Markers of Insulin Sensitivity in 12-Year-Old Children Born from Preeclamptic Pregnancies

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Objective To determine whether maternal preeclampsia influences insulin sensitivity (IS) or its biochemical markers in offspring.

Study design Sixty children born from a preeclamptic pregnancy (PRE) and 60 matched control subjects born from a normotensive pregnancy (non-PRE) were studied at age 12 years. IS was estimated using the Quantitative Insulin Sensitivity Check Index (QUICKI), and serum concentrations of adiponectin, leptin, insulin-like growth factor (IGF)-1, IGF-2, IGF-binding protein-1 (IGFBP-1), sex hormone-binding globulin, lipids, and casual blood pressure (BP) were measured.

Results The mean values of QUICKI, serum adiponectin, leptin, IGF-1, IGF-2, IGFBP-1, and sex hormone-binding globulin did not differ between the PRE group and non-PRE group ($P > .05$ for all). The PRE subjects with the lowest IS (the lowest QUICKI tertile; n = 20) had significantly higher mean serum leptin ($P = .007$), triglyceride ($P = .008$), and IGF-1 ($P = .005$) levels and systolic BP ($P = .019$), and lower serum IGFBP-1 level ($P = .007$) compared with PRE subjects with higher QUICKI values (n = 40). Similarly, in logistic regression analysis, higher serum leptin (OR, 1.2; $P = .009$), triglyceride (OR, 1.2; $P = .040$), and IGF-1 (OR, 1.1; $P = .031$) levels and systolic BP (OR, 5.8; $P = .024$) were associated with low QUICKI in the PRE group.

Conclusion Maternal preeclampsia did not produce decreased IS in offspring by age of 12 years. However, the offspring with the lowest IS had higher mean serum triglyceride level and systolic BP, suggesting that components of the metabolic syndrome may cluster in this subgroup. *(J Pediatr 2015;167:125-30)*.

Preeclampsia is a pregnancy-specific disorder complicating 2%-8% of pregnancies and resulting in substantial maternal and fetal morbidity and mortality.[1] Various maternal factors can predispose to this disorder, including obesity, chronic hypertension, diabetes, hyperandrogenism, low socioeconomic status, and specific ethnic backgrounds (ie, African-American and Filipino).[1-3] The cause of preeclampsia is largely unknown, but a genetic contribution has been established.[2] Preeclampsia may recur across generations, and the fetal genotype (both maternal and paternal factors) contributes to the risk.[4,5] It is hypothesized that the pathophysiological events proceed in 2 phases. In early pregnancy, the placental function is probably disturbed by abnormal maternal immune responses to the trophoblast. In the second stage, systemic maternal disease is characterized by endothelial dysfunction and a generalized hyperinflammatory state.[1]

Kaaja et al[6] have shown that preeclampsia is a state of increased insulin resistance that may persist after pregnancy. Consequently, insulin resistance could be a mechanism involved in the pathogenesis of preeclampsia.[3] Previous meta-analyses have confirmed the association between preeclampsia and cardiovascular disease in later life; women who develop preeclampsia during pregnancy are at increased risk for hypertension, ischemic heart disease, and stroke.[7,8] It has been proposed that persistent endothelial damage caused by preeclampsia could explain these associations.[8] On the other hand, a predisposition to the metabolic syndrome may induce women to develop preeclampsia during pregnancy.[9-11] Several studies have shown an association between maternal preeclampsia and elevated blood pressure (BP) in the offspring during childhood and adolescence.[12-19] Other studies have reported on glucose metabolism in the offspring of mothers with preeclampsia.[20-22]

The aim of the present study was to determine, using the Quantitative Insulin Sensitivity Check Index (QUICKI), whether preeclampsia influences insulin sensitivity (IS) in the offspring of affected mothers. In addition, insulin-like growth factor (IGF)-1 associated with transient physiological insulin resistance of puberty,[23] and IGF-binding protein-1 (IGFBP-1) and sex hormone-binding globulin (SHBG), 2 commonly used markers of IS,[24]

AGA	Appropriate for gestational age	IS	Insulin sensitivity
BMI	Body mass index	LDL	Low-density lipoprotein
BP	Blood pressure	PRE	Preeclamptic pregnancy
CV	Coefficient of variation	PSEH	Parent-specific expected height
ELISA	Enzyme-linked immunosorbent assay	QUICKI	Quantitative Insulin Sensitivity Check Index
HDL	High-density lipoprotein	SGA	Small for gestational age
IGF	Insulin-like growth factor	SHBG	Sex hormone-binding globulin
IGFBP-1	IGF-binding protein-1		

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were measured. Levels of the adipose tissue-specific cytokines adiponectin and leptin were also compared in the preeclamptic pregnancy (PRE) and non-PRE groups at age 12 years.

Methods

All children were born at Kuopio University Hospital during a 22-month period between 1984 and 1986. The group of children born to mothers with preeclampsia consisted of every third term-born child and all preterm-born children, with the exception of extremely preterm children born before week 28 of gestation. Altogether, 84 nonmalformed children with maternal preeclampsia were included in the present study as the PRE group. At age 12 years, 60 children (71.4%) in the PRE group participated in this study. The PRE subjects (29 girls and 31 boys; 33 preterm and 27 full-term; 16 small for gestational age [SGA] and 44 appropriate for gestational age [AGA]) and the 60 control subjects born to normotensive mothers (non-PRE group) were matched for sex, gestational age (±1 week), and size at birth (SGA vs SGA, AGA vs AGA). Matching for size at birth did not succeed completely, because 6 preterm PRE subjects born SGA had a control subject born AGA instead of SGA. The mean ± SD age of the children in both groups was 12.3 ± 0.2 years. None of the participating children had prenatal exposure to exogenous glucocorticoids. The study protocol was approved by the Research Ethics Committee of Kuopio University Hospital. Informed written consent was obtained from each child and a parent. The BP values and serum lipid, insulin, and adrenal hormone concentrations of this study cohort have been reported previously.[14]

Preeclampsia was defined as the development of hypertension and proteinuria (>300 mg of urinary protein in 24 hours) after 20 weeks of gestation.[25] Hypertension was defined as BP >140/90 mmHg or a rise of 30/15 mmHg from baseline level, confirmed by 2 measurements obtained at least 6 hours apart. Full-term indicates infants born between 37 and 42 weeks of gestation, and preterm indicates those born before the week 37 of gestation (calculated from the beginning of the last menstruation). SGA was defined as birth weight and/or length >2 SDS below the respective mean for the gestational age and sex. AGA was defined as birth weight and birth length ≥ −2 SDS and ≤ +2 SDS of the respective mean for gestational age and sex.[26] Parent-specific expected height (PSEH) (corresponding to target height) was calculated as determined by Pere et al.[27] QUICKI was calculated as 1/[log (fasting insulin, μU/mL) + log (fasting glucose, mg/dL)].[28]

Perinatal data, including anthropometric measures, have been reported previously.[14] Pubertal development was classified by Tanner stage according to breast development (B) in girls and genital development (G) in boys. Perinatal characteristics, anthropometric measures, and pubertal development at age 12 years are presented in Table I.

Blood samples were obtained in the morning, between 9:00 a.m. and 10:00 a.m., after an overnight fast. An intravenous cannula was placed in the antecubital vein for blood sampling. After the child had rested for 1 hour in a recumbent position, a blood sample was drawn through the cannula. Plasma and serum specimens were immediately frozen and stored at −70°C until analysis. Serum insulin concentrations were determined by radioimmunoassay (Phadeseph Insulin RIA; Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The intra-assay and interassay coefficients of variation (CVs) for insulin were 5.3% and 7.6%, respectively. Blood glucose concentrations were analyzed by a glucose oxidase method (Enzyme Electrode; Nova Biomedical, Waltham, Massachusetts), with intra-assay and interassay CVs of 3% and 5%. Serum total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured enzymatically by an automatic photometric method (Roche Molecular Biochemicals, Mannheim, Germany). Low-density lipoprotein (LDL) cholesterol concentrations were calculated with the Friedewald-Fredrickson formula [LDL cholesterol = total

Table I. Anthropometric characteristics of the PRE and non-PRE groups at birth and age 12 years

Variables	PRE (n = 60; 29 girls, 31 boys)	Non-PRE (n = 60; 29 girls, 31 boys)	*P* value*
At birth			
Gestational weeks	36.6 (35.7-37.5)	36.7 (35.7-37.6)	.489
Birth weight, g	2622 (2406-2837)	2868 (2657-3079)	<.001
Birth weight, SDS	−1.16 (−1.49 to −0.83)	−0.54 (−0.85 to −0.22)	.001
Birth length, cm	46.7 (45.6-47.8)	47.5 (46.5-48.6)	.026
Birth length, SDS	−0.68 (−1.03 to −0.34)	−0.26 (−0.58 to 0.07)	.057
At age 12 y			
Weight, kg	44.4 (41.8-46.9)	46.5 (43.5-49.4)	.377
Weight for height, %	106 (102-110)	106 (100-111)	.792
Height, cm	152.4 (150.4-154.4)	155.3 (153.4-157.2)	.018
Height, SDS	0.20 (−0.07 to 0.48)	0.58 (0.33-0.83)	.019
BMI, kg/m^2	18.9 (18.1-19.7)	19.1 (18.1-20.1)	.680
Waist circumference/height ratio	0.44 (0.42-0.45)	0.44 (0.42-0.45)	.808
Pubertal development (B/G 1 / B/G 2-5, n)			
Girls	2/27	3/26	1.000†
Boys	9/22	8/23	

Data are mean (95% CI) (partly reported by Tenhola et al[14]).
*Wilcoxon signed-rank test for the differences.
†McNemar test.