ORIGINAL ARTICLE *Reproductive endocrinology*

Diagnosis delayed: health profile differences between women with undiagnosed polycystic ovary syndrome and those with a clinical diagnosis by age 35 years

Renae C. Fernandez [1,2,3,]*, **Vivienne M. Moore**[2,3,4], **Alice R. Rumbold**[3,5], **Melissa J. Whitrow**[2,3], **Jodie C. Avery** [3], and **Michael J. Davies**[1,3]

[1]The University of Adelaide, Discipline of Obstetrics & Gynaecology, Adelaide, South Australia, Australia [2]The University of Adelaide, School of Public Health, Adelaide, South Australia, Australia [3]Robinson Research Institute, Adelaide, South Australia, Australia [4]Fay Gale Centre for Research on Gender, Adelaide, South Australia, Australia [5]SAHMRI Women and Kids, South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia

*Correspondence address. The University of Adelaide, Discipline of Obstetrics & Gynaecology, Adelaide, South Australia 5005, Australia. E-mail: renae.fernandez@adelaide.edu.au http://orcid.org/0000-0003-2617-2989

STUDY QUESTION: Are reproductive, metabolic or psychological health profiles of women with clinically diagnosed polycystic ovary syndrome (PCOS) different from those with undiagnosed PCOS?

SUMMARY ANSWER: Obtaining a clinical diagnosis of PCOS is strongly linked to the experience of fertility problems, but not clinical depression or poor metabolic health, although these were highly prevalent in women with PCOS irrespective of when they were diagnosed.

WHAT IS KNOWN ALREADY: PCOS is an endocrine disorder that is relative common, but heterogeneous in presentation. This may impact on the pathways to diagnosis and timely treatment.

STUDY DESIGN, SIZE, DURATION: A cross-sectional analysis of a community-based cohort of 974 women, established retrospectively when women were around 30 years of age.

PARTICIPANTS/MATERIALS, SETTING, METHODS: In this cohort of women born in Adelaide, South Australia, half of women who met the Rotterdam criteria for PCOS were previously undiagnosed. We compared women with prior clinical diagnosis of PCOS, those diagnosed through participation in this research, and the remainder in the cohort. Sociodemographic characteristics, reproductive, metabolic and psychological health, including medical conditions and medications were considered. Logistic regression was undertaken to identify independent predictors of prior clinical diagnosis.

MAIN RESULTS AND THE ROLE OF CHANCE: There were 56 women with a prior clinical diagnosis of PCOS (5.7%) and a further 64 (6.6%) were undiagnosed until study entry. The great majority of women with a prior diagnosis of PCOS reported having had problems with periods (95%) and excess body hair (63%). Corresponding proportions for women undiagnosed until study participation were slightly lower (81% and 45%, respectively). Although the proportion of women attempting or achieving pregnancy was similar across all groups, those with a prior diagnosis of PCOS were four times more likely to have reported difficulties becoming pregnant than those undiagnosed (odds ratio = 4.05, 95% CI 1.74–9.45) and frequently sought medical assistance. Metabolic problems were higher in both PCOS groups compared to women without PCOS. In both PCOS groups, the prevalence of clinical depression was 50% higher than in those with no PCOS ($P = 0.021$).

LIMITATIONS, REASONS FOR CAUTION: The number of women who were diagnosed with PCOS both prior to and during the study limited statistical power available to detect modest differences between the PCOS groups. Some women in the group classified as not having PCOS may have remained undiagnosed, but any bias from this source would contribute to more conservative findings.

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine condition, with metabolic, reproductive and psychological sequelae (Escobar-Morreale, 2018). It may affect 6–18% of reproductive-aged women, although prevalence estimates vary by the source population and diagnostic criteria applied (March et al., 2010; Escobar-Morreale, 2018; Witchel et al., 2020).

Cardinal symptoms of PCOS include irregular or absent periods, excessive hair growth and difficulty becoming pregnant (Escobar-Morreale, 2018). These reflect the underlying hormonal imbalance (hyperandrogenaemia) and ovarian dysfunction that are hallmarks of the syndrome. As well, some women with PCOS are susceptible to weight gain and have increased risks of metabolic complications including insulin resistance, diabetes, hypertension and dyslipidaemia (Cooney and Dokras, 2018). Elevated anxiety and depression are consistently reported in women with PCOS (Barry et al., 2011; Karjula et al., 2017), although it is uncertain whether this reflects perturbed endocrinology or distress created by PCOS symptoms, or the stigma of receiving a diagnosis (Karjula et al., 2017; Fernandez et al., 2018).

Historically, most women have not received a diagnosis of PCOS until they sought fertility treatment (Homburg, 1996; Lujan et al., 2008). The development of international diagnostic criteria for PCOS and evidence-based guidelines has led to increased awareness of the syndrome among healthcare providers and women. However, gaining a diagnosis still seems to be problematic as women report that multiple consultations with several different health professionals were often required (Gibson-Helm et al., 2017).

Timely diagnosis of PCOS may enable women to receive support for managing aspects of the condition that affect health, slowing progression of comorbidities. Knowledge of the condition could also be useful for family planning, and promote lifestyle modifications that may reduce the recourse to fertility treatment (Huber-Buchholz et al., 1999; Crosignani et al., 2003). Conversely, it has been argued that diagnosis of women with mild symptoms could constitute unnecessary disease labelling and result in psychological harms through stigmatisation (Copp et al., 2017, 2019).

It is not known whether women who receive a diagnosis of PCOS have a specific symptomology. The inverse care law suggests it might be women who are most economically advantaged (O'Dea and Kilham, 2002; Marmot, 2018), since they are most likely to have the personal and financial resources to consult medical specialists.

In our community-based cohort study, half of women with PCOS were not diagnosed until they participated in the research (March et al., 2010). We therefore have a unique opportunity to examine characteristics of women who were diagnosed through their own encounters with the healthcare system and those who were diagnosed through study participation. The aim of this study was to compare these groups of women, and the remainder of the cohort, in order to identify the sociodemographic and health profiles of women who received an earlier diagnosis.

Materials and methods

Study recruitment/participants/ establishment of the cohort

The establishment of the cohort and the study protocol have been published previously (March et al., 2010; Moran et al., 2015; March et al., 2018). Cohort participants were born in 1973–75 in a large maternity hospital in Adelaide, South Australia. Around 30 years later, the 2199 eligible female births were traced. There were 1984 (90.2%) women confirmed still to be living, without any severe impairment, and these were invited to participate by letter and telephone. After acceptance, core first wave data were obtained from 974 (49.1%) women at a median age of 30.2 years.

Participants were broadly representative of all eligible female births at the maternity hospital, although with a slightly greater proportion of mothers from the highest socio-economic category (8.8% vs. 5.5%, derived from postcode of residence (Trewin, 2003)). The sociodemographic profile of participants' mothers was similar to that of all women giving birth in Adelaide at the time, reflecting the fact that the hospital was then one of only two major maternity hospitals in the city, with a geographically large catchment area.

Study protocol/diagnosis of PCOS

A core set of information was obtained through a structured interview with a trained nurse, usually in person. The interview covered many aspects of women's lives and medical history, including symptoms of PCOS, whether a clinical diagnosis of PCOS had been obtained, and details of any pregnancies. For women seen in person, height and weight were measured following standard protocols, otherwise self-reports were obtained. All women were invited to provide a fasting

blood sample following the interview, for biochemical analysis. Subsequently, women with at least one symptom of PCOS (menstrual dysfunction or hyperandrogenism) were referred to a reproductive medicine clinic for a transvaginal ultrasound. Women who did not report a clinical diagnosis of PCOS before participation in the study were classified as having PCOS if they met the Rotterdam criteria for diagnosis.

Menstrual irregularity was defined as chronic amenorrhoea, or cycle length of less than 21 days or more than 35 days, or variation of more than 4 days between cycles. Hyperandrogenism was based on measurement of free testosterone in the blood sample and/or the modified Ferriman-Gallwey (mF-G) score for hirsutism of >7 (Hatch et al., 1981). Polycystic ovaries (PCO) were identified by the presence of either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume ($>10 \, cm^3$) in at least one of the ovaries (Balen et al., 2003).

For the present work, the cohort was divided into three comparison groups. The first consisted of women who reported a diagnosis of PCOS before participating in the study (prior diagnosis group). The second group comprised women who were diagnosed through participation in our research and undergoing testing in the first wave of follow-up of the cohort (study diagnosis group), and the third was women who did not receive a diagnosis of PCOS through either of these pathways (no PCOS group). This last group may contain some women with undiagnosed PCOS as not all women with either menstrual irregularity or hyperandrogenism accepted the invitation to have an ultrasound, including 15 of those who reported a prior diagnosis of PCOS. Of the 56 with a prior diagnosis, 33 (59%) fulfilled the criteria for PCOS at the time of the study, a further 15 (27%) may have, and 8 (14%) did not.

Description of explanatory variables

Age of diagnosis was obtained directly from women's self-report or derived from the reported year of diagnosis. Eight women with a prior PCOS diagnosis did not provide either information, so age was estimated based on reports of when treatment commenced (n = 2) or diagnostic tests were performed (n = 1) or, in the absence of that information, when symptoms were experienced (n = 3). Two women indicated that they were diagnosed after the birth of their last child, so age of diagnosis was estimated as birth year of that child, plus 1 year.

Women reported their ethnicity and educational attainment. An area-level index of socioeconomic status was derived from current postcode of residence (Trewin, 2003). Women's BMI at the time of interview was calculated as weight (kg) divided by the square of height (m); women were classified as overweight or obese using cut-offs of 25, 30 and 35 kg/m², respectively. Current BMI was not available for 32 women who were missing height (n = 27) and/or weight (n = 32) measurements. For 19 women, BMI was imputed from self-reported heaviest or lowest weight (ascertained in a specific question) if the corresponding year was at most 2 years before study participation in combination with either measured height or the average height of the cohort (164 cm).

Daily intake of alcohol was classified as none, one, two or more standard drinks. Other health risk factors were classified as present or absent, including daily smoking and ever having a clinical diagnosis of high blood pressure, high cholesterol, high blood glucose levels,

diabetes or depression. Current symptoms of depression were assessed using the Center for Epidemiological Studies Depression Scale (CES-D), with a score of 16 or more indicating the presence of clinical depression (Radloff, 1977; Weissman et al., 1977). Current medications were recorded, with use of metformin, antidepressants and asthma medications and thyroxine extracted for this analysis.

As part of the medical histories, women reported the age at which they first menstruated (age of menarche), and whether or not they had 'ever had problems' with weight, acne, excess body hair or periods, and whether they had ever used the contraceptive pill to manage period problems. Women were asked whether they had ever been pregnant and, if so, to provide details of all outcomes: number of live births, stillbirths, miscarriages, ectopic pregnancies and terminations. Women who had attempted or achieved pregnancy were asked whether they ever had any difficulty getting pregnant and, if so, to describe the difficulty and whether a healthcare practitioner was consulted.

After the clinical interview, women completed the Multidimensional Body-Self Relations Questionnaire—Appearance Scales (MBSQ-AS). This is a validated 34-item questionnaire assessing body image on five subscales; Appearance Evaluation (feelings about physical attractiveness), Appearance Orientation (extent of investment in one's appearance), Body Areas Satisfaction Scale (BASS, satisfaction with discrete aspects of one's appearance), Overweight Preoccupation (fat anxiety and weight vigilance) and Self-Classified Weight (how one perceives one's weight) (Brown et al., 1990; Cash, 2000). Higher scores on the Appearance Evaluation and Body Areas Satisfaction subscales indicate greater satisfaction with one's appearance and more positive body image construct. Higher scores on the Appearance Orientation, Overweight Preoccupation and Self-Classified Weight indicate lower satisfaction with one's appearance or more negative body image construct.

Statistical analysis

The average age of diagnosis for women who reported being diagnosed with PCOS before participation in the study was computed. Age at diagnosis was also categorized in 5-year age bands.

Characteristics of women in three mutually exclusive groups were compared: those with a prior diagnosis of PCOS, those diagnosed through study participation, and those without a diagnosis. Distributions of sociodemographic, health-related and reproductive variables were tabulated. Group differences in categorical variables were assessed using chi-square tests. Continuous variables were presented as means and standard deviations, or medians and interquartile ranges and group differences assessed using Student's t-test or Mann–Whitney U as appropriate.

For each question in the MBSRQ-AS, participants indicated a score on Likert scales. An average score was computed for each of the five subscales for each woman. Comparison of average scores on each of the subscales were compared across the three groups using one-way ANOVA.

Multivariable logistic regression was undertaken to identify independent predictors of prior diagnosis, presented as odds ratios and 95% CI. Potential predictive variables were included in the model if the P-value was ≤0.20 in univariate analyses comparing the prior and study

diagnosis groups. All tests used the 5% significance level. Data analysis was performed using Stata version 14.2.

Ethical approval

The study was approved by the Queen Elizabeth Hospital and University of Adelaide ethics committees (H/36/99, March 2000) and all participants gave written informed consent.

Results

The average age of diagnosis for the 56 women who had received a clinical diagnosis of PCOS before participating in the cohort study was 24.4 years. A prior diagnosis was received at less than 20 years for 9 women (16.1%), at 20–24 years for 16 women (28.6%), 25–29 years for 28 women (50.0%) and 30–35 years for 3 women (5.4%). There were 64 women who received a diagnosis of PCOS through participation in the study (during 2003–2007) at an average age of 30.4 years, range 28.7–32.2 years.

The full distribution of socio-economic status was represented in the cohort (Table I), roughly in proportion to the wider population (from quartile bands). Educational attainment was similar to that of all Australian women in this age group born in the same period (Tunny, 2006). The low number of Asian women is expected in a birth cohort from this era. Although there were no statistically significant differences between the PCOS groups, it is notable that the group with a prior diagnosis had the smallest proportion of women with university qualifications and the largest proportion of women living in the most disadvantaged areas.

Compared with women diagnosed with PCOS during the study, among those with a prior diagnosis there were more reports of 'problems with periods' ($P = 0.02$) (Fig. 1). Differences between these two groups in reports of ever having problems with acne ($P = 0.06$) or excess body hair ($P = 0.06$) were of borderline statistical significance. All comparisons that included the remainder of the cohort as a third group were statistically significant.

Over half of both groups of women with PCOS had clinical hirsutism (prior diagnosis n = 31, 55.4%, and study diagnosis n = 45, 70.3%). The difference in proportions was not statistically significant ($P = 0.09$), but box and whisker plots (Fig. 2) suggested that women with the most extreme hirsutism scores may be in the prior diagnosis group. Among women without PCOS, the median hirsutism score was low, although a proportion of this group had clinical hirsutism (n = 127, 14.9%).

Lifestyle variables did not differ substantially between the prior diagnosis and study diagnosis groups at age 27–34 years (Table I) although the proportion of women in the former group that smoked (37.5%) and of the latter group with BMI of at least 35 kg/m^2 (38.1%) are noteworthy. While the proportions of the prior diagnosis group with medical conditions and taking medications were consistently higher than those for the study diagnosis group, only the increase for metformin was statistically significant. Half of women in the prior diagnosis group and the study diagnosis group had current symptoms of depression consistent with clinical depression (CES-D > 16). Thus, both groups had relatively poor health profiles compared with those with no PCOS.

By age 35 years, over two-thirds of women in all three groups had attempted or achieved pregnancy (Table II). Among these women, 33 in each of the two PCOS groups (72–73%) had a live birth and 503 (83%) of those without PCOS ($P = 0.1$). Women diagnosed with PCOS prior to the study were significantly more likely to have experienced difficulties becoming pregnant compared to women diagnosed as part of the study. Of note, 57.8% of the prior diagnosis group consulted a medical practitioner for infertility compared with 19.6% of the study diagnosis group and 9.1% of the no PCOS group; treatment frequently ensued. Aside from use of the oral contraceptive pill to manage period problems, there were no other statistically significant differences in reproductive history and pregnancy outcomes between these groups, although data were sparse for uncommon outcomes; patterns observed in the data suggested that the adverse outcome of pregnancy loss may be elevated among women with PCOS.

One-way ANOVA analysis of the MBSRQ-AS subscales across the three groups indicated that the mean scores differed significantly ($P < 0.001$) for all but the Appearance Orientation subscale (Fig. 3). However, the prior and study diagnosis groups did not differ in their mean scores for any of the five MBSRQ-AS subscales.

In the logistic regression analyses, experiencing difficulties becoming pregnant was the only variable that was statistically significant and independently associated with diagnosis of PCOS prior to study entry in comparison with diagnosis through study participation (Table III). Other characteristics that approached statistical significance were self-reported acne and self-reported period problems. Several variables that were potentially associated with prior PCOS diagnosis in univariate analysis (i.e. $P \leq 0.2$) could not be included in regression models due to collinearity (consulted health practitioner for infertility) or sparse data (specific medications). Ever using the oral contraceptive pill to manage period problems was entered into the model, but not retained ($P = 0.56$). Likewise, year of birth was not retained ($P = 0.44$).

Discussion

In this community-based cohort, around 6% of women reported a prior diagnosis of PCOS and a similar proportion were diagnosed through study participation when aged around 30 years. With regard to the pathways to a diagnosis, the great majority of women with a prior diagnosis of PCOS reported having had 'problems with periods' including irregular cycles and amenorrhoea, and at least half reported problems with acne and excess body hair. That these proportions were somewhat higher than for women diagnosed through study participation suggests symptom severity and/or concerns about symptoms contributed to gaining a diagnosis. Some support for more severe objective symptoms is provided by the finding that the group with a prior diagnosis of PCOS contained women with the most extreme clinical hirsutism scores.

Commencement of the oral contraceptive pill for irregular menstrual cycles or acne may delay diagnosis of PCOS (Prelevic *et al.*, 1993). Consistent with women's reports of pill use for period problems, it seems that this occurred quite widely when these women were teenagers and young adults in the late 1980s and through the 1990s. Recent recommendations from the International Evidence-based Guideline for the Assessment and Treatment of PCOS promote the

Table I Demographic, lifestyle and health characteristics of women by polycystic ovary syndrome diagnosis group.

	PCOS diagnosis				
	Prior diagnosis (N = 56)	Study diagnosis (N = 64)	Prior vs Study P-value[a]	No PCOS (N = 854)	Three-group comparison P-value[a]
Age at follow-up					
Median (IQR)	30.6 (30.0–31.4)	30.2 (29.9–30.8)	0.20	30.6 (30.0–31.5)	0.02
Sociodemographics	**n (%)**	**n (%)**		**n (%)**	
Educational attainment			0.47		0.50
Some high school	19 (33.9)	24 (37.5)		253 (29.6)	
Completed high school	26 (46.4)	23 (35.9)		377 (44.2)	
University	11 (19.6)	17 (26.6)		224 (26.2)	
Socio-economic index for area			0.75		0.21
Quartile 1 (most disadvantaged)	19 (33.9)	17 (26.6)		188 (22.0)	
Quartile 2	14 (25.0)	20 (31.3)		212 (24.8)	
Quartile 3	11 (19.6)	11 (17.2)		236 (27.6)	
Quartile 4 (least disadvantaged)	12 (21.4)	16 (25.0)		218 (25.5)	
Ethnicity			0.63		0.23
Asian	0 (0.0)	0 (0.0)		9 (1.1)	
European	53 (94.6)	59 (92.2)		809 (94.7)	
Pacific/aboriginal	3 (5.4)	4 (6.3)		18 (2.1)	
Other/unknown	0 (0.0)	1 (1.6)		18 (2.1)	
Health risk factors	**n (%)**	**n (%)**		**n (%)**	
Current BMI[b]			0.67		<0.001
Underweight/normal (<25)	14 (25.5)	15 (23.8)		412 (48.9)	
Overweight (25–<30)	14 (25.5)	13 (20.6)		232 (27.5)	
Obese 1 (30–<35)	13 (23.6)	11 (17.5)		109 (12.9)	
Obese 2/3 (35+)	14 (25.5)	24 (38.1)		90 (10.7)	
Current smoker	21 (37.5)	19 (29.7)	0.37	230 (26.9)	0.22
Current alcoholic drinks per day					
0	14 (25.0)	11 (17.2)	0.53	147 (17.4)	0.09
1	16 (28.6)	18 (28.1)		344 (40.6)	
≥2	26 (46.4)	35 (54.7)		356 (42.0)	
Medical conditions (ever diagnosed)					
High blood pressure	10 (17.9)	5 (7.8)	0.10	43 (5.0)	<0.001
High cholesterol	9 (16.1)	6 (9.4)	0.27	44 (5.2)	0.002
High blood sugar	6 (10.7)	4 (6.3)	0.38	14 (1.6)	<0.001
Diabetes	0 (0.0)	1 (1.6)	0.35	5 (0.6)	0.52
Depression	18 (32.1)	20 (31.3)	0.92	175 (20.5)	0.021
Asthma	21 (37.5)	17 (26.6)	0.20	209 (24.0)	0.092
Thyroid condition	3 (5.4)	5 (7.8)	0.59	28 (3.3)	0.14
Clinical depression from symptom score[c]	26 (51.0)	29 (50.0)	0.92	235 (29.2)	<0.001
Current medication use					
Any medication	27 (48.2)	20 (31.3)	0.06	226 (26.5)	0.002
Metformin	5 (8.9)	0 (0.0)	0.02	1 (0.1)	<0.001
Antidepressant	4 (7.4)	3 (4.7)	0.57	38 (4.5)	0.65
Asthma medications	4 (7.1)	2 (3.1)	0.31	39 (4.6)	0.57
Thyroxine	0 (0.0)	3 (4.7)	0.11	9 (1.1)	0.03

[a]Pearson's Chi^2 test.
[b]BMI data was missing for 13 women (Prior PCOS = 1, Study PCOS = 1, No PCOS = 11).
[c]Center for Epidemiological Studies Depression Scale (CES-D) > 16; score missing for 60 women (Prior PCOS = 5, Study PCOS = 6, No PCOS = 49).
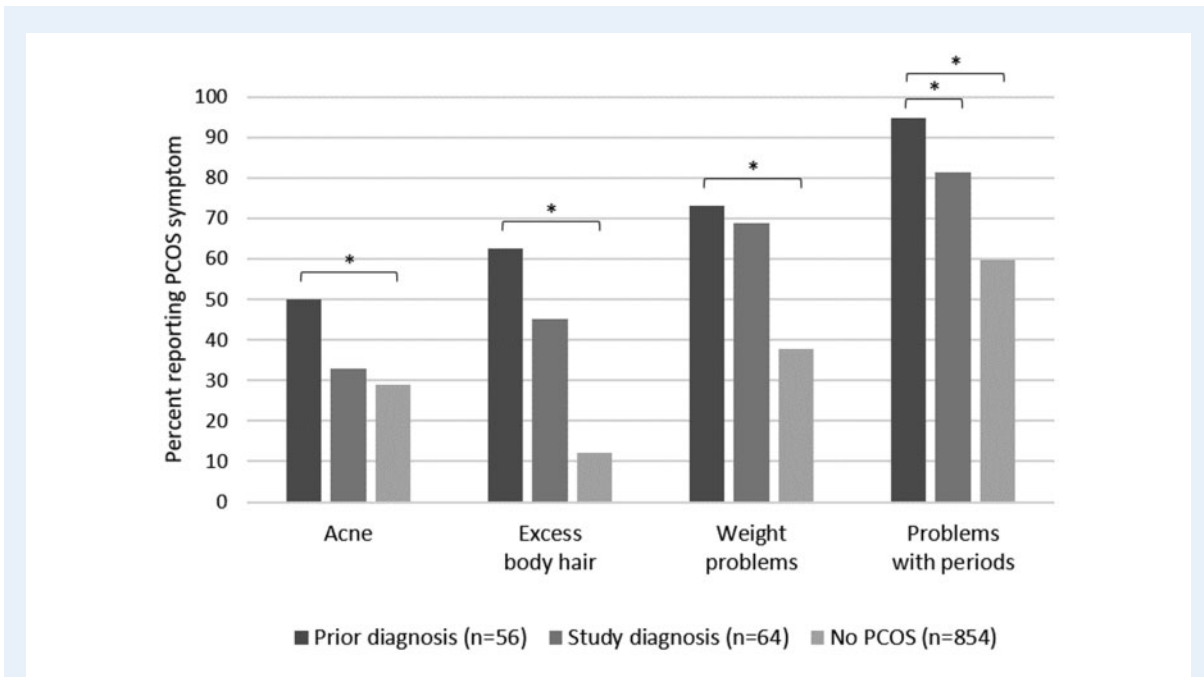IQR, interquartile range; PCOS, polycystic ovary syndrome.

Figure 1. Frequency of self-reported polycystic ovary syndrome (PCOS) symptoms in women by PCOS diagnosis group. *P < 0.05.
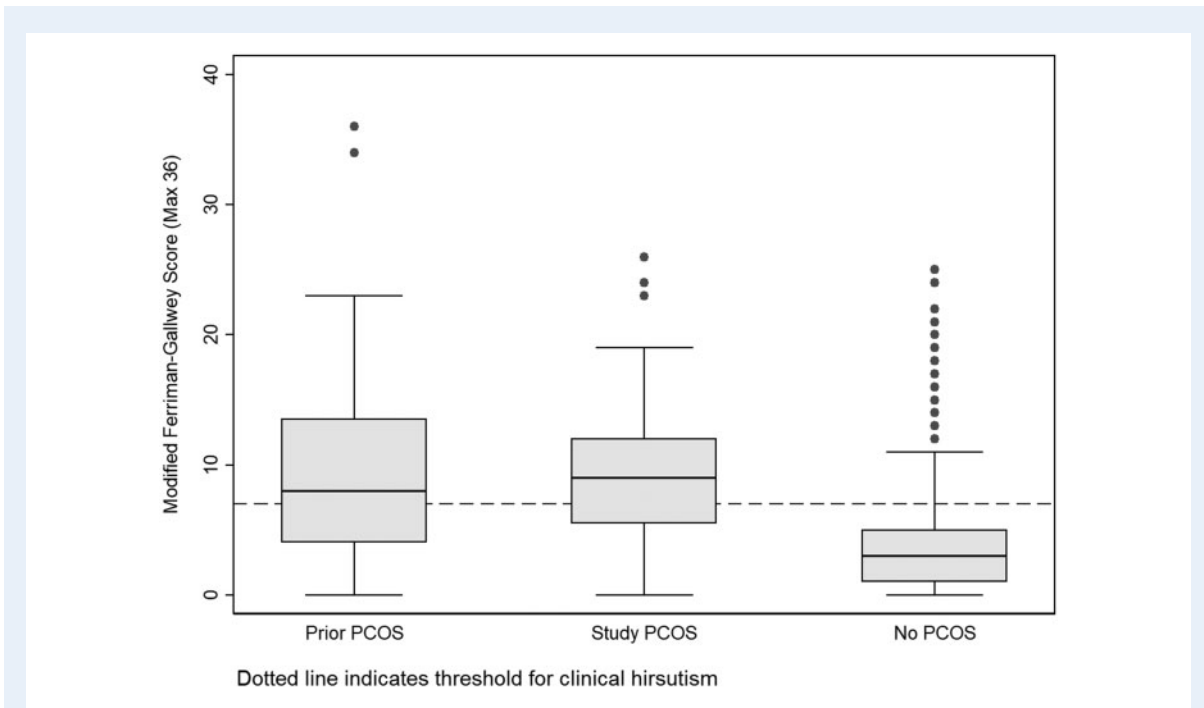

Figure 2. Distribution of the modified Ferriman-Gallwey Score by polycystic ovary syndrome (PCOS) diagnosis group. Dotted line indicates threshold for clinical hirsutism. Upper and lower bounds of the boxes represent the upper (75%) and lower (25%) quartiles. Median values are indicated by the horizontal bar across the boxes. Whiskers indicate the spread of the data, and are calculated as 1.5 × interquartile range above the upper quartile (upper whisker) and below the lower quartile (lower whisker). Points above the box and whisker plots indicate outliers.

Table II Reproductive history of women by polycystic ovary syndrome diagnosis group.

	PCOS diagnosis				
	Prior diagnosis (N = 56)	Study diagnosis (N = 64)	Prior vs study P-value[a]	No PCOS (N = 854)	Three-group comparison P-value[a]
	n (%)	n (%)		n (%)	
Age of menarche			0.68		0.37
<11 years	3 (5.4)	4 (6.3)		32 (3.8)	
11 to <12 years	7 (12.5)	14 (21.9)		110 (12.9)	
12 to <13 years	18 (32.1)	18 (28.1)		241 (28.2)	
13 to <14 years	15 (26.8)	13 (20.3)		231 (27.1)	
≥14 years	13 (23.2)	14 (21.8)		238 (27.9)	
Ever used oral contraceptive pill to manage period problems	35 (62.5)	32 (50.0)	0.17	305 (35.7)	<0.001
Attempted or achieved pregnancy	45 (80.4)	46 (71.9)	0.28	614 (71.9)	0.39
Among those who attempted or achieved pregnancy	N = 45	N = 46		N = 614	
Difficulties becoming pregnant	32 (71.1)	17 (37.0)	0.001	114 (18.6)	<0.001
Consulted health practitioner for infertility	26 (57.8)	9 (19.6)	<0.001	56 (9.1)	<0.001
Pregnancy outcomes, among those ever pregnant	N = 41	N = 44		N = 586	
One or more terminations	7 (17.1)	11 (25.0)	0.37	165 (28.2)	0.29
One or more ectopic pregnancies, miscarriages or stillbirths	15 (36.6)	15 (34.1)	0.81	139 (23.7)	0.07
One or more live births	33 (80.5)	33 (75.0)	0.54	503 (85.8)	0.11

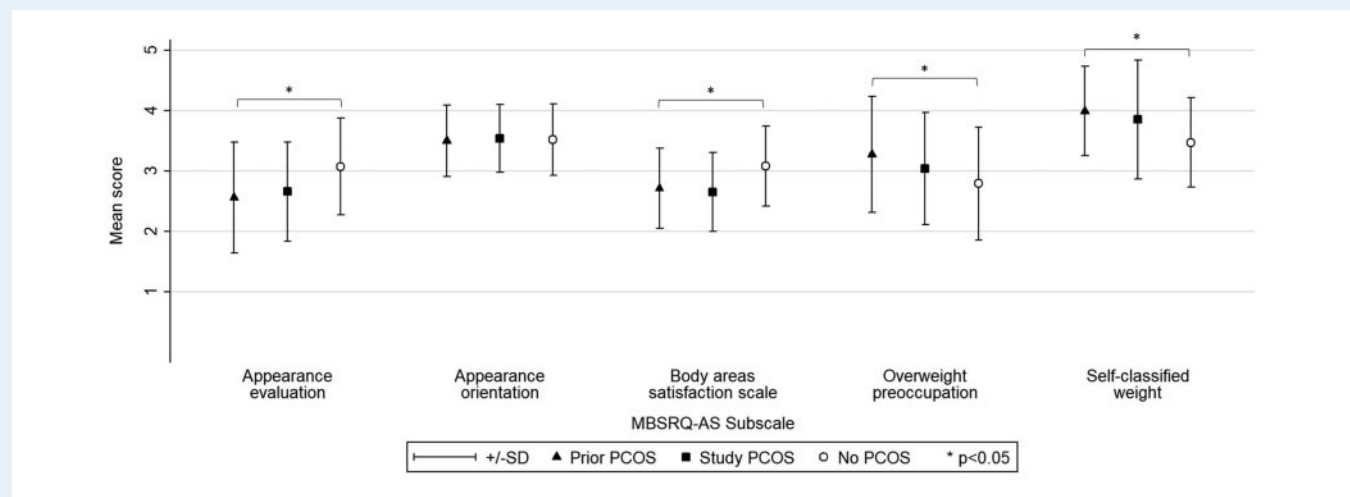[a]Pearson's Chi[2] test.
PCOS, polycystic ovary syndrome.

Figure 3. Mean and SD of scores for the Multidimensional Body-Self Relational Questionnaire—Appearance Scale components by polycystic ovary syndrome (PCOS) diagnosis group. *$P < 0.05$.

identification of 'at risk' girls who should receive follow-up and re-assessment for PCOS at reproductive maturity (3 years post-menarche), whilst also being provided with immediate support and treatment for presenting symptoms (Peña et al., 2020).

The great majority of the group of women with a prior diagnosis of PCOS had attempted or achieved pregnancy. The socio-economic background of this group is consistent with somewhat earlier plans for family formation. Difficulties becoming pregnant were commonly experienced in those desiring parenthood in this group, with over half having sought assistance. Thus it is highly plausible that fertility concerns contributed to clinical contact and a diagnosis of PCOS. Gaining a diagnosis in this way may partly reflect greater knowledge of PCOS among

Table III Logistic regression analysis of factors associated with gaining a prior diagnosis of polycystic ovary syndrome compared with diagnosed through study participation (n = 120).

Factor	Odds ratio [95% CI][a]
Self-reported acne	2.11 [0.90–4.93]
Self-reported excess body hair	1.67 [0.72–3.87]
Self-report weight problems	0.84 [0.34–2.10]
Self-reported period problems	3.27 [0.81–13.16]
Difficulties becoming pregnant	
No difficulties/never attempted	Reference
Difficulties	4.05 [1.74–9.45]
Ever diagnosed with high blood pressure	2.98 [0.80–11.10]
Any medication use	1.76 [0.76–4.10]

[a]Multiple logistic regression analysis, including all variables presented in the table.

gynaecology and fertility specialists, whereas women with PCOS symptoms other than fertility problems may have consulted healthcare practitioners who were less alert to the possibility. It is noteworthy that around a third of women attempting pregnancy in both PCOS groups had experienced ectopic pregnancy, miscarriage or stillbirth; while not reaching statistical significance, this finding is consistent with other reports for women with PCOS (Bahri Khomami *et al.*, 2019).

Socio-economic advantage did not appear to explain why women did or did not gain a diagnosis of PCOS through their own encounters with the healthcare system, ruling out the inverse care law—at least in Australia which has universal health coverage. The two groups of women with PCOS were in many ways more similar to each other than to the remainder of the cohort, suggesting an arbitrary aspect to gaining a diagnosis. The association between socio-economic status and PCOS is likely to be complicated, if poor psychological health is a feature of the condition as our data suggest, since this affects engagement with schooling, further study, employment and careers (Lagerveld *et al.*, 2010; Finning *et al.*, 2019). A Danish study of socio-economic factors and PCOS considers the further complexity of migration and ethnic background in relation to socio-economic status (Rubin *et al.*, 2019).

The current health profiles of women not diagnosed with PCOS until they participated in the study raise some concerns. Over one third had severe (class 2/3) obesity. That they had fewer diagnosed metabolic conditions compared with those with a prior PCOS diagnosis (among who a quarter had severe obesity) points to lack of appropriate health care, rather than better health.

These findings do not support the argument that remaining undiagnosed avoids harms that may come with a disease label (Copp *et al.*, 2017). To the contrary, irrespective of when the PCOS diagnosis occurred, almost a third of women with PCOS had experienced clinically diagnosed depression, a prevalence 50% higher than for women without PCOS. In addition, half of women with PCOS reported depressive symptoms consistent with current clinical depression (assessed using CES-D, a validated scale), compared with 30% of women without PCOS. This provides evidence that poor psychological health is a feature of the condition, rather than produced by the label, consistent

with the findings of Karjula *et al.* (2017). Furthermore, it suggests that this aspect of health had not received appropriate attention and care in women known to have PCOS. These findings reinforce new recommendations in the international evidence-based PCOS guideline to screen all women with PCOS for depression and anxiety (Jacob and Balen, 2019).

Regardless of when they were diagnosed, women with PCOS scored similarly on the MBSQ-AS subscales for assessing body image. Specifically, feelings about physical attractiveness, extent of investment in one's appearance, satisfaction with aspects of appearance, anxiety about fatness, vigilance around weight and perception of weight were similar. On all but one subscale (Appearance Orientation), scores for women with PCOS indicated more negative body image compared to women without PCOS. Negative perceptions of body image have been found previously among women with PCOS and are likely to contribute to their poorer psychological health (Deeks *et al.*, 2011; Alur-Gupta *et al.*, 2019) although we emphasise that this does not adequately account for or diminish the seriousness of mental health problems experienced by women with PCOS (Veltman-Verhulst *et al.*, 2012).

While it is hoped that early symptoms of PCOS receive more attention now, inconsistent knowledge and practices regarding PCOS diagnosis by care providers continues to be a concern (Dokras *et al.*, 2017; Gibson-Helm *et al.*, 2018; Piltonen *et al.*, 2019). A recent qualitative study also found that a negative response to diagnosis of PCOS, particularly among women with milder phenotypes, was influenced by diagnostic experience, doctor communications and lack of evidence-based information about the condition (Copp *et al.*, 2019). We welcome the substantial clinician and patient education strategies accompanying the implementation of the international evidence-based PCOS guideline to improve the timely diagnosis of PCOS (Teede *et al.*, 2018). This is a critical step in improving the support women receive to manage the distressing and often debilitating consequences of this complex condition. Furthermore, our study shows that despite the high likelihood of difficulties in becoming pregnant among the women with a diagnosis of PCOS who desired motherhood, the proportion achieving a live birth was similar to that of their peers by the time of the study. This could provide women with PCOS reassurance about their prospects of having children (with medical assistance if required) and suggests healthcare attention should be directed to improved management of other aspects of the condition.

A strength of this study is that it involved the use of data from an unselected community-based cohort of women. This overcomes the limitations of clinic-based cohorts, which tend to comprise women with the most severe manifestations of PCOS who have concerns about fertility. Other strengths are that women from across the spectrum of socio-economic status were represented in the cohort and the demographic profile of participants was broadly similar to that of the wider population of women the same age. Also, women reported on their history of clinically diagnosed depression and current depression symptoms before they knew they met criteria for PCOS. We note that the international guideline published in 2018 recommends new diagnostic criteria for PCOS (mF-G score greater than 3, 20 follicles but same ovarian volume threshold for PCO) (Teede *et al.*, 2018). However, the relevant comparison group in this study was identified with the criteria that then applied, comprising women who did not receive the clinical attention that they merited and could have gained at the time.

A limitation is that the number of women who were diagnosed with PCOS both prior to and during the study was small relative to effect sizes, resulting in limited statistical power to detect modest but potentially clinically meaningful differences between the PCOS groups. The protocol for the present study may have misclassified some cases as not having PCOS, but any bias would be in a conservative direction, as this would render the group without PCOS more similar to the other two. Study participants were predominantly white, reflecting the 'white Australia' migration policy that was in place until 1973 and created an ethnically narrow population (Windschuttle, 2004). Sparse data for rarer outcomes, such as ectopic pregnancy and stillbirth, meant that several types of pregnancy loss were reported in a combined variable, despite different biological mechanisms. Another limitation is that anxiety was not assessed. In the Northern Finland Birth Cohort 1966, women who were aware that they had PCOS had moderate anxiety symptoms to a greater extent than women who met criteria for PCOS but were not aware of this; however, the two groups were similar in terms of severe anxiety and depression (Karjula et al., 2017).

Conclusion

In this community-based cohort, half of women who met the Rotterdam criteria for PCOS were undiagnosed by age 35 years. Women with fertility problems were most likely to gain a diagnosis. Women who were undiagnosed experienced an excess of period problems, and hirsutism, perhaps to a slightly lesser degree than women with a prior diagnosis. Importantly, both groups had relatively poor psychological health, evidence that anxiety and depression in women with PCOS is not a consequence of the disease label and clinical contact. Together, findings reinforce the need for monitoring symptomatic women from adolescence, so that timely diagnosis and appropriate health care may be provided.

Data availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. Any requests will be considered by the corresponding author.

Acknowledgements

We gratefully acknowledge the contribution from the women who participated in the study. We are also grateful to Kendall Smith for the study co-ordination and management of the interviews and Nanette Kretschmer for her involvement in tracing the women, and Fred Amato and staff at Repromed for their assistance with blood assays. Also, thank you to the many other staff members involved in the interviews, database construction and data entry.

Authors' roles

Authors M.J.D. and V.M.M. were the principal investigators of the Lucina cohort. Together with R.C.F. and A.R.R. they formulated the research question reported in the manuscript and directed its implementation. R.C.F. planned and conducted the statistical analysis, and with

V.M.M. drafted the manuscript. All authors contributed to the interpretation of analyses, the critical revision of important intellectual content and final approval of the manuscript.

Conflict of interest

The authors report no conflict of interest.

References

Alur-Gupta S, Chemerinski A, Liu C, Lipson J, Allison K, Sammel MD, Dokras A. Body-image distress is increased in women with polycystic ovary syndrome and mediates depression and anxiety. *Fertil Steril* 2019;**112**:930–938.e1.

Bahri Khomami M, Joham AE, Boyle JA, Piltonen T, Silagy M, Arora C, Misso ML, Teede HJ, Moran LJ. Increased maternal pregnancy complications in polycystic ovary syndrome appear to be independent of obesity—a systematic review, meta-analysis, and meta-regression. *Obes Rev* 2019;**20**:659–674.

Balen AH, Laven JSE, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update* 2003;**9**:505–514.

Barry JA, Kuczmierczyk AR, Hardiman PJ. Anxiety and depression in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod* 2011;**26**:2442–2451.

Brown TA, Cash TF, Mikulka PJ. Attitudinal body-image assessment: factor analysis of the body-self relations questionnaire. *J Pers Assess* 1990;**55**:135.

Cash TF. The Multidimensional Body-Self Relations Questionnaire (MBSRQ) users' manual, 3rd Revision. 2000, Norfolk VA. Available from: http://www.body-images.com/assessments/mbsrq.html.

Cooney LG, and, Dokras A. Beyond fertility: polycystic ovary syndrome and long-term health. *Fertil Steril* 2018;**110**:794–809.

Copp T, Hersch J, Muscat DM, McCaffery KJ, Doust J, Dokras A, Mol BW, Jansen J. The benefits and harms of receiving a polycystic ovary syndrome diagnosis: a qualitative study of women's experiences. *Hum Reprod Open* 2019;**2019**:hoz026.

Copp T, Jansen J, Doust J, Mol BW, Dokras A, McCaffery K. Are expanding disease definitions unnecessarily labelling women with polycystic ovary syndrome? *BMJ* 2017;**358**:j3694.

Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Hum Reprod* 2003; **18**:1928–1932.

Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? *Hum Reprod* 2011;**26**:1399–1407.

Dokras A, Saini S, Gibson-Helm M, Schulkin J, Cooney L, and, Teede H. Gaps in knowledge among physicians regarding diagnostic criteria and management of polycystic ovary syndrome. *Fertil Steril* 2017;**107**:1380–1386.e1.

Escobar-Morreale HF. Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nat Rev Endocrinol* 2018;**14**:270.

Fernandez RC, Moore VM, Van Ryswyk EM, Varcoe TJ, Rodgers RJ, March WA, Moran LJ, Avery JC, McEvoy RD, MD. Sleep disturbances in women with polycystic ovary syndrome: prevalence, pathophysiology, impact and management strategies. *Nat Sci Sleep* 2018;**2018**:45–64.

Finning K, Ukoumunne OC, Ford T, Danielsson-Waters E, Shaw L, Romero De Jager I, Stentiford L, Moore DA. The association between child and adolescent depression and poor attendance at school: a systematic review and meta-analysis. *J Affect Disord* 2019; **245**:928–938.

Gibson-Helm M, Dokras A, Karro H, Piltonen T, and, Teede HJ. Knowledge and practices regarding polycystic ovary syndrome among physicians in Europe, North America, and Internationally: an online questionnaire-based study. *Semin Reprod Med* 2018;**36**: 19–27.

Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed diagnosis and a lack of information associated with dissatisfaction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2017;**102**: 604–612.

Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 1981;**140**: 815–830.

Homburg R. Polycystic ovary syndrome—from gynaecological curiosity to multisystem endocrinopathy. *Hum Reprod* 1996;**11**: 29–39.

Huber-Buchholz M-M, Carey DGP, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 1999;**84**:1470–1474.

Jacob S, Balen AH. How will the new global polycystic ovary syndrome guideline change our clinical practice? *Clin Med Insights Reprod Health* 2019;**13**:1179558119849605.

Karjula S, Morin-Papunen L, Auvinen J, Ruokonen A, Puukka K, Franks S, Järvelin M-R, Tapanainen JS, Jokelainen J, Miettunen J et al. Psychological distress is more prevalent in fertile age and premenopausal women with PCOS symptoms: 15-year follow-up. *J Clin Endocrinol Metab* 2017;**102**:1861–1869.

Lagerveld SE, Bültmann U, Franche RL, van Dijk FJH, Vlasveld MC, van der Feltz-Cornelis CM, Bruinvels DJ, Huijs JJJM, Blonk RWB, van der Klink JJL et al. Factors associated with work participation and work functioning in depressed workers: a systematic review. *J Occup Rehabil* 2010;**20**:275–292.

Lujan ME, Chizen DR, Pierson RA. Diagnostic criteria for polycystic ovary syndrome: pitfalls and controversies. *J Obstet Gynaecol* 2008; **30**:671–679.

March WA, Moore VM, Willson KJ, Phillips DIW, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod* 2010;**25**:544–551.

March WA, Whitrow MJ, Davies MJ, Fernandez RC, Moore VM. Postnatal depression in a community-based study of women with polycystic ovary syndrome. *Acta Obstet Gynecol Scand* 2018;**97**: 838–844.

Marmot M. An inverse care law for our time. *BMJ* 2018;**362**:k3216.

Moran LJ, March WA, Whitrow MJ, Giles LC, Davies MJ, and, Moore VM. Sleep disturbances in a community-based sample of women with polycystic ovary syndrome. *Hum Reprod* 2015;**30**: 466–472.

O'Dea JF, Kilham RJ. The inverse care law is alive and well in general practice. *Med J Aust* 2002;**177**:78–79.

Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, Garad R, Dabadghao P, Teede H. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. *BMC Med* 2020;**18**:72.

Piltonen TT, Ruokojärvi M, Karro H, Kujanpää L, Morin-Papunen L, Tapanainen JS, Stener-Victorin E, Sundrström-Poromaa I, Hirschberg AL, Ravn P et al. Awareness of polycystic ovary syndrome among obstetrician-gynecologists and endocrinologists in Northern Europe. *PLoS One* 2019;**14**:e0226074.

Prelevic GM, Wurzburger MI, Balint-Peric L. 24-hour serum cortisol profiles in women with polycystic ovary syndrome. *Gynecol Endocrinol* 1993;**7**:179–184.

Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;**1**:385–401.

Rubin KH, Andersen MS, Abrahamsen B, Glintborg D. Socioeconomic status in Danish women with polycystic ovary syndrome: a register-based cohort study. *Acta Obstet Gynecol Scand* 2019;**98**:440–450.

Teede H, Misso ML, Costello M, Dokras A, Laven JS, Moran LJ, Piltonen T, Norman RJ. *International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome.* Melbourne, Australia: Monash University, 2018.

Trewin D. *Information Paper: Census of Population and Housing Socio-Economic Indexes for Areas, Australia, 2001.* Canberra, Australia: Australian Bureau of Statistics, 2003.

Tunny G. Educational attainment in Australia. *Econ Roundup* 2006;**2**: 1–10.

Veltman-Verhulst SM, Boivin J, Eijkemans MJ, Fauser BJ. Emotional distress is a common risk in women with polycystic ovary syndrome: a systematic review and meta-analysis of 28 studies. *Hum Reprod Update* 2012;**18**:638–651.

Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977;**106**:203–214.

Windschuttle K. *The White Australia Policy.* Sydney: Macleay Press, 2004.

Witchel SF, Teede HJ, Peña AS. Curtailing PCOS. *Pediatr Res* 2020; **87**:353–361.