Birthweight and thinness at birth independently predict symptoms of polycystic ovary syndrome in adulthood

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BACKGROUND: The aetiology of polycystic ovary syndrome (PCOS) is unknown and contested. While it has been suggested that PCOS could have origins in perturbed development, epidemiological findings have been inconclusive. We aimed to examine potential fetal origins of PCOS.

METHODS: A retrospective birth cohort of 948 singleton female babies born at one hospital in South Australia in 1973–1975 was assembled. Birth characteristics were obtained from hospital records and PCOS symptoms were identified through interview and clinical examination when women were ~30 years old. Based on the combination of PCOS symptoms, women formed seven outcome groups. A multinomial logistic regression analysis was used to investigate associations between birth characteristics and these outcome groups.

RESULTS: After adjusting for gestational age, two distinct birth characteristics were associated with two PCOS symptom groups. Each 100 g increase in birthweight increased the risk of hyperandrogenism (as a single symptom) in adulthood by 5% [relative risk ratio: 1.05, 95% confidence interval (CI): 1.01–1.09]. In contrast, each one unit increase in the ponderal index at birth decreased the risk of all three key PCOS symptoms (hyperandrogenism, menstrual dysfunction and polycystic ovaries) by 21% (0.79, 95% CI: 0.66–0.93).

CONCLUSIONS: These results suggest two discrete fetal programming pathways (related to high birthweight and to thinness at birth) are operating. Our findings point to differing aetiologies for symptom clusters, and inform the debate over symptoms that best represent the disorder.

Key words: PCOS / fetal programming / hyperandrogenism / menstrual dysfunction / polycystic ovaries

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, affecting between 8 and 18% of the female population depending on the diagnostic criteria used (March et al., 2010). This syndrome has a heterogeneous presentation, with the key symptoms being hyperandrogenism, menstrual dysfunction and polycystic ovaries (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). The aetiology of PCOS is unknown and contested, which not only hinders research efforts but also the ability to provide appropriate diagnosis and treatment. One line of recent research suggests an explanation may lie in prenatal development (Cresswell et al., 1997; Ibanez et al., 2007), which is supported by work with prenatally androgenized monkeys (Abbott et al., 1998) who have accompanying transient gestational hyperglycemia (Abbott et al., 2010).

According to the ‘developmental origins of adult disease’ hypothesis, prenatal exposures can give rise to an increased susceptibility to chronic disease (Barker, 1994, 1995). Associations between birth characteristics (which are indicators of intrauterine conditions) and insulin resistance, type 2 diabetes and the metabolic syndrome have been reported (Phillips, 1996; Godfrey and Barker, 2001; Iliadou et al., 2004). As insulin resistance is commonly associated with PCOS, this syndrome may also have fetal origins (Cresswell et al., 1997).

Epidemiological findings on the developmental origins of PCOS have not been consistent. For example, two studies reported a positive association between birthweight and the presence of polycystic ovaries in adult women (Cresswell et al., 1997; Michelmore et al., 2001), but other studies have found negative associations between birthweight and the presence of PCOS symptoms in adolescents and young...
women (Ibanez et al., 1998; Pandolfi et al., 2008; Melo et al., 2010). A further three studies reported no association between birthweight and PCOS symptoms in adulthood (Laitinen et al., 2003; Sadrzadeh et al., 2003; Legro et al., 2010).

Inconsistent findings may be a product of either the birth characteristics examined or the way the PCOS symptom profile was considered. Birthweight and gestational age are the only birth characteristics examined to date (Laitinen et al., 2003; Sadrzadeh et al., 2003; Legro et al., 2010). However, a range of birth characteristics should be drawn upon in investigations of fetal programming. Importantly, thinness at birth (indicated by a low ponderal index) has been linked to later insulin resistance (Phillips, 1996), and may therefore be implicated in the aetiology of PCOS. In addition, other abnormalities in the conditions for fetal growth can be detected by comparing birthweight to placental weight, which indicates relative growth restriction. Another reason for inconsistent findings may be analysis of PCOS as a single entity (Laitinen et al., 2003; Sadrzadeh et al., 2003). As PCOS is a heterogeneous collection of symptoms, different presentations or symptoms may have different underlying aetiologies (Davies and Norman, 2002; Abbott et al., 2005).

This study therefore aims to investigate associations between four birth characteristics (weight, the ratio of birth to placental weight, length and ponderal index), taking into account gestational age and PCOS symptoms in a cohort of women who were ~30 years of age. The analysis is structured so that, if present, multiple pathways could be detected.

### Methods

#### Study population

We assembled a retrospective birth cohort based on consecutive female babies born during 1973–1975 at one hospital in Adelaide, South Australia. Potential participants were traced when they were around 30 years of age. See March et al. (2010) for full details of eligibility and tracing. Of the 2199 eligible women, 2046 (93%) were traced, with 62 children identified as deceased or disabled (3%), leaving 1984 (90%) invitees. At 30 years of age, 945 women agreed to a study interview, a response rate of 49%. Only singleton births were considered in the present analysis, as multiplicity affects birth characteristics. Thus, the available sample for analysis was 948. Participants were representative of all female babies born at the hospital in the same time period with respect to birthweight, birth order and country of origin of mother, but had slightly higher socio-economic status than their counterparts (March et al., 2010).

#### Study protocol

The study was approved by the relevant ethics committees of the hospital and the University of Adelaide, and all participants gave written informed consent. The research study procedures conformed to the principles of the Declaration of Helsinki.

Measurements recorded at birth (body weight, length and placental weight) were obtained from hospital records (Table I). Women were interviewed in adulthood by a research nurse and a medical history was obtained, which included an assessment of symptoms of PCOS (Table II). Menstrual dysfunction was assessed as the presence of chronic amenorrhea, or a usual cycle length of <21 days or >35 days, or >4-day variation between cycles (March et al., 2010). Where circumstances existed that disrupted a woman’s natural menstrual cycle (e.g., hormonal contraception, pregnancy, hysterectomy), she was asked to report her former, usual, menstrual cycle. The modified Ferriman-Gallwey method was used to assess hirsutism and women were defined to have clinical hyperandrogenism if their score was ≥8.

### Table I Birth characteristics of study participants (singleton).

<table>
<thead>
<tr>
<th>Birth characteristic</th>
<th>n_{avail}</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthweight (g)</td>
<td>948</td>
<td>3305.6 (± 506.1)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>919</td>
<td>51.0 (49.0–52.5)</td>
</tr>
<tr>
<td>Ponderal index (kg/m³)</td>
<td>919</td>
<td>25.3 (23.1–27.4)</td>
</tr>
<tr>
<td>Birthweight (g): placental weight (if complete) (g)</td>
<td>904</td>
<td>5.8 (5.2–6.4)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37</td>
<td>51</td>
<td>5.4%</td>
</tr>
<tr>
<td>37–42</td>
<td>844</td>
<td>89.1%</td>
</tr>
<tr>
<td>≥42</td>
<td>52</td>
<td>5.5%</td>
</tr>
<tr>
<td>Birth order</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>388</td>
<td>40.9%</td>
</tr>
<tr>
<td>2nd</td>
<td>318</td>
<td>33.5%</td>
</tr>
<tr>
<td>3+</td>
<td>154</td>
<td>25.5%</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>945</td>
<td>95.6%</td>
</tr>
</tbody>
</table>

Data represented as mean ± SD, median (IQR) or percentages. n_{avail} the number of women available for each characteristic measured.

### Table II Characteristics of study participant as adults (n = 948).

<table>
<thead>
<tr>
<th>Adult characteristic</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.8 (± 1.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 (22.3–30.5)</td>
</tr>
<tr>
<td>Currently taking hormonal contraceptives</td>
<td>298 (31.4)</td>
</tr>
<tr>
<td>PCOS per NIH definition</td>
<td>76 (8.0)</td>
</tr>
<tr>
<td>PCOS per Rotterdam definition</td>
<td>100 (10.5)</td>
</tr>
<tr>
<td>PCOS symptom groups</td>
<td></td>
</tr>
<tr>
<td>R (reference group, no menstrual dysfunction or hyperandrogenism)</td>
<td>578 (61.0)</td>
</tr>
<tr>
<td>MD (menstrual dysfunction) only</td>
<td>129 (13.6)</td>
</tr>
<tr>
<td>A (hyperandrogenism) only</td>
<td>141 (14.9)</td>
</tr>
<tr>
<td>A + PCO (hyperandrogenism + polycystic ovaries)</td>
<td>11 (1.2)</td>
</tr>
<tr>
<td>MD + PCO (menstrual dysfunction + polycystic ovaries)</td>
<td>13 (1.4)</td>
</tr>
<tr>
<td>MD + A (menstrual dysfunction + hyperandrogenism)</td>
<td>59 (6.2)</td>
</tr>
<tr>
<td>MD + A + PCO (menstrual dysfunction + hyperandrogenism + polycystic ovaries)</td>
<td>17 (1.8)</td>
</tr>
</tbody>
</table>

Data represented as mean ± SD, median (IQR) or n (%).
Details of the extended biochemical and clinical assessment of PCOS in these women have been reported previously (March et al., 2010). In brief, a proportion of the interviewed women consented to blood tests to assess biochemical hyperandrogenism (n = 270). Free testosterone was calculated from the total testosterone and sex hormone-binding globulin levels. Women with a free testosterone level above the 95th percentile (34.2 pmol/l) were classified as hyperandrogenic. The 370 women who had at least one PCOS symptom based on the initial interview were offered a transvaginal ultrasound to ascertain the presence of polycystic ovaries and 112 accepted.

### Statistical analysis

All statistical analyses were carried out in Stata version 10.1 (StataCorp LP, College Station, Texas). Descriptive statistics presented in Tables I and II were generated after checking continuous variables for normality, and means with standard deviations or medians and interquartile ranges reported as appropriate.

Women formed seven outcome groups, based on possible combinations of the three key PCOS symptoms: hyperandrogenism (clinical and/or biochemical), menstrual dysfunction and polycystic ovaries (Table II). Four of these symptom groups comprised women with PCOS according to (contrasting) recognized criteria and two groups had one symptom only. The reference group consisted of the women with no known PCOS symptoms (Group R in Table II).

A subset of women with one or more PCOS symptom agreed to have a transvaginal ultrasound (112/370, 30%). Since the majority of those who underwent ultrasound had normal ovarian morphology (71/112, 63%), in the primary analyses we attributed normal morphology to those women without ultrasound information. We also used multiple imputation techniques (as detailed at the end of this section) in which women with missing ultrasound information were assigned normal or cystic ovaries on a statistical basis. This technique allowed the stability of the primary results to be examined.

Multinomial logistic regression was used to investigate associations between birth characteristics, adjusted for gestational age and the PCOS symptom groups. Relative risk ratios (RRRs) were reported and can be interpreted as showing how a one unit change in the birth characteristic leads to the corresponding increase (or decrease) in risk of that symptom group, relative to the reference group. RRRs for larger increments in a particular birth characteristic can be calculated by multiplying the relevant multinomial logistic regression coefficient by the appropriate increment prior to exponentiation. For example, an RRR of 1.2 associated with a one unit change in a birth characteristic has a corresponding regression coefficient $\beta$ of $\ln(1.2) = 0.18$. Therefore, the RRR associated with, say, a three-unit change in this birth characteristic is equal to $\exp(3 \times \beta) = 1.7$.

Gestational age was calculated using the time elapsed between the last menstrual period and the delivery date, or where this information was not available, using clinical estimates of the delivery date at prenatal visits. (Ultrasound dating was not routinely used at the time.) Sensitivity analyses examined the effect of excluding gestational ages that were based upon less accurate data, as well as excluding all babies born at <37 complete weeks of gestation.

The primary analyses were undertaken using all available data, and thus the total number of observations differed slightly for each model (as reported). There were no missing values for birthweight, and one gestational age and 29 length measurements were missing (and thus the ponderal index was not able to be calculated). Only complete placentas were used in analyses of the ratio of birthweight to placental weight, resulting in 44 missing values. Complete case analysis excluded the 74 individuals with missing information on any birth characteristic variable, and results were compared with those of the analyses using all available data.

Finally, we used multiple imputation analyses (Rubin, 1987; Sterne et al., 2009) to address missing information concerning ovarian morphology. PCO status was assumed to be missing at random; this appeared reasonable as there were no significant differences in birth characteristics for the group of women who had a transvaginal ultrasound compared with the group of women who did not have ultrasonography. In the imputation step, missing values of PCO status were imputed 100 times using a logit model with predictor variables of hyperandrogenism and menstrual dysfunction (based on the findings of Farquhar et al., 1994). This generated 100 data sets. In the analysis step, the primary analyses were repeated for each of the imputed data sets, and the results combined according to Rubin’s rules.

### Results

#### The study population

Birth characteristics are presented in Table I, which also shows that the great majority of births occurred after 37 weeks of gestation. Almost the entire study group was of Caucasian ethnicity. In adulthood (Table II), most women were interviewed when they were 30 years old. At interview, 31% of women were taking hormonal contraceptives, and so they reported their previous (unregulated) menstrual cycle.

The proportion of women assessed as having PCOS under the National Institutes of Health (NIH) criteria was 8% (n = 76) and under the Rotterdam criteria this increased to 11% (n = 100; Table II). Upon dividing the women into seven groups based on PCOS symptoms, 61% (n = 578) had no known clinical symptoms of PCOS (the reference group). Of those with symptoms, the majority possessed only one symptom, with 14% (n = 129) having menstrual dysfunction and 15% (n = 141) hyperandrogenism as their only known symptom. There were 6% (n = 59) with menstrual dysfunction + hyperandrogenism, and the remaining three groups, which all included polycystic ovaries with one or more additional symptom, comprised <2% each.

#### Associations between birth characteristics and PCOS symptom groups

Associations between four birth characteristics and each PCOS symptom group in adulthood are depicted in Figure 1. The figure shows the RRR and confidence intervals (CI) for four multinomial logistic regression analyses.

In the first analysis summarized within Fig. 1, birthweight was positively associated with the hyperandrogenism group (Group A in Table II); for each 100-g increase in birthweight the risk of hyperandrogenism alone increased by 5% (RRR = 1.05; 95% CI: 1.01–1.09). Note that the RRR depends on the specified increment in exposure; for increases in birthweight of 200 g, 500 g and 1 kg the RRR (95% CI) would be 1.10 (1.01–1.19), 1.27 (1.04–1.55) and 1.61 (1.08–2.41), respectively.

In the second analysis, the ratio of birthweight to placental weight was considered as the exposure. This birth characteristic was positively associated with the symptom group of hyperandrogenism + polycystic ovaries (Group A + PCO in Table II); for each one unit increase
in the ratio, the risk of having both of these symptoms increased by 80% (RRR = 1.80; 95% CI: 1.04–3.13). However, the confidence interval was considerably wider than for other statistically significant associations; moreover the association was unstable (see below).

In the third analysis within Fig. 1, the exposure was birth length, and no statistically significant associations were evident. However, when the ponderal index was considered as the exposure, it was inversely associated with the risk of having all three key PCOS symptoms (MD + A + PCO in Table II); for each one unit increase in the ponderal index, the risk of having all three symptoms decreased by 21% (RRR = 0.79; 95% CI: 0.66–0.93). Alternatively, each one unit decrease in the ponderal index increased the risk of having all three symptoms by 27% (RRR = 1.27; 95% CI: 1.07–1.51). Note that this was not an effect of either birthweight or length alone, but a specific effect of weight for length.

The complete case analyses (n = 873), which excluded individuals with any missing birth characteristic data, produced slight attenuation of effects but all statistically significant relationships remained, with one exception: the association between birthweight relative to placental weight and the symptom group of hyperandrogenism + polycystic ovaries was not statistically significant. Results did not change substantially in sensitivity analyses which excluded babies born at <37 weeks of gestation, or gestational ages based on less accurate data. There was no evidence of any statistically significant non-linear relationships.

Finally, we used multiple imputation analyses to see whether results changed if alternative assumptions about the PCO status of women with missing ultrasound data were made. The results of these analyses were in close agreement with the original analyses. In particular, the RRR for each 100 g increase in birthweight and the risk of hyperandrogenism alone was 1.05 (95% CI: 1.00–1.10) and the RRR for each one unit increase in the ponderal index and the risk of all three key PCOS symptoms was 0.84 (95% CI: 0.73–0.97). There was no association between the ratio of birthweight to placental weight and the symptom group of hyperandrogenism + polycystic ovaries.

### Discussion

Two distinct birth characteristics were associated with different profiles of PCOS symptoms in adulthood: high birthweight was associated with hyperandrogenism (as a single symptom), while low ponderal index was associated with the presence of all three key PCOS symptoms (menstrual dysfunction, hyperandrogenism and polycystic ovaries). An association between high birthweight relative to placental weight and the symptom subset of hyperandrogenism and polycystic ovaries was less precise and not stable when different approaches to missing data were used.

In contrast to previous studies (Ibanez et al., 1998; Pandolfi et al., 2008; Melo et al., 2010) we did not find that low birthweight (in absolute terms) was implicated in PCOS or other symptom subsets. We did, however, observe an effect of low weight for length, or thinness at birth (as indicated by a low ponderal index) which can occur in babies that are of relatively normal birthweight, and reflects a lack of muscle growth (Phillips et al., 1994). Our finding that thinness at birth was associated with increased likelihood of a woman having all three key PCOS symptoms is consistent with the proposed link between PCOS and insulin resistance, as there are established associations between thinness at birth and other disorders related to insulin resistance, including type 2 diabetes and the metabolic syndrome (e.g. Phillips et al., 1994; Jarvelin, 2000; Godfrey and Barker, 2001; Hales and Barker, 2001). Whether thinness at birth is a ‘thrifty phenotype’ (Hales and Barker, 1992) or reflects a ‘thrifty genotype’ (Hattersley and Tooke, 1999) is still the subject of debate.

We also observed that high birthweight was associated with hyperandrogenism in adulthood. This isolated symptom is referred to as functional androgen excess. This single symptom does not correspond to PCOS under the current NIH or Rotterdam criteria, although in the past it has occasionally been considered to signify PCOS (Escobar-Morreale et al., 2005). We suggest that tracking of body size and fat mass from birth to adulthood is a potential contributor to functional androgen excess, as high birthweight correlates with high BMI in adulthood (Baird et al., 2005) and adipose tissue is androgenic (Kershaw and Flier, 2004). It is plausible that there is a direct genetic contribution, possibly from the fat mass and obesity-associated gene (FTO gene) to both body composition across the life course and risk of PCOS. Consistent with this, placental FTO expression is related to fetal growth (Bassols et al., 2010), variants of the FTO gene are associated with hyperandrogenemia and metabolic parameters in women.
with PCOS (Wehr et al., 2010), and women with PCOS are themselves at increased risk of having large babies (Anderson et al., 2010).

Placental inefficiency in converting androgens to estrogens could also be an underlying factor. During pregnancy, quantities of dehydroepiandrosterone sulfate (DHEAS) and 16α-DHEAS produced by the fetal and maternal adrenal glands are converted initially to androstenedione and 16α-androstenedione, and thereafter to estrogens by placental aromatase. The enzyme should protect a female fetus from androgen excess (Holt et al., 2005). However, maternal exposure to increased concentrations of insulin and/or insulin-like growth factors (IGFs) in pregnancy can inhibit aromatase activity and decrease serum estrogen levels (Nestler, 1993). An increased fetal growth rate may therefore reflect positive feedback of androgens on IGF metabolism.

Previous studies have also identified a relationship between high birthweight and presence of polycystic ovaries (Cresswell et al., 1997; Michelmore et al., 2001). Whether women in those studies possessed other PCOS symptoms is not known. This, and the fact that our study was not designed to identify women with polycystic ovaries alone, limits direct comparisons with our results.

The main limitation of this study is a degree of under-ascertainment of polycystic ovaries, as in the primary analyses we assumed that women had normal ovarian morphology when ultrasound information was unavailable. The reference group in particular is likely to have contained a proportion of women with (undiagnosed) polycystic ovaries as their only symptom as they were not offered an ultrasound. This would arguably have a conservative influence on both the ability to identify associations and on the reported effect sizes. However, varying the assumption made about ovarian morphology, using multiple imputation techniques, did not change the results concerning birthweight and ponderal index, supporting the stability of the findings.

Around half of the women invited to join this cohort study did so. It is known that health conscious individuals and those with the outcome of interest are most likely to participate in research. While this may affect prevalence estimates, it does not necessarily bias estimates of association between exposures and outcomes, especially when biological relationships are under investigation. Further reassurance that observed associations were unlikely to be affected by selection bias is provided by the fact that there were no differences in birth characteristics between participants and non-participants. In addition, assessments of PCOS symptoms were undertaken by staff with no knowledge of birth characteristics.

Strengths of this study include the nature of the sample, being community based (drawn from a set of birth records), rather than a convenience sample of adult women seeking clinical care for specific symptoms. Also, birth measurements were obtained from records made within a single hospital (rather than being self-reported). Furthermore, both a number of birth characteristics and symptom subsets of PCOS were considered, whereas previous studies have only considered birthweight, and have analysed PCOS as an undifferentiated collection of symptoms (Laitinen et al., 2003; Sadrzadeh et al., 2003) or the analysis has been limited by the design of the study (Pandolfi et al., 2008; Legro et al., 2010). Our sample was almost entirely composed of Caucasian women and this may have contributed to differences between our results and those of previous studies, especially if genetic susceptibility plays a role.

In conclusion, the results of this study support the hypothesis that PCOS is linked to factors present in fetal life, with specific birth characteristics associated with specific PCOS symptom profiles. This study thus offers a way to reconcile previous inconsistent findings, and may inform future research efforts and diagnostic debate. Research in this area continues to be hampered by methodological difficulties relating to enrolling an appropriate study population, engaging the participation of well women in research about reproductive function and controversies around diagnostic criteria.

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Authors’ roles
V.M. and M.D. were the principal investigators of the study and formulated the research question. All authors contributed to drafting the article and interpretation of data. W.M., K.W. and L.G. conducted the analyses. All authors contributed to the critical revision of important intellectual content and final approval of the manuscript.

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Ethical approval
The study was approved by the ethics committees of the Queen Elizabeth Hospital and the University of Adelaide and all participants gave written informed consent.

Data sharing
No additional data available.

Conflict of interest
None declared.

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