ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Endocrine and cardiometabolic cord blood characteristics of offspring born to mothers with and without polycystic ovary syndrome

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Objective: To compare the endocrine and cardiometabolic cord blood characteristics of offspring of mothers with polycystic ovary syndrome (PCOS) with those of healthy controls.
Design: Cross-sectional case control study.
Setting: University medical centers.
Patient(s): Offspring from mothers with PCOS (n = 61) and healthy controls (n = 82).
Intervention(s): Cord blood withdrawal from neonates.
Main Outcome Measure(s): Cord blood estradiol, androstenedione, dehydroepiandrosterone sulfate (DHEAS), testosterone, sex hormone-binding globulin, free androgen index (FAI), insulin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, c-reactive protein, adiponectin, and leptin.
Result(s): Androstenedione and leptin concentrations were increased in the offspring of women with PCOS compared with the controls: androstenedione median 2.9 (interquartile range [IQR] 2.3–3.9) nmol/L vs. 2.2 [IQR 1.6–2.7] nmol/L; and leptin median 13.6 [IQR 8.3–22.9] μg/L vs. 9.8 [IQR 6.0–16.5] μg/L. After adjusting for maternal and pregnancy-related confounders (such as maternal age, gestational age, birth weight), androstenedione appeared associated with PCOS in both male (relative change 1.36 [1.04; 1.78]) and female offspring (relative change 1.40 [1.08; 1.82]). Similarly, in male offspring the leptin concentrations appeared associated with PCOS after correction for confounders (relative change 1.55 [1.12; 2.14]). After correction for multiple testing, these associations attenuated.
Conclusion(s): Observed results suggest that androstenedione concentrations are increased in the cord blood of male and female offspring of women with PCOS, although this requires confirmation. This finding would support the hypothesis that a maternal hyperandrogenic environment during pregnancy in women with PCOS may predispose their offspring to fetal hyperandrogenism. The potential associations between fetal hyperandrogenism and long-term health effects remain to be elucidated.
Clinical Trial Registration Number: NCT00821379. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Androgens, cord blood, PCOS offspring

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Polycystic ovary syndrome (PCOS), a heterogeneous condition characterized by ovulatory dysfunction, polycystic ovary morphology, and/or hyperandrogenism, affects up to 15% of the general female population (1, 2). Frequently PCOS is accompanied by various metabolic abnormalities, including obesity, hyperinsulinemia and dyslipidemia, which may result in the development of type 2 diabetes mellitus, atherosclerosis, and

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cardiovascular disease in later life (2–5). Moreover, pregnancies in women with PCOS are more often complicated by gestational diabetes, pregnancy-induced hypertension, preeclampsia, and premature delivery (6).

Family studies, including twin studies, demonstrate a distinct heritability of PCOS, particularly of hyperandrogenism (7, 8). It is likely that PCOS originates from a complex interaction between an inherent genetic predisposition along with environmental factors (9, 10). Intrauterine conditions may potentially contribute to the development of PCOS and associated complications in the later life of exposed offspring (11). Studies in primates have established that excess prenatal exposure to androgens may induce the development of PCOS in offspring (12, 13).

Circulating androgen levels may be increased in pregnant women with PCOS, providing a potential source of fetal androgen excess (14, 15). Moreover, hyperinsulinemia in pregnant women with PCOS may contribute to fetal androgen excess through the inhibition of placental aromatase activity, which decreases the conversion of maternal and fetal androgens to estrogens (16, 17).

Umbilical cord blood characteristics reflect maternal, placental, and fetal conditions, and may therefore indicate potential derangements in the endocrine or metabolic intrauterine fetal environment. Few studies with limited sample size have previously compared cord blood characteristics of offspring of mothers with PCOS with non-PCOS controls, generating conflicting outcomes. Some studies have reported increased androgens levels in the cord blood of offspring of mothers with PCOS (18, 19), but others have observed decreased androgen concentrations (15, 20) or no differences compared with controls (21). The current study was undertaken to compare both endocrine and cardiometabolic cord blood characteristics between a carefully phenotyped population of offspring of mothers with PCOS and non-PCOS controls. Due to the expected differences in sex hormone levels in male and female offspring, and potential differences in correlations with metabolic biomarkers, subanalyses for gender were performed.

MATERIALS AND METHODS

Study Population

Cord blood was collected from children born to PCOS mothers who were included in a multicenter study that was conducted in the Netherlands between April 2008 and April 2012 (clinicaltrials.gov, trial number NCT00821379). The primary aim of this study was to design a multivariable prediction model for maternal and perinatal complications in women with PCOS (22). Women diagnosed with PCOS according to the Rotterdam criteria and who wanted to conceive underwent a standardized preconception screening before inclusion (4, 23). Subsequently, most of the women underwent ovulation induction or in vitro fertilization as infertility treatment (24). Once a pregnancy was established, the women were observed through repeated antenatal care visits and a postpartum visit at 6 weeks. All study procedures have previously been described in detail elsewhere (22).

For the current study we included mixed arteriovenous cord blood samples of singleton PCOS pregnancies that were obtained and stored at the University Medical Center Utrecht (n = 61). After withdrawal, cord blood samples were processed and first stored at −20°C (for a maximum of 3 years), and thereafter stored at −150°C.

For the control population, cord blood samples were provided from the Rotterdam Periconceptional Cohort Study, the design of which has been described in detail elsewhere (25). This study represents an ongoing prospective birth cohort, which was initiated in 2009 within the Erasmus Medical Center Rotterdam (www.birthcohorts.net, PREDICT). Among other goals, this study focuses on determinants of periconceptional health, reproductive performance, pregnancy course, and outcomes. All women scheduled for a first antenatal visit at the outpatient clinic of the Erasmus Medical Center with a gestational age less than 12 weeks were invited to participate. Upon inclusion, the women completed questionnaires that included preconceptional data on menstrual cycle regularity and duration of menstrual cycles. Furthermore, all women underwent a standardized examination followed by a three-dimensional ultrasound examination. For the current study, women previously diagnosed with PCOS were excluded based on their preconception medical records (25). We included all available mixed arteriovenous cord blood samples of singleton non-PCOS pregnancies (n = 82) that were collected between August 2011 and May 2014. After withdrawal the cord blood samples were processed and stored at −80°C.

Both studies were conducted with permission of local institutional ethical review boards. Written, informed consent was obtained from all participants.

Endocrine Assessments

Dehydroepiandrosterone sulfate (DHEAS) was measured using an electrochemiluminescence immunoassay on the Cobas E411 (Roche Diagnostics GmbH); the lower limit of detection was 0.05 μmol/L, and the interassay variation ranged from 6% to 4.5% at 0.5–17 μmol/L. We measured sex hormone-binding globulin (SHBG) using an electrochemiluminescence immunoassay on the Cobas E411 (Roche Diagnostics GmbH); the lower limit of detection was 2 nmol/L, and the interassay variation was <4% in the range of 10–120 nmol/L. Estradiol was measured using an electrochemiluminescence immunoassay on the Cobas E411 (Roche Diagnostics GmbH), and the lower limit of detection was <40 pmol/L. Samples were diluted 11 times, and the interassay variation ranged from 11% at 70 pmol/L to <4% at 190–560 pmol/L.

Testosterone and androstenedione were measured on the Thermo Vantage liquid chromatography with tandem mass spectrometer (LC-MS/MS) (Thermo Fisher Scientific BV). The samples were extracted using tert-butylmethyl ether, after which the components were separated on a RP C18 Hypersil Gold column and then injected into the LC-MS/MS using atmospheric pressure chemical ionization. The interassay coefficient of variations were as follows: androstenedione: 8% at 1.0 nmol/L and <5% at 3–23 nmol/L; and testosterone 7.4% at 0.95 nmol/L and <3.8% at