was not the rule in these women and that a clear hyperandrogenic state (increases of testosterone, unbound testosterone and androstenedione and an increased androgen response to gonadotrophins) was observed in only two out of 15 PAO/PCO women (13.3%). Three other PAO/PCO women had solitary increases in unbound testosterone or androstenedione. Nevertheless one could conclude that taken together, up to 33% of normal ovulatory women with PAO/PCO may have increased androgen secretion.

A characteristic endocrine feature of patients with PCOS is a low concentration of IGFBP-1 (Suikkari *et al.*, 1989; Carmina *et al.*, 1995). In PCOS, this finding has been thought to be related to hyperinsulinaemia and/or obesity (Suikkari *et al.*, 1988; Conover *et al.*, 1992). However, recently we have observed that the control of IGFBP-1 secretion may also be abnormal in PCOS (Carmina *et al.*, 1995). The normal ovulatory women with PAO/PCO in this study had lower concentrations of IGFBP-1 although not as low as the women

with PCOS who had increased body weight. Interestingly, women with PAO/PCO and PCOS with normal body weight had similar values of IGFBP-1 which, nevertheless, were also lower than values found in ovulatory women with normal ovaries (NAO) with similar body weight. These findings may suggest that body weight contributes to the metabolic and endocrine features of PCOS (increased serum insulin and lowered IGFBP-1) but do not completely explain the changes of IGFBP-1. The lower concentrations of IGFBP-1 in PAO/PCO women and the normal weight women with PCOS may be the result of a mild insulin resistance. It has been shown in PCOS that a mild insulin resistance may exist with normal body weight and normal basal insulin concentrations (Dunaiv *et al.*, 1989; Carmina *et al.*, 1992).

In addition, other possibilities may be considered. The decrease of serum IGFBP-1 could represent the manifestation of an incompletely expressed genetic disorder which, in its complete form (associated with increased insulin secretion), would result in classic PCOS. For several years it has been considered that PCOS has a genetic mode of inheritance (Hague *et al.*, 1988) although no characteristic pattern of inheritance has been uncovered (Jahanfor *et al.*, 1995). It is possible that PCOS is a polygenic syndrome and that women with PAO/PCO represent an incompletely expressed form of the syndrome. Consistent with this hypothesis were the findings of reduced IGFBP-1 both in normal PAO/PCO women and in PCOS.

If a genetic predisposition, directly or mediated via hyperinsulinaemia, were to lead to reduced IGFBP-1, how does this relate to PAO/PCO? At least one possibility is that small increases in IGF-1 might alter the balance between follicular recruitment and follicular atresia without significantly increasing ovarian androgen secretion. It is known that IGF-1 within the ovary is an important factor for the survival of ovarian follicle cells (Hsueh *et al.*, 1994) and may be involved in the process of atresia. Interestingly, it has been reported that 'cystic ovaries' may result from a decreased rate of follicular atresia (Erickson, 1992). However, an important difference was found

between the PAO/PCO group and women with PCOS who had normal body weight. Normal weight women with PCOS, by definition, had endocrine characteristics of the syndrome including elevated LH and serum androgen concentrations.

Taken together these findings suggest that women with PAO/PCO may form part of the spectrum of patients with PCOS. Only a minority (no more than a third) have some evidence of hyperandrogenism, and most are endocrinologically normal. However, the finding of PAO/PCO clearly suggests that a cryptic form of PCOS may exist, or that the women may be susceptible to developing PCOS in the future. It is anticipated that uncovering the pathophysiology of PCOS will be linked to discovering what factors are responsible for the morphological findings of PAO/PCO and what determines the presence or absence of the full characteristics of PCOS in women with PAO/PCO.

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