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A review of 300 consecutive cases of Polycystic ovarian syndrome: clinical presentation and management

Abstract

Background: Polycystic ovary syndrome (PCOS) is a common heterogeneous endocrine disorder. The prevalence of PCOS varies depending on which criteria are used to make the diagnosis, but can be as high as 15%–20%.

Aim and objectives: To review the demographic details, presenting symptoms, biochemical features and management in women with PCOS and differentiate patients who have polycystic ovarian morphology (PCOM) and have hypothalamic amenorrhoea.

Method: Retrospective observational study of 300 consecutive new cases with suspected PCOS were referred to the reproductive endocrinology clinic in a tertiary referral hospital (Kings college hospital, London) from 2008-2015. Electronic medical records were reviewed and Microsoft Excel software was used for data collection and analysis.

Inclusion and exclusion criteria's: All patients with suspected PCOS fulfilling Rotterdam criteria were included in the study. Phenotypically similar androgen excess disorders like congenital adrenal hyperplasia (CAH), androgen secreting-tumor and Cushing's syndrome were excluded.

Results: The mean (+/-SD) age was 30 (+/-6.7) years [range 14-49].

A total of 213 (71%) had oligomenorrhoea, 61 (20.3%) had amenorrhoea, while 26 (8.6%) had regular cycles. 135 (45%) presented with subfertility, while 93 (31%) had hirsutism. Mean (+/-SD) FSH and LH were 5.5 IU/L (+/-2.8) and 17.8 IU/L (+/-7.9), respectively, while mean (+/-SD) estradiol level was 253.4 pmol/L (+/-267.1). 27/61 (44.2%) women with amenorrhoea, had low estradiol [mean (+/-SD) <176 pmol/l (123.8+/-30.8)]. Mean (+/-SD) anti-Mullerian hormone (AMH) was 44.6 pmol/L (+/-33.1). 39/45 (87%) had elevated AMH while 6/45 (13%) had normal AMH levels.

Mean (+/-SD) testosterone level was 2.0nmol/L (+/-1.5) and 36 (16%) patients had elevated total testosterone levels. Mean (+/-SD) Sex Hormone Binding Globulin (SHBG) and Free Androgen Index (FAI) were 45.9 (+/- 29.4) and 5.8 (+/- 6.6). 20/43 (47% of women assessed) had elevated androstenedione levels with a Mean (+/-SD) of 13.06 (+/- 7.5). Elevated triglycerides and/or total cholesterol was noted in 13/44 (29.5% of women assessed). 13/28 (46.4% of women assessed) had raised HbA1C. In a total of six (2%) patients, the ovaries did not appear polycystic.

Conclusion: A significant proportion of women with hypothalamic amenorrhea with PCOM were classed as PCOS.

Keywords: polycystic ovarian syndrome, polycystic ovarian morphology, Amenorrhea, Oligomenorrhea, Hyperandrogenism, testosterone

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Abbreviations: PCOS, polycystic ovary syndrome; PCOM, polycystic ovarian morphology; AMH, anti-mullerian hormone; AFC, antral follicle count; GnRH, gonadotrophin releasing hormone; CAH, congenital adrenal hyperplasia; TSH, thyroid stimulating hormone

Introduction

Polycystic Ovary Syndrome (PCOS) was first described by Stein and Leventhal in 1935,[1] however, since then there has been much debate over the diagnostic criteria and this is ongoing. It's prevalence depends on the definition used and the reference population.[2]

The current day commonly used criteria, the Rotterdam criteria proposed in 2003,[2] have been subject of much debate and criticism due to the flexibility of the criteria and inclusion of other disorders with other etiologies.[3]

The Rotterdam criteria define PCOS by the presence of at least two of the following three features: irregular menstrual cycles or anovulation, clinical or biochemical hyperandrogenism and polycystic ovarian morphology.

This leads to the four different phenotypes (Table 1), which are not all universally accepted as being part of the same syndrome. The phenotype that remains most controversial as mentioned above in table 1 is type D, which includes patients with polycystic ovarian morphology, irregular cycles and no signs or symptoms of hyperandrogenism.[4]

Table 1 Four different phenotypes of PCOS, which are not universally accepted as being part of the same syndrome

	Oligo-anovulation (OA)	Hyperandrogenism (HA)	Polycystic ovarian morphology (PCOM)
A	Yes	Yes	Yes
B	Yes	Yes	No
C	No	Yes	Yes
D	Yes	No	Yes

It has long been argued that hyperandrogenism is central to the pathogenesis of PCOS[5] with exposure to excess androgens in utero commencing the cycle. It is likely that the pathogenesis of PCOS is a multifaceted one involving uncontrolled ovarian steroidogenesis, aberrant insulin signaling, excessive oxidative stress, genetic and environmental factors.[6]

Whilst androgen excess remains in the opinion of many as the cornerstone of the disease challenges persist in defining this and measuring it objectively.

Most current assays for plasma androgens have poor sensitivity and the advent of mass spectrometry does not seem to have improved this considerably. Serum testosterone is arguably the most important androgen in women and measurement of free testosterone seems much more sensitive than total testosterone for diagnosing hyperandrogenic disease. But this also has limitations. An alternative is to measure Free Androgen Index (FAI) which requires measuring both total testosterone and Sex Hormone Binding Globulin (SHBG). However SHBG production at liver level is extremely sensitive to the negative effect of insulin, therefore FAI is raised artificially when there is hyperinsulinism.[7]

An alternative has been suggested to use Anti-Mullerian Hormone (AMH) or Antral Follicle Count (AFC) at ultrasound as an indirect marker of hyperandrogenism; the argument being follicular excess is most likely secondary to intra-ovarian hyperandrogenism.[8]

The presence of hyperandrogenism may help differentiate between women with PCOS and the group of patients who have polycystic ovarian morphology and oligo-anovulation with a hypothalamic component. This group has a deficiency in the pulsatile release of Gonadotrophin Releasing Hormone (GnRH) which is often associated with excessive exercise, weight loss or psychological stress.[9] Their symptoms may be reversed with weight gain or reduction in exercise. Moreover, they may benefit from exogenous estrogen replacement.[10] The diagnosis of hypothalamic hypogonadism in normogonadotrophic women remains a challenge. The challenge is even greater in women who have PCOM according to the current criteria.

The main objective of this study is to find out patients with PCOM who are misdiagnosed as PCOS and appropriately addressing health issues associated with low oestrogen. The diagnosis of hypothalamic amenorrhoea is important in view of its long-term implications for the individual woman's health and quality of life and misdiagnosis can lead to a lifetime of mismanagement in terms of fertility outcomes and long-term health.

Methods

This was a retrospective observational uncontrolled study, of 300 patients with PCOS who presented to the Reproductive Endocrinology clinic in a tertiary referral hospital from 2008-2015. Rotterdam criteria were used to define cases with polycystic ovaries and initial batteries of investigations were done in reproductive medicine clinic. Quality improvement lead approval and departmental approval was taken before conducting this observational study and ethical approval was not needed for conducting this study.

Patients were followed up in clinic 3-6 monthly depending on the desire for fertility versus management of hypothalamic amenorrhoea.

All patients with suspected PCOS fulfilling Rotterdam criteria were included in the study. Phenotypically similar androgen excess disorders like congenital adrenal hyperplasia (CAH), androgen secreting-tumor and Cushing's syndrome were excluded.

Electronic medical records were reviewed to screen cases of PCOS and Microsoft Excel software was used for data collection and analysis.

Data was collected on demographic details including age, ethnicity and parity. Presenting complaints were assessed specifically looking at irregular or absent periods, amenorrhoea was defined as absence of menstrual periods >90 days. Biochemical investigations were reviewed looking mainly at gonadotrophins (FSH and LH) and estradiol, androgen profile, specifically free testosterone (T), Free Androgen Index (FAI), androstendione, AMH, prolactin, thyroid stimulating hormone (TSH) and free thyroxine.

Metabolic markers assessed included lipid profile and Glycosylated haemoglobin (HbA1c). Elevated levels were defined as elevated cholesterol (>5.0 mmol/ Litre) or triglycerides (>2.0 mmol/Litre).

Ultrasound appearances of ovaries were also assessed to identify PCOM, using the definition of ≥12 follicles per ovary measuring 2-9mm.

Finally management options utilised were explored looking at medical therapies used, whether metformin was prescribed or not and any fertility interventions.

Results

Demographics

The mean (+/-SD) age was 30 (+/- 7.9) with a range of 14-49. The majority of the women in the study were nulliparous 226 (75.3%).

180 (60%) of the women were Caucasian, 60 (20%) were Afro-Caribbean and 60 (20%) were of Asian background (Table 2).

Table 2 Demographic details of our study

Demographics		Number (total 300)	Percentage
Ethnicity			
	Caucasian	180	60%
	Afro-Caribbean	60	20%
	Asian	60	20%
Parity			
	Nulliparous	226	75.30%
	Multiparous	74	24.70%

Presenting symptoms

Irregular cycles was the most common presenting complaint in our group with 274 (91.4%) stating this as their main complaint. Within this group 213(71%) had oligomenorrhoea and 61 (20.3%) were amenorrhoeic. Almost half of the patients in the group 135 (45%) complained of subfertility. Almost a third of the patients 93 (31%) complained of symptoms of hyperandrogenism namely acne and hirsutism (Table 3).

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Table 3 Main Presenting Features in our study

Presenting symptoms		Number	Number
Menstrual irregularities		274	93%
	Oligomenorrhoea	213	77.70%
	Amenorrhoea	61	22.20%
Subfertility		135	45%
Hirsutism, acne		93	31%

Table 4 Biochemical measurements in Study group

Hormone		Number (total 300)	Mean	SD
Gonadotrophins				
	FSH (IU/L)	300	5.5	+/- 2.8
	LH (IU/L)	300	17.8	+/- 7.9
	LH:FSH ratio	300	3.24	
Oestradiol		300	253.4	+/- 267.1
Anti-Mullerian hormone		45	44.6	+/- 33.1
Androgens				
	Testosterone (nmol/L)	300	2	+/-1.5
	Androstenedione (nmol/L)	43	13.06	+/- 7.40
	Free androgen index	300	5.7	+/- 6.6
Other hormones				
	Prolactin (mIU/L)	226	224.3	+/- 126.3
	Thyroid stimulating hormone (mIU/L)	244	1.68	+/- 0.92
	Thyroxine(pmol/L)	244	13.7	+/-2.6

Gonadotrophins

We found the mean (SD+/-) FSH and LH to be 5.5IU/L (+/-2.8) and 17.8 IU (+/-7.9) respectively, with the mean LH/FSH ratio of 3.56.

The mean estradiol (+/- SD) was 253.4 (+/- 267.1). Within the group of women with amenorrhoea, 27/61 (44.2%) had serum estradiol levels, which were below normal (176 pmol/Litre) with mean (SD+/-) 123.9 (+/- 30.8). Estradiol level varies according to the phases of cycle and was done during their first visit to the clinic. Three (1%) women had elevated prolactin levels. Prolactin was measured in patients who had symptoms of galactorrhoea.

Androgens

In our study 23/300(7.3%) had elevated free testosterone levels (> 2.6nmol/Litre) 20/43 (47%) had elevated serum androstenedione levels (> 11.5 nmol/Litre). Women with amenorrhoea had a mean (+/-SD) testosterone level of 1.74(+/- 0.77) nmol/ Litre, while the subgroup of women with amenorrhoea and low oestradiol had a mean (+/- SD) testosterone level of 1.8 (+/- 1.03) nmol/Litre.

In women with raised testosterone 18/35 (51%) had symptoms of hyperandrogenism, while in women with raised androstenedione 11/20 (55%) had symptoms of hyperandrogenism.

On the other hand, in women with symptoms of hyperandrogenism 28/113 (25%) had either elevated testosterone, androstenedione or both.

Anti-Mullerian Hormone (AMH)

In our group 45 patients underwent testing for ovarian reserve in the form of AMH assessment. AMH testing was publicly funded in our unit much later as compared to the start of our study analysis as it was more accepted by the trust for patients contemplating fertility treatment along with amenorrhoea. The mean (+/- SD) was 44.6 (+/- 33.1) pmol/Litre. 87% (39/45) had levels>19.9 pmol/Litre and 6/45 (13%) had levels <19.9 pmol/Litre.

Pelvic Ultrasound

Within our group only 6/300 (2%) patients did not have a polycystic ovarian appearance (<12 antral follicles per ovary).

Lipid profile

Lipid profile was assessed in 44/300 (14.6%) patients and within this group 29.5% had elevated lipid levels. Mean (+/-SD) for total cholesterol and triglycerides was 4.0 (+/- 0.91) mmol/Litre and 1.28 (+/- 0.90) mmol/Litre, respectively.

HbA1c was assessed in 28/300 (9.1%) women and of these 46.4% had elevated levels (>6%) with a mean (+/- SD) of 6.3% (+/- 1.29%).

Body Mass Index (BMI)

Number (%) of patients with PCOS who had a BMI>25 and BMI <25 were 83/129 (64%) and 46/129 (36%) respectively.

Mean (+/- SD) BMI for the entire population was 28.65 (+/- 7.48). In the group with amenorrhoea this was 26.79 (+/- 7.63). In the group with amenorrhoea and low oestradiol level this was 20.99 (+/3.1). When the group with amenorrhoea and low oestradiol were excluded from the analysis the mean (+/- SD) BMI in the population was 32.45 (+/-8.02).

Women with a BMI under 25 and who had amenorrhoea (N=10/12) were significantly (P< 0.05) more likely to have low oestradiol levels (and thus a diagnosis of hypothalamic amenorrhoea rather than PCOS) compared to women with amenorrhoea who had a BMI above 25 (N=8/9).

Management

Women with PCOS had different therapeutic interventions depending on the main presenting feature.

A total of 85/300 (28.3%) women had the combined oral contraceptive pill, 14/300 (4.6%) had progesterone only intake and 15/300 (5%) had both metformin and the combined oral contraceptive pill.

In women with subfertility concerns, a total of 138/300 (46%) had metformin alone, 30/300 (10%) had metformin plus ovulation induction, while 18/300 (6%) had ovulation induction only without metformin. Patients who had concerns about irregular periods, biochemical or clinical signs of hyperandrogenism were given hormonal treatment. 85/300 (28.3%) had combined oral contraceptive, 14/300 (4.6%) had progesterone only pills and 15/300 (5%) had both metformin and combined oral contraceptive.

Discussion

Our findings were consistent with other studies in terms of presenting symptoms and biochemical markers and raised similar questions with regards to the adequacy of the current diagnostic criteria for PCOS.[11]

The majority of our patients presented with cyclical irregularities and more than half complained of subfertility.

Our data revealed only a small proportion of patients to have an elevated testosterone level but almost a half of those who had a measurement of their androstenedione level had elevated levels. Interestingly, despite this biochemical picture almost half of the patients in the entire cohort of patients we looked at, complained of symptoms of hyperandrogenism.

In a study by Dewailly et al.[12] looking at women with oligo-anovulation and polycystic ovarian morphology with no overt symptoms or biochemical markers of hyperandrogenism, it was found that whilst this group had mean androgen levels within the normal range, they were noted to be significantly higher than controls.

This indeed questions the binary approach to the question of whether a patient is hyperandrogenic or not, the problem being compounded by poor sensitivity of androgen assays.

A large proportion of our patients who had their AMH measured had an elevated value. Our data of patients who had AMH measurements is not large enough to provide sufficient evidence to support using AMH values as a marker of PCOS as previously suggested.[12,13] However, it does suggest more research is required on this front.

In the proportion of women who had their metabolic markers assessed we found a large proportion to have an elevated lipid profile and HBA1c, further highlighting the long term health consequences for women with PCOS.

Our data revealed an elevated BMI in our group of patients, which falls within the overweight classification (>25). However, Women with a BMI under 25 and who had amenorrhoea were significantly more likely to have low oestradiol levels and thus a diagnosis of hypothalamic amenorrhoea rather than PCOS compared to women with amenorrhoea who had a BMI above 25.

What we found most interesting from our findings was a confirmation of the concerns long raised with regards to the laxity of the Rotterdam criteria. This is for a multitude of reasons. There are studies that suggest one fifth of women with regular cycles have ovaries that appear polycystic if the current criteria of> 12 follicles per ovary is applied.[14]

Other authors have argued that up to a third of women with regular cycles have polycystic ovary-like abnormalities such as PCOM on USS or elevated AMH levels.[15] There are also reports that PCOM is present in 30-50% of women with hypothalamic amenorrhoea.[16-18] However, different definitions of PCOM were utilised in these studies and some study populations were small.

This therefore leads to the mistaken diagnosis of hypothalamic amenorrhoea as PCOS,[15,19] as many women with functional hypothalamic amenorrhoea have PCOM and gonadotrophins within the normal range and are thus misclassified as WHO group II.

In our group almost half of the women in the group with amenorrhoea had a low oestrogen confirming indeed a hypothalamic component, supporting the above argument.

There are authors who argue that women with PCOM and hypothalamic amenorrhoea have inherently hyperandrogenic ovaries but are quiescent because of low gonadotrophin from hypothalamic inactivity and it is possible that over time they can fluctuate between hypothalamic amenorrhoea and PCOS depending on the status of the hypothalamic activity.[13,20] Wang et al.[20] found that PCOM in hypothalamic amenorrhoea is associated with increased ovarian androgen production when stimulated with low-dose gonadotrophin, comparable to levels found in patients with PCOS.[20]

However it is more commonly accepted that hypothalamic amenorrhoea with presence of PCOM is a completely different entity from PCOS and that the Rotterdam criteria due to it's laxity allows for the in accurate inclusion of this group in the PCOS category.

There is a growing number of authors who are proposing a change in the definition of PCOM and many suggestions have been proposed.

It has been suggested to raise the follicle threshold to 19 antral follicles or to use anti- Mullerian hormone (AMH)>35 pmol/l as a diagnostic marker of PCOM.[21] A threshold of 27 has also been suggested.[22] A task force report by the by the Androgen Excess and Polycystic Ovary Syndrome society recommends using 25 follicles per ovary following a systematic review comparing normative data from 1127 women of reproductive age.[23]

Lauitsen et al.[24] assessed a group of anovulatory infertile women with WHO Group II classification. The aim of their study was to evaluate a revised follicle threshold value for the definition of PCOM

as well as an increased cut off for AMH value. The Rotterdam PCOM threshold (>12 follicles) was fulfilled in 93% of these women. When the follicle cut- off threshold to diagnose PCOM was raised to 20, the prevalence was lowered to 68.0% (95% CI: 56.8–77.5), and when using the threshold of 25 follicles, the PCOM prevalence was further lowered to 52.0% (95% CI: 40.9–62.9). A cut-off value of AMH>35 pmol/l produced a prevalence of PCOM of 76.0% (95% CI: 65.2–84.3) The non-PCOM group as per the revised AFC threshold in comparison to the PCOM group contained a significantly lower number of patients with LH> 10 IU/L, LH/FSH ratio >2 and clinical and biochemical markers of hyperandrogenism. The authors found the characteristics of the women in the non-PCOM group were more compatible with hypothalamic anovulation, thereby helping to reduce the number of women with a hypothalamic component who were originally classified as PCOS.

Our data confirmed that these women can be identified using assessment of their estradiol levels as well as clinical acumen observing for other co-existing factors such as weight loss, excessive exercise or periods of stress.

Correct identification of these women allows for their appropriate management and care and prevention of long term effects of hypo-oestrogenaemia.

The strength of our study lies in the large number of patients assessed. However, the weakness lies in the retrospective collection of data and the presence of some missing investigations due to the somewhat heterogeneous approach to assessment and management of PCOS.

Conclusion

All in all what is abundantly clear, is that more research is required into this area, with more focus on patients with functional hypothalamic amenorrhoea who are misdiagnosed as PCOS due to PCOM. This supports also the need for a review of definition of PCOM, in light of vast improvements to USS technology and advancement.

Conflicts of interest

None by any authors.

Ethics

No ethical approval was needed for this study.

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