Metabolic parameters in cord blood of newborns of women with polycystic ovary syndrome

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Objective: To assess metabolic parameters in the cord blood of newborns of women with polycystic ovary syndrome (PCOS) and to correlate these parameters with those of mothers with PCOS during midgestation.
Design: Case-control study.
Setting: Unit of Endocrinology and Reproductive Medicine.
Patient(s): Thirty newborns of mothers with PCOS (PCOSn) and 34 newborns of control mothers (Cn) were studied.
Intervention(s): A sample of cord blood was obtained at delivery. In all mothers, an oral glucose tolerance test (oGTT) with measurement of glucose and insulin was performed at 22–28 weeks of gestation. In cord blood and in the fasting sample of the oGTT, serum leptin, adiponectin, insulin, glucose, and lipids (triglycerides, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol) were determined.
Result(s): PCOSn showed significantly higher leptin concentrations than Cn. Moreover, in PCOSn, leptin concentrations in cord blood were correlated with birth weight ($r = 0.495$) and body mass index of the mother at midpregnancy ($r = 0.644$).
Conclusion(s): The metabolic parameters in the cord blood of PCOSn are similar to those observed in controls, except for leptin concentrations, which are significantly higher. The latter could be related to the fetal adiposity or the metabolic condition of the mother. (Fertil Steril® 2009;92:277–82. ©2009 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, cord blood, leptin

Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder affecting women of reproductive age; it characterized by menstrual irregularity and hyperandrogenism (1–4). In addition, PCOS is associated with hyperinsulinemia, insulin resistance, lipid-related abnormalities, glucose intolerance, and type 2 diabetes (5–7). Thus, women with PCOS constitute a high-risk group for pregnancy complications such as gestational diabetes and pregnancy-induced hypertension (8–11).

In the last years, several studies have suggested that the maternal intrauterine environment might result in "programming" of later disease (12–14). In this regard, the offspring born to mothers with gestational diabetes, which is strongly associated with hyperinsulinemia and insulin resistance, have shown an increased risk of obesity (12, 15) and abnormal glucose tolerance in adult life (14, 16). Moreover, newborns exposed to maternal diabetes in utero exhibit elevated concentrations of insulin, leptin, and lipids in cord blood, which could have implications in the high risk of later metabolic complications (17–19). In previous studies, we have established that hyperinsulinemia, insulin resistance, and lipid-related abnormalities are enhanced during pregnancy in women with PCOS (20, 21). Therefore, it is possible to propose that newborns of women with PCOS will be exposed to an abnormal metabolic milieu during fetal life, similar to that of gestational diabetes. Therefore, our aim was to assess metabolic parameters in the cord blood of newborns of women with PCOS and to correlate these parameters with those of mothers with PCOS during midgestation.

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MATERIALS AND METHODS

Subjects

We studied 30 newborns born to mothers with PCOS (PCOS newborns [PCOSn]). As a control group, we included 34 newborns born to mothers with regular menses and without hyperandrogenism (control newborns [Cn]).

Mothers with PCOS were recruited for the study from patients attending the Unit of Endocrinology and Reproductive Medicine, University of Chile, who desired fertility; they were placed on a 6-month diet and exercise treatment program as described elsewhere (22). Diagnosis of PCOS was made according to the criteria for PCOS of the National Institutes of Health consensus (2) and the Rotterdam European Society for Human Reproduction and Embryology/American

Society for Reproductive Medicine–sponsored PCOS consensus workshop group (23). Preconceptional inclusion criteria were chronic oligomenorrhea or amenorrhea, hirsutism, serum T concentration >0.6 ng/mL and/or free androgen index >5.0, androstenedione concentration >3.0 ng/mL, and a characteristic ovarian morphology on ultrasound, based on the criteria described by Adams et al. (1). Normoglycemic patients with and without clinical signs of hyperinsulinemia (waist-hip ratio >0.85) and with different grades of hyperinsulinemia evaluated by an oral glucose tolerance test (oGTT) were included. All women had been anovulatory as indicated by P measurements and ultrasound examinations. We excluded patients with hyperprolactinemia, androgen-secreting neoplasm, Cushing's syndrome, and late-onset 21-hydroxylase deficiency as well as those with thyroid disease.

As control mothers, we selected 34 women of similar socioeconomic levels as the patients with PCOS. The control women had a history of regular 28- to 32-day menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and absence of galactorrhea and thyroid dysfunction. All were healthy and were not receiving any drug therapy. These women were recruited from the antenatal care unit of our hospital from the 12th week of gestation during the same time period.

Only nonsmoking and non-alcohol- or non-drug-abusing PCOS and control pregnant women were included in the study. Women of both groups with gestational diabetes, pregnancy-induced hypertension, and a preterm delivery in the present pregnancy were not included. Both groups of newborns were born at term from singleton pregnancies. This investigation was approved by the Institutional Ethics Committee, and an informed written consent was obtained from all subjects.

Study Protocol

Cord blood Blood samples were collected as umbilical mixed arterial-venous cord blood samples at delivery. The samples were immediately centrifuged. The serum was frozen at −70°C until further analyses. In all samples, serum glucose, insulin, adiponectin, leptin, and lipid concentrations (triglycerides, cholesterol, high-density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol) were determined. Immediately after delivery, a physical examination of the newborn was performed. Anthropometric measurements at birth were recorded, including weight, length, and head circumference. Weight and length were transformed into standard deviation score (SDS) using local normative data for newborns (24), adjusting for differences in gestational age and gender. The SDS was calculated using the formula SDS = (x-mean)/SD. Infants were defined as small for gestational age (SGA) infants (birth weight <5th percentile), appropriate for gestational age (AGA) infants (birth weight >5th and <90th percentile), and large for gestational age (LGA) infants (birth weight >90th percentile) (25) using the Chilean birth weight reference (24, 26). Infants showing evidence of malformations or genetic disorders were excluded from the study.

Pregnant Women

In all pregnant women, initial body mass index (BMI), BMI during third trimester, and weight gain during pregnancy were recorded.

Moreover, in gestational weeks 22–28 (midpregnancy), the women were admitted to the Clinical Research Center in the morning (8:30–9:00 A.M.) after an overnight fast of between 8 and 12 hours. A 2-hour, 75 g oGTT was performed in accordance with published criteria (27). Serum glucose and insulin were measured before the glucose load and 30, 60, 90, and 120 minutes after. In all cases, homeostatic model assessment (HOMA-IR) (28) and insulin sensitivity index (ISI) composite (29) were calculated. Moreover, serum adiponectin, leptin, and lipid concentrations (triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol) were determined in the fasting sample.

Assays

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The intra-assay coefficient of variation of this method was <2.0%. The lipid profile was determined by standard colorimetric assays (Photometric Instrument 4010). Estimation of serum LDL cholesterol concentration was calculated by Friedewald's formula [LDL cholesteral = total cholesterol − HDL cholesterol − (triglycerides/5)] (30). The coefficient of variation of these methods was less than 3.0%. Serum insulin was assayed by radioimmunoassay (Diagnostic Systems Laboratories, Inc., Webster, TX). The intra- and interassay coefficients of variation were 5.0% and 8.0%, respectively. Serum adiponectin was assayed by radioimmunoassay (Linco-Research Inc., St. Charles, MO), with a sensitivity of 1.0 ng/mL and intra- and interassay coefficients of variation of 1.8% and 9.0%, respectively. Leptin concentrations were measured by radioimmunoassay (Linco-Research Inc.), with a sensitivity of 0.5 ng/mL and intra- and inter-assay coefficients of variation of 3.9% and 4.7%, respectively. All hormones were determined in duplicate and were run in the same assay in each period.

Statistical Analysis

Data are expressed as median and range. Normal distribution was assessed by the Kolmogorov-Smirnov test. Differences among study groups were assessed with the Student's *t*-test when data were normally distributed or the Mann-Whitney test when not normally distributed. Comparisons within groups were performed by the Kruskal-Wallis test. Categorical data were analyzed using the χ^2-test or Fisher's exact test. The association between continuous variables was assessed through Spearman correlation analysis. According to previous studies, leptin concentrations in cord blood are 1.5- to 2.0-fold higher in newborns of mothers with gestational