Endocrine Indices of PCOS in Women with Polycystic Ovaries but without Diagnostic Features of PCOS: A Study of an Infertility Clinic Population

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Abstract

Background: The presence of polycystic ovarian morphology (PCO) without the other characteristics of the polycystic ovarian syndrome (PCOS) is insufficient for the diagnosis of PCOS and there is little justification for follow up in endocrine clinics for women with PCO morphology alone. A few studies have been reported regarding the endocrine features of asymptomatic women with PCO with conflicting data about endocrine profiling. The aim of this study was to assess whether women with PCO, but who have no symptoms of PCOS differ, endocrinologically, from women with normal ovaries. Methods: We analysed the results of ultrasound and endocrine investigations in 576 consecutive women who attended the infertility clinic between 1993 and 1995 at the Reproductive Medicine Unit of St Mary’s Hospital, Imperial College Healthcare NHS Trust, London, UK. Results: Three hundred and twenty eight women had PCO and 248 had normal ovaries. Among the 328 women with PCO, 169 (51.5%) had PCOS according to Rotterdam criteria. The remaining women with PCO had no symptoms of the syndrome (n = 159); they had a history of regular menses, had proven ovulatory cycles and had neither clinical nor biochemical evidence of hyperandrogenism. However, these women had higher timed LH [median (IQR) 5.3 (4.2) IU/l vs 4.8 (3.4) IU/l, respectively; p = 0.044] and testosterone [2.0 (0.8) nmol/l vs 1.8 (0.8), respectively; p = 0.009] compared with women with normal ovaries (although by definition within the normal range). There was no difference in BMI or FSH.
between the two groups. Among the 169 women with PCOS, 45.0% \((n = 76)\) were anovulatory without hyperandrogenism, 34.3% \((n = 58)\) fulfilled the NIH criteria and 20.7% \((n = 35)\) were ovulatory with hyperandrogenism. The proportion of hyperandrogenism among anovulatory women with PCO is 43.3% \((58 \text{ out of } 134)\). Conclusions: Women with PCO, but no symptoms of the syndrome, differ endocrinologically compared with women with normal ovaries: they had higher timed LH and testosterone (although by definition within the normal range). These data suggest that despite the lack of symptoms of PCOS, women presenting to an infertility clinic with PCO represent a milder phenotype of those with overt PCOS, but fall on the same spectrum.

Keywords
Polycystic Ovary Syndrome, Polycystic Ovarian Morphology, Ultrasound Scan, Infertility Clinic

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder to affect women of reproductive age. Its phenotypic expression is heterogeneous and its aetiology remains uncertain. There has been no universal agreement about its definition and diagnostic criteria. The National Institutes of Health (NIH) criteria for PCOS propose that PCOS should be defined as the presence of both anovulation and hyperandrogenism (biochemical and/or clinical) without reference to ovarian morphology [1]. In 2003 in Rotterdam at a consensus meeting of the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM meeting) it was proposed that the presence of two out of the three criteria (chronic anovulation, hyperandrogenism and polycystic ovaries (PCO) on ultrasound scan) would define PCOS, provided other aetiologies have been excluded (the “Rotterdam” criteria for PCOS) [2]. By using the possible combinations of these criteria, four different phenotypes of PCOS are now identified: 1) hyperandrogenism (clinical or biochemical) and anovulation, 2) hyperandrogenism and PCO on ultrasound but with ovulatory cycles, 3) anovulation and PCO without hyperandrogenism and 4) hyperandrogenism, anovulation and PCO [3]. Furthermore in 2006, the Androgen Excess PCOS Society (AEPCOS) suggested that PCOS is a mainly hyperandrogenic disorder and should be defined by the presence of hyperandrogenism and that the second criterion necessary for the diagnosis could be either chronic anovulation or PCO morphology [4]. The metabolic and long-term impact of the different PCOS phenotypes has been extensively studied [5].

Although the original description of the syndrome was based on ovarian morphology [6], there is an ongoing debate about whether PCO morphology is
an essential element for PCOS diagnosis [7]. The presence of PCO morphology without the other characteristics of the syndrome, is insufficient for diagnosis of PCOS and there is little justification for follow up in endocrine clinics for women with PCO morphology alone. A few studies have been reported regarding the endocrine features of asymptomatic women with PCO, but these have generally involved small numbers of subjects and with conflicting data about endocrine profiling [8] [9] [10] [11]. A more recent and larger study investigated endocrine and metabolic indices among women with PCO morphology in the general population and found marginally higher serum concentrations of androstenedione (but not of testosterone or LH) than in the reference population [12]. The aim of our study was to investigate whether among women presenting to a single infertility clinic, those who were found to have PCO morphology without clinical manifestations of PCOS following detailed investigations, differ in gonadotrophin and androgen levels from women who have normal ovaries. We analysed endocrine results in 576 women that attended the infertility clinic in Reproductive Medicine clinic at Imperial College NHS Trust (St Mary’s Hospital, London) a subgroup of whom who had previously been studied to determine the prevalence of polycystic ovaries in women with infertility [13].

2. Methods

Between 1993 and 1995, 576 women attended the infertility clinic at the Reproductive Medicine Unit of St Mary’s Hospital (Imperial College Healthcare NHS Trust). Anthropometry, clinical history and routine clinical investigations, including ovarian morphology on the ultrasound scan, were recorded in an electronic database at that time. The following (anonymised) data were retrieved from the database for the purpose of the current study: age, BMI, Ferriman-Gallwey score for hirsutism, gonadotrophin and testosterone measurements and ovarian ultrasound morphology. Women were considered hirsute if the Ferriman-Gallwey score was >5 [14].

All women underwent cycle monitoring (Table 1). This included a series of ultrasound scans and timed hormone measurements to assess ovarian morphology and to confirm ovulation. The first ultrasound scan was performed on day 8 of the cycle and serum luteinizing hormone (LH), follicle stimulating hormone

| Tests performed                                      | Day 8                                         | Day 10 - 12                                      | Day 21                                         |
|------------------------------------------------------|-----------------------------------------------|-------------------------------------------------|------------------------------------------------|
| Serum FSH, LH and Testosterone.                      | Ovarian ultrasound to assess ovarian morphology. | Ovarian ultrasound to assess follicular growth and estimate the day of ovulation. | Serum progesterone to assess ovulation. Ovarian ultrasound to assess the corpus luteum and endometrial thickness. |

Table 1. Series of ultrasound scans and timed hormone measurements during cycle monitoring in women attending the infertility clinic.
(FSH) and testosterone levels were measured on the same day. For those women with oligo- or amenorrhoea, a withdrawal menstrual bleed was induced following administration of a progestogen (medroxyprogesterone acetate, 5 mg/day for 7 days) and endocrine tests performed at baseline and 8 days after onset of vaginal bleeding. Ovarian morphology was assessed and PCO were diagnosed using the criteria established by Adams et al. (i.e. PCO was defined by the presence of multiple follicles, 2 - 8 mm in diameter arranged either peripherally around a dense core of stroma or scattered throughout an increased amount of stroma) [15], by a small and experienced team of ultrasound operators (and mainly by one operator: DMW). The reproducibility of ultrasound diagnosis had been previously assessed for each operator. Repeat ultrasound scans were undertaken at 3 - 4 day intervals to assess follicular growth and estimate the day of ovulation. Ovulation was confirmed by a serum progesterone measurement 7 days post ovulation. A serum progesterone measurement greater than 30 nmol/l in 2 successive cycles was considered to be satisfactory evidence of ovulation and all women were categorised according to whether they were ovulatory or anovulatory on the basis of both cycle monitoring and mid-luteal progesterone levels. These investigations were performed according to standard operating practice in our infertility clinic and data were anonymised before analysis. Also during the study our laboratory participated in the UK national quality control programme.

PCOS according to the “Rotterdam” criteria was defined by the presence of two (or more) of the three criteria: chronic anovulation, hyperandrogenism and PCO on ultrasound scan [2]. PCOS according to the NIH criteria was defined as the presence of both anovulation and hyperandrogenism (biochemical and/or clinical) [1].

The data included in this retrospective study were recorded as part of our routine infertility clinic service (no additional clinical information was obtained and no additional investigations were performed) and, therefore, obtaining neither specific ethical approval nor informed consent was appropriate. All data were anonymised when setting up the clinic database on which these findings were based.

Data are presented as median (interquartile range). Statistical analyses were performed in SPSS 11.0 for Windows and group by group comparison was made using the Mann Whitney test.

3. Results

Among the 576 women, 328 (57%) had PCO morphology on ultrasound scan and 248 (43%) had normal ovaries. None of 248 women with normal ovaries had evidence of PCOS (oligo- or anovulation or hyperandrogenism). Among the 328 women with PCO morphology, 159 (48.5%) had PCO morphology without fulfilling the diagnostic criteria for PCOS i.e. they had a history of regular menses, had proven ovulatory cycles and had neither clinical nor biochemical evidence of
hyperandrogenism; 169 (51.5%) had PCOS according to Rotterdam criteria, including 58 (17.7%) who had PCOS according to the NIH criteria (Table 2).

When the 159 ovulatory women with PCO morphology (but without PCOS) were compared with those women with normal ovaries (n = 248), serum levels of LH and testosterone were significantly higher in the PCO group, although testosterone was, by definition, within the normal range (Table 2). The women with PCO morphology and the women with PCOS were younger at presentation to the infertility clinic than women with normal ovaries (Table 1), as had been previously observed [13].

The 169 women with PCOS had, as expected, higher BMI, LH and testosterone levels compared to women with normal ovaries (Table 2). Among the 169 women with PCOS, 58 (34%) fulfilled the NIH diagnostic criteria (anovulatory with hyperandrogenism), 76 (45%) were anovulatory without hyperandrogenism and 35 (21%) were ovulatory with biochemical and/or clinical hyperandrogenism (Table 3). The 58 women with PCOS who fulfilled the NIH diagnostic criteria

Table 2. Characteristics of 248 women with normal ovaries, 159 women with PCO morphology without PCOS and 169 women with PCOS. Comparison of clinical and endocrine data between women with normal ovaries and a. women with PCO morphology without PCOS and b. women with PCOS.

|                          | Women with normal ovaries (n = 248) | PCO morphology without PCOS (n = 159) | Women with PCOS (n = 169) | p value for comparison between women with PCO morphology (n = 159) and control women (n = 248) | p value for comparison between women with PCOS (n = 169) and control women (n = 248) |
|--------------------------|------------------------------------|---------------------------------------|--------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Age (yrs)                | 35.7 (7.4)                         | 30.6 (5.6)                            | 30.2 (6.9)               | <0.001                                                                                          | <0.001                                                                                          |
| BMI (kg/m²)              | 23.1 (5.0)                         | 23.1 (5.6)                            | 24.8 (6.9)               | NS                                                                                              | <0.001                                                                                          |
| FSH (IU/l)-day 8         | 6.1 (2.8)                          | 6.0 (1.9)                             | 6.0 (2.1)                | NS                                                                                              | NS                                                                                              |
|                          | n = 228                            | n = 147                               | n = 153                  |                                                                                                  |                                                                                                  |
| LH (IU/l)-day 8          | 4.8 (3.4)                          | 5.3 (4.2)                             | 7.1 (7.6)                | 0.044                                                                                           | <0.001                                                                                           |
|                          | n = 224                            | n = 146                               | n = 153                  |                                                                                                  |                                                                                                  |
| Testosterone (nmol/l)-day 8 | 1.8 (0.8)                        | 2.0 (0.8)                             | 2.7 (1.1)                | 0.009                                                                                           | <0.001                                                                                           |
|                          | n = 211                            | n = 141                               | n = 146                  |                                                                                                  |                                                                                                  |

Data are described as median (IQR). p values are for comparisons between the two groups by Mann-Whitney test. NS: non significant. PCO: polycystic ovarian morphology, PCOS: polycystic ovary syndrome.

Table 3. Characteristics of 169 PCOS women classified according to three Rotterdam phenotypes: women with PCO, chronic anovulation and hyperandrogenism (who fulfill the NIH criteria) (n = 58), women with PCO and chronic anovulation without hyperandrogenism (n = 76) and ovulatory women with PCO and hyperandrogenism (n = 35).

|                          | Women with PCO who fulfill the NIH criteria (n = 58) | Women with PCO and chronic anovulation without hyperandrogenism (n = 76) | Ovulatory PCO women with hyperandrogenism (n = 35) |
|--------------------------|----------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------|
| Age (yrs)                | 29.9 (7.9)                                         | 29.5 (6.5)                                                             | 31.1 (5.6)                                      |
| BMI (kg/m²)              | 26.2 (6.7)                                         | 24.5 (7.6)                                                             | 22.8 (3.6)                                      |
| FSH (IU/l)-day 8         | 6.0 (2.0)                                          | 6.0 (2.3)                                                              | 6.1 (2.3)                                       |
|                          | n = 228                                            | n = 146                                                                | n = 97                                          |
| LH (IU/l)-day 8          | 11.0 (8.1)                                         | 6.8 (8.8)                                                              | 4.9 (2.3)                                       |
| Testosterone (nmol/l)-day 8 | 3.5 (1.4)                                        | 2.2 (0.8)                                                              | 3.1 (1.0)                                       |

Data are described as median (IQR). PCO: polycystic ovarian morphology, PCOS: polycystic ovary syndrome.
displayed the more severe PCOS phenotype: 1) they had significantly higher LH ($p = 0.009$) and testosterone levels ($p < 0.001$) compared to the 76 women with PCOS who were anovulatory without hyperandrogenism and 2) they had significantly higher LH ($p < 0.001$), testosterone levels ($p = 0.005$) and BMI ($p = 0.002$) compared to the 35 ovulatory PCOS women with hyperandrogenism (Table 3). Among the 134 anovulatory women, 58 (43%) had hyperandrogenism.

4. Discussion

We found that 159 women with PCO morphology, who did not have PCOS (were ovulatory and did not have clinical or biochemical hyperandrogenism), presenting consecutively to an infertility clinic, had subtle but distinct differences in hormonal profile compared to 248 women with normal ovaries; specifically higher LH and higher testosterone (although within the normal range). All women underwent detailed clinical, endocrine evaluation and ultrasound investigations and ovulatory cycles were clearly identified by serial ultrasound scanning and accurately timed blood progesterone measurements. Our study, involving a large number of women, suggests that, at least in women presenting with subfertility, PCO morphology may represent a milder phenotype of PCOS syndrome. Furthermore, PCO morphology is likely to be associated with a disturbance of hypothalamic-pituitary-gonadal axis, leading to a small rise in LH although, still within the normal range. It is not known whether women with PCO (but no PCOS) will at a later stage of their life develop PCOS when exposed to environmental factors, such as increase of body weight and lack of exercise. It is also not known whether PCO morphology carries any long-term metabolic impact.

An eight-year follow-up study by Murphy et al. of 23 asymptomatic women with PCO showed that none within this, albeit small, cohort had developed PCOS [11]. Indeed, a significant minority no longer had obvious PCO on ultrasound. However, this was a volunteer cohort identified within a normal population rather than women who had presented with subfertility, as in our study. Other studies comparing women with PCO morphology with women with normal ovaries found increased androgens, similarly to our study, but no difference in LH levels. In a small study of 15 women with PCO compared with 15 women with normal ovaries no difference was observed in LH, Testosterone, Androstenedione and DHEAS between the two groups, but on an individual basis, an elevation of at least one serum androgen value was observed in one third of them [8]. In a study of 39 non-hirsute women with documented ovulatory cycles and PCO morphology compared with 29 women with normal ovaries, there was no difference in gonadotrophins, E2, and progesterone levels, but androgens were higher and SHBG was lower, whereas insulin levels were higher in a subgroup of these subjects [10]. In a recent, large study of 126 women with PCO morphology compared with 683 women with normal ovaries, there was no difference in gonadotrophins and testosterone between groups (although androstenedione con-
centrations were marginally higher), but systolic blood pressure, high density lipoprotein and androstenedione were higher in the PCO group [12].

Although baseline levels of androgens and gonadotrophins may be normal, it is possible that in women with PCO morphology latent abnormalities would be revealed after pituitary or direct ovarian stimulation. In a study in which 26 ovulatory women with PCO without clinical or biochemical hyperandrogenism were compared with 25 women with normal ovaries, there was no difference in baseline endocrine profile between groups. However, on dynamic testing, hyperandrogenism following a single dose of a GnRH-agonist were observed in the PCO group [9]. These findings mirror those in a study by Gilling-Smith and colleagues [16] in which hyperandrogenism in women with PCO and regular cycles was only revealed after stimulation by a dose of hCG. In a study of women with PCO and regular cycles (but who presented with hirsutism) hypersecretion of LH was uncovered and hyperandrogenaemia was exaggerated in response to a single dose of a GnRH agonist [17].

A significant proportion of women in our infertility clinic population (29%) had clinical and/or biochemical evidence of PCOS. The prevalence of PCOS among the women with PCO morphology was 51.5% according to Rotterdam criteria and 17.7% according to the NIH criteria. The prevalence of PCOS among women with polycystic ovaries has not been extensively studied and the results are often conflicting. In a study of 257 volunteers taken from the normal population, 23% had PCO on ultrasound and, interestingly, the majority of these women reported slightly irregular menstrual cycles even though, by definition, they had not needed to consult a doctor about this symptom [18]. In that study, serum LH levels were above the normal range in 25% of those with PCO, a finding that accords with that in the infertility clinic population. From the estimates of the prevalence of polycystic ovaries in the general population and of the prevalence of polycystic ovaries in women with a diagnosis of PCOS, it may be estimated that about 20% of women with polycystic ovaries have PCOS [4].

Among the 169 women in the current study who had PCOS, the phenotype of oligo- or anovulation but without hyperandrogenism constituted the largest group (45%), 21% were ovulatory with hyperandrogenism and 34% fulfilled the NIH criteria. The overall proportion of hyperandrogenism among anovulatory women with PCO was 43.3%. The distribution of PCOS phenotypes depends on whether the patients were identified after referral for outpatient medical assessment or identified through screening the general population [19]. Other factors that play a part in determining the presenting features of women with PCOS include the nature of clinic to which the patient is referred (e.g. endocrine/metabolic or infertility/gynaecological).

5. Summary

In summary, we observed that women with PCO morphology without signs or symptoms of PCOS had higher LH levels and testosterone (although by defini-
tion within the normal range) compared to women with normal ovaries. The one follow-up study to be published was reassuring about the lack of future development of features of PCOS in women with PCO morphology alone [11]. However, it can be argued that in this group of women, long term follow-up studies are needed to examine long term hormonal and metabolic impact of PCO morphology. Whereas those in the general population may not go on to develop PCOS, the mild but distinct aberrations in endocrine profile in those who present to an infertility clinic may merit follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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