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Insulin resistance and hyperandrogenism have no substantive association with birth weight in adolescents with polycystic ovary syndrome

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Objective: To assess whether birth weight influences the metabolic and hormonal profile of adolescents with polycystic ovary syndrome (PCOS).
Design: Retrospective study.
Setting: University outpatient clinic.
Patient(s): One hundred seventy consecutive adolescents 12 to 19 years of age with PCOS, 15 of whom were small for gestational age (SGA), and 75 healthy female aged-matched adolescents as controls.
Intervention(s): Physical evaluations, fasting blood samples for measuring endocrine and metabolic parameters, and an oral glucose tolerance test.
Main Outcomes Measure(s): Physical, endocrine, and metabolic features.
Result(s): The birth weights of adolescents with PCOS as well as those with hyperinsulinemic or insulin resistance were similar to those of the control group. The PCOS SGA adolescents had basal insulin (15.93 ± 7.16 μU/mL vs. 10.97 ± 5.79 μU/mL) and homeostasis model assessment of insulin resistance values (3.2 ± 1.54 vs. 2.19 ± 1.28) that were statistically significantly higher than in the control group. The mean levels of total testosterone in the SGA adolescents with PCOS were above the upper limit of the normal range (0.80 ng/mL).
Conclusion(s): Low birth weight may influence the appearance of hyperandrogenism and insulin resistance in a portion of adolescents with PCOS, but only 9% of the adolescents with PCOS in this study were SGA. In the majority of adolescents with PCOS, hyperinsulinemia and hyperandrogenism are related to factors other than birth weight alone. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Birth weight, PCOS, SGA

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Polycystic ovary syndrome (PCOS), the most common endocrine and metabolic disease in woman of reproductive age, affects up to 10% of women worldwide (1). The diagnostic features of PCOS are anovulatory dysfunctions, such as oligomenorrhea and amenorrhea, clinical and biochemical hyperandrogenism, and polycystic ovaries (PCO) (1). Polycystic ovary syndrome is also associated with metabolic abnormalities such as insulin resistance (2, 3), obesity, and dyslipidemia (4–7). As a consequence of these clinical and metabolic features, PCOS is associated with long-term morbidity, including infertility, type 2 diabetes mellitus, cardiovascular disease, and obstetric complications (8–10). To date, the etiology of PCOS is unknown, but it is thought that both genetic and environmental factors have a role in the development of this complex disorder (4).

Many investigators have hypothesized that the etiologic mechanisms of PCOS are determined during fetal life,

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leading to hyperandrogenism and insulin resistance later in life. Low birth weight as a result of an intrauterine growth retardation has been considered to play a critical role in PCOS. In 1998, Ibáñez et al. (11) observed that adolescent girls with a history of precocious pubarche during childhood and postmenarchal idiopathic functional ovarian hyperandrogenism had low birth weights. Moreover, the insulin response to glucose load of pubertal girls with lower birth weights was higher than found among healthy controls. Furthermore, the same investigators observed that the prevalence of anovulation was higher for small for gestational age (SGA) girls than for girls who were born at an appropriate weight for gestational age (AGA) (P=.002) (12). In 2003, Barker et al. (13) showed a positive correlation between low birth weight and PCOS. The "catch-up growth" theory (14, 15) has been proposed to explain why SGA features may lead to hyperandrogenism and hyperinsulinemia. In 2004, Ong et al. (16, 17) found that children who had a rapid postnatal weight gain had a waist circumference and a percentage of fat mass that were higher than found in children who had a normal birth weight. Moreover, their insulin resistance and androstenedione and dehydroepiandrosterone-sulfate (DHEAS) levels were higher at 8 years of age. Similarly, in 2011, Ibáñez et al. (18) found that after the completion of catch-up growth and before the start puberty SGA girls had higher levels of circulating insulin, insulin growth factor I (IGF-1), DHEAS, low-density lipoprotein (LDL) cholesterol, and leptin; lower levels of high-molecular-weight adiponectin and sex hormone-binding globulin (SHBG); more total and visceral fat; and an older bone age than AGA girls. Other studies conducted in India (19), Spain (20), and Chile (21) showed that low birth weight and the resultant catch-up growth were associated with insulin resistance with increased central adiposity and higher body mass index (BMI) and waist-to-hip (WHR) values. Together, these data suggest that low birth weight followed by postnatal catch-up growth may be a risk factor for the later development of obesity, central fat deposition, precocious pubarche, and hyperandrogenism. According to these studies, it has been proposed that low birth weight increases the risk of developing clinical and biochemical features of PCOS.

In contrast with these data, in 2009, Legro et al. (22) and Laitinen et al. (23) did not find a statistically significant association between birth weight and the reproductive and metabolic abnormalities of women with PCOS. Conversely, obesity in adolescence and in adulthood were recognized as risk factors for PCOS (23). We assessed whether birth weight influences the metabolic and clinical profile of adolescents with PCOS.

MATERIALS AND METHODS

The study protocol was approved by the institutional review board of Pisa and Cagliari universities. Our study enrolled 170 patients with PCOS aged 12 to 19 years old who had been referred to the Outpatient Clinic of Reproductive Endocrinology of the universities of Pisa and Cagliari between 2009 and 2010. As controls, 75 healthy, aged-matched female adolescents were recruited. Only girls who were at least 2 years after menarche were considered for the study, and informed consent was obtained from all participants and/or their parents before they entered the study. The diagnosis of PCOS was made partially based on the Rotterdam criteria (24–26): [1] clinical and/or biochemical hyperandrogenism (defined as total testosterone [total T] more than 0.8 ng/mL, and/or androstenedione (A) more than 3.1 ng/mL), [2] oligo- and/or anovulation, and [3] PCO at ultrasound (presence of at least 12 follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume >10 mL). However, because our population consisted of adolescents only, the criteria of Carmina et al. (27) for the diagnosis of PCOS in adolescence were taken into account: only girls with the contemporary presence of hyperandrogenism, oligomenorrhea, and ovarian volume >10 mL were considered for the study. As for the clinical signs of hyperandrogenism, only girls with hirsutism or severe acne were considered. In no case was hyperandrogenism defined on the basis of elevated DHEAS levels only.

Patients with congenital adrenal hyperplasia, Cushing syndrome or androgen-secreting tumors, hyperprolactinemia, and hypo- or hyperthyroidism were excluded from this study. None of the patients had a personal history of hypertension, diabetes mellitus, or cardiovascular events, and none had received treatment with oral contraceptives, antiandrogens, insulin sensitizers, or drugs that might interfere with their blood pressure regulation, lipid profile, or carbohydrate metabolism within 6 months of being enrolled in the study. At study entry, information about each participant's birth weight and gestational age at delivery was obtained, which was confirmed by their parents. Only girls born after a full-term pregnancy (gestational age >37 weeks) were enrolled. In no case was a history of gestational diabetes reported.

All girls were evaluated during the follicular phase of their menstrual cycle (3–7 days after the onset of last spontaneous menstrual bleeding). Hirsutism was assessed with the Ferriman-Gallwey score. Height and weight were measured, and BMI was calculated. Waist and hip circumferences were measured, and the WHR was calculated. Blood samples were obtained between 08.00 and 08.30 AM after an overnight fast for determination of total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels. An oral glucose tolerance test (OGTT) was performed. Blood samples for the determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E_2), SHBG, 17-hydroxyprogesterone (17OHP), total T, DHEAS, A, and cortisol (F) were also obtained.

For OGTT, plasma samples for glucose and insulin concentrations were collected before and after a 75-g oral glucose administration at 30, 60, 90, 120, and 180 minutes. None of the participants had an abnormal OGTT value in terms of glucose response. Insulin plasma levels were expressed as the area under the curve after glucose ingestion (AUC-insulin). The AUC was calculated using the trapezoidal rule and was expressed as μU/mL $\times$ 180 minutes. As an indicator of insulin sensitivity, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: (Blood glucose nmol/L $\times$ Insulin μU/mL)/22.5. Values of HOMA-IR $\geq$2.5 were considered indicative of