Associations of Birthweight and Gestational Age with Reproductive and Metabolic Phenotypes in Women with Polycystic Ovarian Syndrome and Their First-Degree Relatives

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Context: Low birthweight has been associated with metabolic and reproductive abnormalities in adults.

Objective: The aim of the study was to examine the relationship between birthweight and gestational age and its association with reproductive and metabolic phenotypes in women with PCOS and their first-degree relatives.

Design and Setting: We conducted a family-based study of PCOS at an academic health center.

Patients or Other Participants: A total of 1038 individuals (845 females and 193 males) from the cohort and 168 controls participated in the study.

Main Outcome Measures: The association between birthweight and familial phenotype was measured.

Results: Self-reported and actual birthweight were highly correlated (Spearman correlation coefficient \( r = 0.81 \); 95% CI, 0.66, 0.89; \( P = 0.001 \)) and concordant (concordance correlation coefficient \( r = 0.86 \); 95% lower limit \( r = 0.78 \)). We noted that birthweight for both genders in PCOS families and controls fell within the 10th and 90th percentiles for gestational age based on U.S. population norms. The 50th percentiles for a gestational age of 40 wk were very similar (3409 g in PCOS, 3455 g for controls, and 3495 g for the United States). There were no significant associations between phenotype and birthweight in PCOS probands. Furthermore, there were not any significant relationships between phenotype and birthweight in female or male family members of the PCOS probands.

Conclusions: Birthweight in PCOS families mirrors control and U.S. population data, even corrected for gestational age, and has no substantive association with reproductive and metabolic abnormalities in women with PCOS, their female relatives, or their male relatives. (J Clin Endocrinol Metab 95: 789–799, 2010)

Polycystic ovary syndrome (PCOS) is a common endocrine disorder characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries (1). It is associated with metabolic abnormalities including insulin resistance, dyslipidemia, and increased risk for type 2 diabetes (2). The etiology is unknown, although like other complex disorders, there are both genetic and environmental influences (1). Obesity is frequently associated

Abbreviations: ANCOVA, Analysis of covariance; CI, confidence interval; DHEAS, dehydroepiandrosterone sulfate; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; uT, unbound T.
with PCOS and exacerbates these underlying metabolic derangements.

Decreased birthweight and relative thinness at birth have been linked with an increased risk for developing obesity, the metabolic syndrome, type 2 diabetes, and cardiovascular disease as an adult in multiple epidemiological studies (3). This potential developmental origin of adult disease is commonly known as the Barker hypothesis (4), which posits that maternal nutritional constraints during pregnancy result in adaptive responses in the fetus that limit growth and preferentially shunt nutritional resources to key organ systems. These adaptive responses can include altered hormonal responses or tissue receptivity to these hormones (4).

It has been proposed that PCOS has developmental origins (5). First, prenatal exposure to androgens can produce a phenocopy of PCOS in rhesus macaques, sheep and rodents (6–8), and humans (9, 10). Second, several studies in humans have suggested that there is an association between low birthweight and features of PCOS (11–13). The human studies, however, have been limited by small sample size, incomplete reproductive or metabolic phenotyping, and the lack of family-based comparison groups. We have prospectively recruited a large cohort of families of women with PCOS for genetic analyses. We have used this cohort to address the following questions: 1) Is birthweight appropriate for gestational age in these families and how does it compare to U.S. population normative data? 2) Is birthweight associated with stigmata of PCOS, such as hyperandrogenism (16–18). 3) Is birthweight associated with insulin resistance or the metabolic syndrome? If there is an adverse nutritional resource to key organ systems. These adaptive responses can include altered hormonal responses or tissue receptivity to these hormones (4). 4) Is birthweight associated with androgens in these families and how does it compare to U.S. population normative data? 2) Is birthweight associated with stigmata of PCOS, such as hyperandrogenism and oligomenorrhea, and are there sex-specific effects? 3) Is birthweight associated with insulin resistance or the metabolic syndrome? If there is an adverse intrauterine environment, we would expect abnormalities in male (i.e. brothers) as well as female offspring.

**Subjects and Methods**

**Subjects**

The study was approved by the Institutional Review Board of the Pennsylvania State University College of Medicine, and subjects were enrolled between 1993 and 2008. Written informed consent was obtained from all participants. We used the National Institute of Health (NIH) diagnostic criteria for PCOS to identify probands (14): no more than six menses per year and either total testosterone (T) greater than 58 ng/dl or non-SHBG-bound T (uT) greater than 15 ng/dl. These criteria levels for T and uT are greater than 2SD values above the mean value that we have established in reproductively normal women aged 18–40 yr in the early follicular phase of the menstrual cycle (15). Other causes of anovulation and hyperandrogenemia were excluded by appropriate tests (15).

We then recruited first-degree relatives of the probands, including fathers, mothers, brothers, and sisters for our ongoing phenotype and genotype studies, and we have previously reported phenotypic and genotypic data on most of them (16–18).

The selection criteria for controls (male and female) were: 1) no major medical or psychiatric illnesses; 2) no personal history of hypertension and no personal or first-degree family history of diabetes; 3) normal glucose tolerance according to the World Health Organization criteria and additionally for female controls; 4) regular 27- to 35-d menstrual cycles throughout their reproductive life; and 5) no clinical or biochemical evidence of hyperandrogenism (16–18).

**Study procedures**

Controls were evaluated on site at Hershey, Pennsylvania (n = 168). Family members who participated in the study were evaluated either on-site at Hershey (n = 470) or off-site in a local hospital or clinical laboratory with phlebotomy and laboratory processing capability (n = 568) as previously described (16). All subjects completed a questionnaire capturing their medical and reproductive history including birthweight and gestational age, which was added to the questionnaire in 2000 (59% of eligible subjects reported birthweight from the

### TABLE 1. Demographics of family members in study

<table>
<thead>
<tr>
<th></th>
<th>Family members</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Proband</td>
<td>Sister</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3242 (565)</td>
<td>3327 (595)</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39.6 (2.5)</td>
<td>39.5 (2.3)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>27.8 (5.7)</td>
<td>31.2 (8.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.6 (8.9)</td>
<td>28.8 (7.8)</td>
</tr>
<tr>
<td>Total T (ng/dl)</td>
<td>79 (35)</td>
<td>41 (25)</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>27 (16)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>191 (38)</td>
<td>185 (36)</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd). Conversion factors: T x 3.467 (nmol/liter); insulin x 6.945 (pmol/liter); cholesterol x 0.0259 (mmol/liter).
start of the study, and 84% reported gestational age once added in 2000). We did not collect smoking history during pregnancy. All had morning blood samples obtained after an overnight fast. Those who were seen on-site also had blood pressure determined. Height and weight in the subjects studied off-site were self-reported, and waist circumference was self-measured (16). Hirsutism grading was performed using the modified Ferriman Gallwey assessment (19).

FIG. 1. A, Self-reported birthweight in PCOS families and controls plotted against self-reported gestational age with a loess smoothed curve (green) through our data as well as superimposed percentile lines from the U.S. population as reported in Alexander et al. (27). B, Frequency distribution of birthweight at 40 wk gestational age with superimposed normal distribution (green) in PCOS families and controls. In addition, the 10th, 50th, and 90th percentiles from the U.S. population are indicated as reported in Alexander et al. (27).
Additional phenotyping

A transvaginal ultrasound of the pelvis was performed in probands (20). Ovarian size was obtained by measuring the largest plane of the ovary in two dimensions and then turning the vaginal probe 90° and obtaining a third measurement. Polycystic ovaries were determined according to criteria of Balen et al. (21) as at least one ovary having a volume greater than 10 cm³ with no cysts or follicles more than 10 mm in mean diameter. We used the strength of the relationship between self-reported birthweight and the medical record from their birth. This study was approved by the Institutional Review Board of the Hershey Medical Center, and all participants gave informed consent. A letter and standard record release consent form were mailed to all PCOS probands and first-degree relatives as identified above. The letter explained the purpose of this study and also asked subjects to provide self-reported birthweight and gestational age at birth. Subjects were asked to sign the record release form and return it along with the recalled information. Participants who did not respond to the letter or who completed the forms incorrectly were contacted by telephone and/or by sending the information by mail. We collected 41 original records for the validation study.

Birthweight validation study

Birthweight was self-reported. We sought to validate the self-reported weight in our cohort against the weight on the medical record from their birth. This study was approved by the Institutional Review Board of the Hershey Medical Center, and all participants gave informed consent. A letter and standard record release consent form were mailed to all PCOS probands and first-degree relatives as identified above. The letter explained the purpose of this study and also asked subjects to provide self-reported birthweight and gestational age at birth. Subjects were asked to sign the record release form and return it along with the recalled information. Participants who did not respond to the letter or who completed the forms incorrectly were contacted by telephone and/or by sending the information by mail. We collected 41 original records for the validation study.

Data analysis

The Spearman correlation coefficient was used to evaluate the strength of the relationship between self-reported birthweight and the medical record birthweight in PCOS families. In addition, the concordance correlation coefficient was calculated to determine the agreement between self-reported and actual (original record) birthweights. We could not assess the accuracy of self-reported gestational age because the birth records we obtained often did not include accurate determination of this endpoint.

The self-reported birthweight was plotted against the self-reported gestational age for both PCOS family members and controls. A nonparametric locally weighted scatterplot smoothened
TABLE 2. Continued

<table>
<thead>
<tr>
<th>PCOS probands</th>
<th>Sistors and mothers</th>
<th>PCOS probands</th>
<th>Sistors and mothers</th>
<th>PCOS probands</th>
<th>Sistors and mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>36.2 (33.1, 39.3) [31]</td>
<td>30.5 (28.1, 32.8) [40]</td>
<td>0.91 [1.00]</td>
<td>0.67 [0.92]</td>
<td>0.61 [1.00]</td>
<td>0.46 [0.92]</td>
</tr>
<tr>
<td>104 (97, 111) [30]</td>
<td>96 (90, 102) [39]</td>
<td>0.91 [1.00]</td>
<td>0.21 [0.63]</td>
<td>0.76 [1.00]</td>
<td>0.28 [0.84]</td>
</tr>
<tr>
<td>4.0 (3.1, 4.9) [30]</td>
<td>10.5 (9.4, 11.6) [38]</td>
<td>0.85 [1.00]</td>
<td>0.26 [0.78]</td>
<td>0.11 [1.00]</td>
<td>0.07 [0.21]</td>
</tr>
<tr>
<td>12.6 (8.4, 16.8) [13]</td>
<td>5.9 (1.8, 10.0) [9]</td>
<td>0.72 [1.00]</td>
<td>0.70 [1.00]</td>
<td>0.70 [1.00]</td>
<td>0.61 [1.00]</td>
</tr>
<tr>
<td>17.1 (12.5, 21.7) [10]</td>
<td>N/A</td>
<td>0.68 [1.00]</td>
<td>N/A</td>
<td>0.03 [0.42]</td>
<td>N/A</td>
</tr>
<tr>
<td>80 (68.0, 92.6) [31]</td>
<td>35 (27, 43) [40]</td>
<td>0.69 [1.00]</td>
<td>0.32 [0.96]</td>
<td>0.52 [1.00]</td>
<td>0.04 [0.12]</td>
</tr>
<tr>
<td>24 (19, 30) [31]</td>
<td>9 (6, 12) [39]</td>
<td>0.12 [1.00]</td>
<td>0.04 [0.12]</td>
<td>0.89 [1.00]</td>
<td>0.28 [0.84]</td>
</tr>
<tr>
<td>2261 (1894, 2628) [31]</td>
<td>1479 (1219, 1739) [39]</td>
<td>0.78 [1.00]</td>
<td>0.18 [0.54]</td>
<td>0.50 [1.00]</td>
<td>0.44 [1.00]</td>
</tr>
<tr>
<td>67 (49, 84) [25]</td>
<td>108 (63, 153) [36]</td>
<td>0.76 [1.00]</td>
<td>0.36 [1.00]</td>
<td>0.87 [1.00]</td>
<td>0.03 [0.09]</td>
</tr>
<tr>
<td>42 (38, 46) [30]</td>
<td>53 (48, 57) [39]</td>
<td>0.99 [1.00]</td>
<td>0.34 [1.00]</td>
<td>0.56 [1.00]</td>
<td>0.63 [1.00]</td>
</tr>
<tr>
<td>112 (101, 124) [29]</td>
<td>117 (106, 128) [38]</td>
<td>0.21 [1.00]</td>
<td>0.54 [1.00]</td>
<td>0.57 [1.00]</td>
<td>0.43 [1.00]</td>
</tr>
<tr>
<td>185 (172, 198) [30]</td>
<td>201 (189, 213) [40]</td>
<td>0.20 [1.00]</td>
<td>0.15 [1.00]</td>
<td>0.76 [1.00]</td>
<td>0.89 [1.00]</td>
</tr>
<tr>
<td>163 (115, 211) [30]</td>
<td>197 (158, 235) [40]</td>
<td>0.49 [1.00]</td>
<td>0.04 [0.84]</td>
<td>0.73 [1.00]</td>
<td>0.02 [0.44]</td>
</tr>
<tr>
<td>120 (114, 125) [25]</td>
<td>121 (116, 126) [34]</td>
<td>0.27 [1.00]</td>
<td>0.66 [1.00]</td>
<td>0.62 [1.00]</td>
<td>0.66 [1.00]</td>
</tr>
<tr>
<td>76 (72, 80) [25]</td>
<td>73 (69, 76) [34]</td>
<td>0.83 [1.00]</td>
<td>0.08 [1.00]</td>
<td>0.90 [1.00]</td>
<td>0.77 [1.00]</td>
</tr>
<tr>
<td>89 (83, 96) [31]</td>
<td>94 (86, 102) [39]</td>
<td>0.98 [1.00]</td>
<td>0.81 [1.00]</td>
<td>0.22 [1.00]</td>
<td>0.81 [1.00]</td>
</tr>
<tr>
<td>24 (18, 29) [31]</td>
<td>17 (13, 21) [39]</td>
<td>0.32 [1.00]</td>
<td>0.46 [1.00]</td>
<td>0.31 [1.00]</td>
<td>0.63 [1.00]</td>
</tr>
<tr>
<td>17 (11, 23) [30]</td>
<td>13 (9, 17) [38]</td>
<td>0.42 [1.00]</td>
<td>0.61 [1.00]</td>
<td>0.51 [1.00]</td>
<td>0.62 [1.00]</td>
</tr>
<tr>
<td>0.8 (0.6, 1.0) [30]</td>
<td>0.8 (0.6, 0.9) [38]</td>
<td>0.70 [1.00]</td>
<td>0.87 [1.00]</td>
<td>0.42 [1.00]</td>
<td>0.40 [1.00]</td>
</tr>
<tr>
<td>5.5 (3.9, 7.1) [31]</td>
<td>4.3 (2.3, 6.3) [39]</td>
<td>0.39 [1.00]</td>
<td>0.57 [1.00]</td>
<td>0.38 [1.00]</td>
<td>0.92 [1.00]</td>
</tr>
<tr>
<td>141 (115, 167) [12]</td>
<td>111 (85, 138) [5]</td>
<td>0.50 [1.00]</td>
<td>0.14 [0.28]</td>
<td>0.78 [1.00]</td>
<td>0.21 [0.42]</td>
</tr>
<tr>
<td>164 (93, 236) [12]</td>
<td>104 (48, 159) [5]</td>
<td>0.88 [1.00]</td>
<td>0.10 [0.20]</td>
<td>0.98 [1.00]</td>
<td>0.01 [0.91]</td>
</tr>
<tr>
<td>17,598 (14,975, 20,222) [11]</td>
<td>N/A</td>
<td>0.69 [1.00]</td>
<td>N/A</td>
<td>0.79 [1.00]</td>
<td>N/A</td>
</tr>
<tr>
<td>17,911 (11,296, 24,527) [11]</td>
<td>N/A</td>
<td>0.85 [1.00]</td>
<td>N/A</td>
<td>0.85 [1.00]</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Hg, obesity with a waist circumference greater than 88 cm for females and greater than 102 cm for males, triglycerides of at least 150 mg/dl, and HDL cholesterol less than 50 mg/dl for females and less than 40 mg/dl for males. A logistic regression model was fit to assess the association between metabolic syndrome and birthweight, adjusting for current subject age. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin (μU/ml) * glucose (mg/dl)/405.

Sisters of probands were classified into four predetermined reproductive phenotypes as previously reported (15): 1) PCOS based on elevated T levels and irregular menses; 2) hyperandrogenic based on elevated T levels and regular menstrual cycles; 3) unaffected based on normal T and DHEAS levels and normal menses; and 4) unknown based on inability to measure T levels due to confounding medications, pregnancy, menopause, hysterec- tomy, etc. A generalized logits model was fit to assess the effect of birthweight on the reproductive phenotypes in sisters of probands, adjusting for current subject age (29).

All hypothesis tests were two-sided, and 95% confidence intervals (CIs) are reported where appropriate. To account for multiple hypothesis testing, the adaptive Holm adjustment to the stepdown Bonferroni method was used to correct P values (30). The adaptive Holm adjustment to the stepdown Bonferroni procedure is less conservative than the traditional Bonferroni correction method because it takes into account an estimate of the proportion of true null hypotheses; but, it still controls for the familywise error rate. These multiple hypothesis test adjustments to the P values were done within a data subset (PCOS probands, sisters and mothers of PCOS probands, and male family mem-
bers of PCOS probands) as well as within outcome parameter group (e.g., demographic, reproductive, and metabolic). Both the unadjusted and adjusted P values are reported. All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Birthweight validation

Self-reported and actual birthweight (Spearman correlation coefficient = 0.81; 95% CI, 0.66, 0.89; P = 0.001) were highly correlated. We also found a high degree of agreement between self-reported and actual birthweight. The concordance correlation coefficient for agreement was 0.86, with a lower 95% confidence limit of 0.78. Recall of birthweight was found to be highly accurate (within 10 g) in 39% of cases, accurate (within 100 g) in 76% of cases, and within 250 g in 83% of cases.

Demographics of population and birth parameters

Overall in PCOS families, we had self-reported birthweight data on 845 females, the majority of them probands, in 193 males, and in 82 male and 86 female controls (Table 1). The male infants, on average, weighed approximately 300 g more than the female infants. We noted that birthweight for both males and females mainly fell within the 10th and 90th percentiles for gestational age based on recent U.S. population data (27) (Fig. 1A). Our fitted loess curve through birthweight and gestational age closely parallels the 50th percentile from the U.S. national data from 30–40 wk gestation, with an upward skewing noted post-term in PCOS families. Similarly, we noted a normal distribution at 40 wk gestation in PCOS families and in controls, again with a close concordance with the U.S. population data at the 10th and 90th percentiles (Fig. 1B). The 50th percentiles at 40 wk gestational age were very similar: 3409 g for our PCOS familial sample, 3435 g for the controls, and 3495 g for the U.S. population. The percentage of low and high birthweight individuals was quite similar between PCOS family members and controls. Within the PCOS families, low birthweight was observed in 4% of the males and 10% of the females, and high birthweight was observed in 25% of the males and 8% of the females. Within the controls, low birthweight was observed in 6% of the males and 13% of the females and high birthweight was observed in 20% of the males and 9% of the females.

Association of birthweight with reproductive phenotypes in PCOS families

Women with PCOS

There was no association of birthweight with reproductive parameters of the PCOS phenotype, including the number of self-reported menstrual bleeding episodes, hirsutism score, or serum hormone levels (Table 2). There was a positive linear association between birthweight and ovarian size, but this effect was not significant when corrected for multiple hypothesis testing (P = 0.42) (Fig. 2). These findings were unaffected using the formula of Balen et al. (21) for ovarian volume (length × height × width × 0.5).

Female relatives

When corrected for multiple hypothesis testing, we found no significant associations (Table 2). We further examined the mean birthweights in sisters of probands according to our predetermined sister phenotypes: 1) PCOS based on elevated T levels and irregular menses (mean ± sd, 3250 ± 666 g; n = 29); 2) hyperandrogenic based on elevated T levels and regular menstrual cycles (3025 ± 736 g; n = 19); 3) unaffected based on normal T and DHEAS levels and normal menses (3422 ± 527 g; n = 97); and 4) unknown based on inability to measure T levels due to confounding medications, pregnancy, menopause, hysterectomy, etc. (3286 ± 563 g; n = 85). Adjusting for current age, the odds of a female in a PCOS family being hyperandrogenic phenotype are 1.13 times that of being unaffected phenotype for every 100-g increase in birthweight (95% CI, 1.04, 1.22; P = 0.006). However, there was no significant effect of birthweight comparing PCOS phenotype with the unaffected phenotype.
TABLE 3. Reproductive and metabolic parameters in male family members

<table>
<thead>
<tr>
<th></th>
<th>Low birthweight (&lt;2500 g)</th>
<th>Normal birthweight (2500–4000 g)</th>
<th>High birthweight (&gt;4000 g)</th>
<th>Quadratic trend P valueb</th>
<th>Linear trend P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.1 (22.3, 31.9) [8]</td>
<td>29.6 (28.4, 30.7) [137]</td>
<td>30.2 (28.3, 32.3) [48]</td>
<td>0.54 [1.00]</td>
<td>0.24 [0.96]</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>97 (86, 108) [8]</td>
<td>100 (98, 103) [131]</td>
<td>104 (99, 108) [46]</td>
<td>1.00 [1.00]</td>
<td>0.27 [0.96]</td>
</tr>
<tr>
<td>Reproductive</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>T (ng/dl)</td>
<td>497 (380, 614) [8]</td>
<td>461 (433, 490) [136]</td>
<td>469 (420, 517) [47]</td>
<td>0.54 [1.00]</td>
<td>0.66 [1.00]</td>
</tr>
<tr>
<td>uT (ng/dl)</td>
<td>234 (164, 305) [8]</td>
<td>198 (181, 215) [136]</td>
<td>212 (183, 241) [47]</td>
<td>0.23 [1.00]</td>
<td>0.57 [1.00]</td>
</tr>
<tr>
<td>DHEAS (ng/ml)</td>
<td>2890 (2057, 3723) [8]</td>
<td>2363 (2160, 2566) [135]</td>
<td>2204 (1857, 2552) [46]</td>
<td>0.46 [1.00]</td>
<td>0.14 [1.00]</td>
</tr>
<tr>
<td>SHBG (nmol/liter)</td>
<td>61 (41, 82) [8]</td>
<td>63 (57, 68) [117]</td>
<td>56 (47, 66) [37]</td>
<td>0.54 [1.00]</td>
<td>0.66 [1.00]</td>
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<tr>
<td>Metabolic</td>
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<tr>
<td>HDL (mg/dl)</td>
<td>45 (37, 54) [8]</td>
<td>43 (41, 45) [135]</td>
<td>43 (40, 47) [47]</td>
<td>0.70 [1.00]</td>
<td>0.70 [1.00]</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>103 (81, 126) [8]</td>
<td>119 (113, 125) [128]</td>
<td>111 (102, 121) [45]</td>
<td>0.09 [1.00]</td>
<td>0.52 [1.00]</td>
</tr>
<tr>
<td>Total</td>
<td>177 (151, 203) [8]</td>
<td>194 (188, 201) [135]</td>
<td>188 (178, 199) [47]</td>
<td>0.14 [1.00]</td>
<td>0.42 [1.00]</td>
</tr>
<tr>
<td>cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>142 (48, 237) [8]</td>
<td>170 (147, 193) [135]</td>
<td>172 (133, 210) [47]</td>
<td>0.64 [1.00]</td>
<td>0.57 [1.00]</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>132 (119, 144) [7]</td>
<td>129 (126, 133) [108]</td>
<td>129 (123, 135) [31]</td>
<td>0.77 [1.00]</td>
<td>0.74 [1.00]</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77 (69, 85) [7]</td>
<td>80 (78, 82) [108]</td>
<td>78 (75, 82) [31]</td>
<td>0.43 [1.00]</td>
<td>0.79 [1.00]</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>99 (82, 116) [8]</td>
<td>97 (93, 101) [135]</td>
<td>101 (94, 108) [47]</td>
<td>0.54 [1.00]</td>
<td>0.85 [1.00]</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>18 (11, 25) [8]</td>
<td>18 (16, 19) [136]</td>
<td>18 (15, 21) [46]</td>
<td>1.00 [1.00]</td>
<td>0.99 [1.00]</td>
</tr>
<tr>
<td>Proinsulin (mg/dl)</td>
<td>16 (6, 27) [8]</td>
<td>19 (16, 21) [133]</td>
<td>21 (16, 25) [46]</td>
<td>0.96 [1.00]</td>
<td>0.46 [1.00]</td>
</tr>
<tr>
<td>Proinsulin-insulin ratio</td>
<td>0.9 (0.2, 1.6) [6]</td>
<td>1.1 (1.0, 1.3) [133]</td>
<td>1.4 (1.1, 1.7) [46]</td>
<td>0.90 [1.00]</td>
<td>0.22 [1.00]</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>4.4 (1.8, 7.0) [8]</td>
<td>4.5 (3.9, 5.1) [135]</td>
<td>4.4 (3.3, 5.5) [46]</td>
<td>0.86 [1.00]</td>
<td>0.98 [1.00]</td>
</tr>
</tbody>
</table>

Birthweight data are presented as mean (95% CI) [n]. P values are presented as unadjusted P value [adjusted P value]. Conversion factors to SI units: T and uT × 3.467 (nmol/liter); DHEAS × 0.062714 (pmol/liter); glucose × 0.0551 (mmol/liter); insulin × 6.945 (pmol/liter); cholesterol × 0.0259 (mmol/liter); triglycerides × 0.0113 (mmol/liter).

a Results reported from ANCOVA model adjusted for current age.
b Adaptive Holm adjustment of the stepdown Bonferroni method to correct P values for multiple hypothesis testing.

Male relatives
We noted no significant associations between birthweight and any phenotype (Table 3).

Association of birthweight with metabolic parameters in PCOS families
Overall 407 (43%) of 950 evaluable subjects had the metabolic syndrome. There was no association of metabolic syndrome with birthweight. Of these subjects with metabolic syndrome, 41 had a birthweight less than 2500 g (46% of all subjects in this category), 323 had a birthweight of 2500–4000 g (43% of all subjects in this category), and 43 had a birthweight of more than 4000 g (41% of all subjects in this category).

PCOS probands
We found no significant metabolic changes in relation to birthweight (Table 2). Furthermore, there were no differences in insulin and glucose levels during the OGTT according to birthweight category (Fig. 3).

Female and male relatives
After correcting for multiple hypothesis testing, there were no significant associations noted in either female or male relatives.

Discussion
It has been proposed that PCOS has developmental origins (5). To test this hypothesis, we examined the relationship between birthweight and features of PCOS in a large cohort of affected women and their male as well as female first-degree relatives. We validated the use of self-reported birthweight for this study by documenting a high concordance between self-reported and actual birthweight.
Overall, we found that there was little to no association between birthweight and the PCOS phenotype in affected women. Similarly, birthweight demonstrated no significant association with PCOS-related reproductive and metabolic features in female or male first-degree relatives. In probands, there was a positive association between ovarian volume and birthweight, but this effect was not significant after adjusting for multiple hypothesis testing. In female and male relatives, there were no associations between birthweight and metabolic or reproductive phenotypes after correcting for multiple hypothesis testing. Finally and perhaps most relevantly, we documented appropriate birthweights for gestational age based on our controls and U.S. population norms.

There have been few previous studies of women with PCOS and birthweight. A study of 236 women from England found associations of PCOS stigmata with length of gestation and birthweight. However, the association was with high birthweight, which was associated with hirsute women with polycystic ovaries who had higher than normal ovarian secretion of androgens (31). Another group in Spain has studied adolescent girls, primarily with prema-
ture pubarche, and has consistently found that low birthweight is associated with more severe reproductive and metabolic abnormalities (11, 12, 32–34). Furthermore, these investigators have shown an inverse association between birthweight and ovarian volume, which persists even after excluding those with polycystic ovary morphology (35, 36). We noted a positive linear association in our PCOS probands, contrary to previous reports; however, this association was not significant after adjusting for multiple testing (we lacked sufficient ultrasound data in first-degree female relatives).

A large Finnish birth cohort study had findings consistent with ours, noting no relationship between birthweight and PCOS symptoms (37). We noted no other associations between birthweight and reproductive abnormalities in women with PCOS. Although our NIH criteria for the diagnosis of PCOS (14) satisfy those promulgated by other expert groups (38, 39), it is possible that the alternate diagnostic criteria may have yielded varying results [e.g., one study noted increasing birthweight in women with polycystic ovary morphology (40), and another found increased birthweight and post mature birth associated with PCOS (31)].

Women with PCOS are thought to be at increased risk for complications of pregnancy such as preeclampsia and preterm labor (41), a finding replicated in a large prospective clinical trial (42), which may lead to reduced birthweight in their offspring through a shortened gestational period. Some studies of women with PCOS have shown a higher prevalence of small for gestational age babies (with no difference in large for gestational age babies) compared with controls (43). However, the Finnish birth cohort study found normal birthweights in women with PCOS symptoms (44). Mothers of women with PCOS show clustering of metabolic and reproductive abnormalities (16, 45), supporting the familial basis of the syndrome and raising the possibility that this abnormal maternal environment might affect fetal growth. However, we found birthweights in PCOS families to mirror those in the larger U.S. population for most gestational ages. This finding provides further support for our conclusion that birthweight contributes little to the PCOS phenotype. Our finding of a positive association between birthweight and a specific phenotypic group, sisters with hyperandrogenemia, that was not paralleled in continuous analyses of the whole cohort, suggests that there may be gene-environment interactions in this group of what we consider to be affected sisters (15, 16).
There are several limitations to our study. Our sample size, although large for the PCOS literature, is relatively small from an epidemiological standpoint, and, therefore, may lack the power to detect the more consistent associations between low birthweight and adverse cardiovascular risk (46–50). Birthweight is just one biometric marker of the intrauterine milieu, and other finer measures of fetal growth, such as head and abdominal circumference, fetal length, etc., may be more accurate predictors of adult disease. Another limitation of our study is that birthweight and gestational age were self-reported. Nonetheless, we found a high correlation and concordance between self-report and actual birth records. Furthermore, multiple studies show that both maternally or self-reported birthweights are a reliable source (47, 51–54). Although we had insufficient data to validate self-report of gestational age, multiple epidemiological studies support that maternal recall of gestational age is very accurate when correlated with birth medical records, with intraclass correlation coefficients ranging from 0.76–0.85 (55–57). Our family-based study had ready access and participation of mothers to supply birthweights and gestational ages.

Our finding of a normal distribution of birthweight for gestational age suggests that the intrauterine milieu in women with PCOS and their families is similar to that in our control and the larger U.S. population. We conclude that birthweight, even corrected for gestational age, has little substantive association with reproductive and metabolic abnormalities in women with PCOS and their relatives. However, there are other intrauterine factors, for instance exposure to elevated androgen levels, that could contribute to a PCOS phenotype and not affect birthweight (9, 10). Finally, accelerated and excessive growth after birth has been found to be an additional risk factor for adult disease (58, 59) as well as PCOS stigmata (60). Longitudinal study of PCOS offspring and likely large sample sizes will be necessary to demonstrate the effects of the postnatal environment on adult health.

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