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Systolic blood pressure and fatty acid-binding protein 4 predict pregnancy-induced hypertension in overweight nulliparous women

A.L. Tuuri [a, 1], M.S. Jauhiainen [b, 2], M.J. Tikkanen [c, 3], R.J. Kaaja [d, *]

[a] Department of Obstetrics and Gynecology, Hospital District of Helsinki and Uusimaa, FIN-00029 Helsinki, Finland
[b] National Institute for Health and Welfare, PL 30, 00271 Helsinki, Finland
[c] Heart and Lung Center, Helsinki University Central Hospital and Folkhälsan Research Center, Biomedicum Helsinki, Haartmansgatan 8 (PB 63), 00014, Helsingfors universitet, Finland
[d] Turku University/Satakunta Central Hospital, 28500 Pori, Finland

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ABSTRACT

Introduction: The insulin-sensitivity regulator adipocyte fatty acid-binding protein 4 (FABP4) integrates metabolic and inflammatory responses. We hypothesize that there is relationship between FABP4 and factors related to metabolic syndrome in pregnancy-induced hypertension (PIH).
Methods: In this prospective observational study, among the 72 relatively overweight (BMI ≥24 kg/m^2) nulliparous women, 14 developed non-proteinuric PIH and 12 developed proteinuric PIH (preeclampsia), whereas 46 had normotensive pregnancies. Insulin sensitivity was assessed via the whole-body insulin sensitivity index (ISI) and the homeostatic model of assessment – insulin resistance (HOMA-IR) at 24 weeks of gestation. Maternal serum levels of FABP4, high-sensitive C-reactive protein (hs-CRP), total testosterone, and non-protein-bound calculated free testosterone (cfT) were determined at 24 and 32 weeks.
Results: Measures of ISI, HOMA-IR, hs-CRP, testosterone and lipids did not differ at 24 and/or at 32 weeks in women who were subsequently hypertensive. SBP was higher at all time points and FABP4 levels tended to be higher at 24 and 32 weeks in patients compared to controls. In logistic regression analysis, baseline FABP4 (OR [95% CI] 1.069 [1.020–1.121], $P = 0.006$) and SBP after 10 min standing (OR [95% CI] 1.087 [1.029–1.149], $P = 0.003$) were associated with the development of PIH. FABP4 levels at 24 weeks did not correlate with insulin sensitivity. Neither was correlation seen between FABP4 levels at 24 and 32 weeks, vs. those of hs-CRP and testosterone.
Discussion and conclusions: Serum FABP4 concentration and SBP after 10 min standing in an orthostatic test at 24 weeks are associated with subsequent development of PIH.

1. Introduction

Pregnancy-induced hypertension (PIH) and preeclampsia have been found to be characterized by insulin resistance [1,2], sympathetic over-activity [3] and exaggerated systemic inflammation [2,4], all features characteristic for metabolic syndrome [5].Hypertensive pregnant women are at an increased risk of later cardiovascular disease (CVD) and mortality [6] regardless of their proteinuric status [7]. This can be explained by the fact that metabolic syndrome is an important risk factor of CVD in women [8].

In nonpregnant individuals a key protein linking obesity to various features of metabolic syndrome is adipocyte fatty acid-binding protein 4 (FABP4 or aP2) [9]. This is an intracytoplasmic lipid chaperone [10], which is actively secreted from mature

Abbreviations: FABP4 or aP2, adipocyte fatty acid-binding protein 4; Angptl6, angiopoietin-like protein 6; BP, blood pressure; BMI, body mass index; cfT, calculated free testosterone; CVD, cardiovascular disease; DBP, diastolic blood pressure; ELISA, enzyme-linked immunosorbent assay; FABPs, fatty acid-binding proteins; HDL, high-density lipoprotein; hs-CRP, high-sensitive C-reactive protein; HOMA-IR, homeostatic model of assessment – insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PIH, pregnancy-induced hypertension; SHBG, sex hormone-binding globulin; SBP, systolic blood pressure; ISI, whole-body insulin sensitivity index.

* Corresponding author. Tel.: +358 44 707 9716; fax: +358 26 276 179.
E-mail addresses: anna.tuuri@hus.fi (A.L. Tuuri), matti.jauhiainen@thl.fi (M.S. Jauhiainen), Matti.J.Tikkanen@helsinki.fi (M.J. Tikkanen), risto.kaaja@utu.fi (R.J. Kaaja).
[1] Fax: +358 193801696.
[2] Fax: +358 29 524 8960.
[3] Tel.: +358 9 1912 5715; fax: +358 9 191 253 82.

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adipocytes, into the blood stream [11] to control liver glucose metabolism [12]. Moreover, FABP4 integrates metabolic and inflammatory response systems [13]. Earlier studies have shown that maternal circulating FABP4 levels are elevated in preeclampsia [14–16]. However, the role of FABP4 in the pathogenesis of preeclampsia is still incompletely understood [14]. In this study we tested the hypothesis that in both proteinuric and non-proteinuric PIH there is a relationship between FABP4 levels and factors related to metabolic syndrome. The aim of the study was to investigate associations between maternal serum FABP4 levels in the second or third trimesters of pregnancy and the indices of possible insulin resistance, sympathetic overactivity, inflammation, or hyperandrogenism in cases of PIH. Further, we aimed to assess if maternal serum levels of FABP4 in the second trimester of pregnancy are associated with subsequent development of hypertensive pregnancy and the indices of possible insulin resistance, sympathetic overactivity, inflammation, or hyperandrogenism in cases of PIH.

2. Materials and methods

2.1. Participants

Women at relatively high risk of developing preeclampsia were recruited for this prospective observational study from consecutive referrals for a routine first-trimester ultrasound scan at Helsinki University Central Hospital maternal policlinic. Women were eligible for the study if they were nulliparous (no prior pregnancies of ≥20 gestational weeks), with a singleton pregnancy, no major health problems, but a pre-pregnancy BMI of ≥24 kg/m^2, blood pressure (BP) <140/90 mmHg and absent proteinuria according to dipstick testing.

For the study 106 women were approached for enrollment, but 34 of them were excluded, including eight with chronic hypertension and six with other pre-existing disorders (three with known thromboembolic complications, one with collagenosis of unknown origin, one with a history of thyroid cancer and one receiving medication for hyperthyroidism) as well as one woman who had undergone assisted reproduction, two women with a pre-pregnancy BMI of <24 kg/m^2, 14 women with inadequate patient notes or labor ward records, and serum was not available from three women. In the study group, 12 subsequently developed preeclampsia and 14 developed non-proteinuric PIH, whereas 46 had normotensive pregnancies. In part, the same patient material was used as in a previous study, where angiopoietin-like protein 6 (Angptl6) concentrations were measured in a subset of 47 women [17]. All women gave informed consent, and the present study was approved by Helsinki University Hospital Ethics Committee.

2.2. Hypertension

Pregnancy-induced hypertension was defined as systolic BP (SBP) elevation to ≥140 mmHg or diastolic BP (DBP) elevation to ≥90 mmHg after 20 weeks of gestation with (preeclampsia) or without proteinuria. Proteinuria was defined as ≥0.3 g protein/24 h or ≥1+ in dipstick testing. Preeclampsia was regarded as severe if severe hypertension was associated with proteinuria or if hypertension was associated with severe proteinuria (≥5 g per day). Hypertension was regarded as severe if SBP was sustained at ≥160 mmHg or DBP was sustained at ≥110 mmHg. Women with and without proteinuria were analyzed as one group, since the pathogenesis of hypertension is similar [2]. Chronic hypertension was diagnosed as SBP elevation to ≥140 mmHg or DBP elevation to ≥90 mmHg repeatedly before 20 weeks of gestation. Normotensive women had normal BP (<140/90 mmHg) and no proteinuria during pregnancy.

2.3. Clinical and biochemical assessments

All women underwent the same study protocol at 24 and at 32 weeks at a single site, and pregnancies underwent routine maternity ward follow-up. After delivery, hospital records were reviewed. At 24 weeks the women first underwent an orthostatic test and then a standard 2-h 75-g oral glucose tolerance test (OGTT). At baseline, a venous sample was drawn from an antecubital vein after at least 12 h' fasting for assay of serum FABP4, total testosterone, sex hormone-binding globulin (SHBG), hs-CRP, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol and insulin, and plasma glucose. During the orthostatic test BP (left arm) and heart rate were measured sequentially after 30 min of resting supine, then after 10 min of standing. After supine and erect BP measurements, venous samples were drawn for measurements of plasma levels of noradrenaline, adrenaline and ghrelin. Mean arterial pressure was calculated as ([2 × DBP] + SBP)/3. Delta systolic BP (ΔSBP) was calculated as SBP after standing minus SBP after rest. During OGTTs, plasma glucose was measured at 0, 0.5, 1 and 2 h, serum insulin at 0, 1 and 2 h and Angptl6 at 0 and 2 h. Insulin sensitivity was measured by calculating the whole-body insulin sensitivity index (ISI):10 000/√([fasting plasma glucose × fasting serum insulin] × [mean OGTT glucose concentration × mean OGTT insulin concentration]) [18] and the homeostatic model of assessment − insulin resistance (HOMA-IR) was calculated [19]. For the calculation of free, non-protein bound, testosterone (cfT), we used the equation published by Andersson et al. [20]: 100 * S-Testo * (testo-V%) = 10 * S-Testo * (2.28−1.38 χ * log [S-SHBG/10]). At 32 weeks, a fasting venous sample was obtained for assay of serum FABP4, total testosterone, SHBG, hs-CRP, Angptl6 and insulin, and plasma glucose, noradrenaline, adrenaline and ghrelin.

Venous blood samples were drawn into heparinized (serum) tubes and EDTA (plasma) tubes on ice, centrifuged (4 °C and 7000 rpm) for 10 min and the samples stored at −20 or −80 °C until analysis. Human serum FABP4 was analyzed by using a non-competetive ELISA (Biovendor RD 191036200R). Intra- and interassay variations were about 2.5% and 5.5%, respectively. The manufacturer reports a normal range of 19.6 ± 8.1 ng/mL (mean ± 1 SD) for 35- to 52-year-old women.

High sensitive CRP (hs-CRP) was measured by particle-enhanced immunoturbidimetric assay (CRP (Latex) HS, Tina-quant C-reactive protein (latex) high sensitive assay, Roche Diagnostics) on a Modular automatic analyzer (Hitachi Ltd, Tokyo, Japan). The intra-assay coefficients of variation were 1.1–0.7% and the inter-assay coefficients of variation were 8.2–3.3%. Serum testosterone concentrations were analyzed on an LC-MS/MS system equipped with an API 2000 triple quadrupole mass spectrometer (PE Sciex, Foster City, CA). Peripherals included an Agilent series 1200 high-performance liquid chromatography system with a binary pump (Waldbronn, Germany). Separation was performed on a SunFire C18 column (2.1 × 50 mm; Waters, Milford, MA). Details of the methods for measuring other biochemical variables (serum Angptl6, total cholesterol, LDL cholesterol, triglycerides, HDL2 cholesterol, ghrelin, noradrenaline, and adrenaline) have been reported previously [17].

2.4. Statistical analysis

Statistical analyses were performed by using an NCSS 2000 statistical package (NCSS Inc., Kaysville, Utah, USA) and SPSS statistical package. Normally distributed data are given as means ± SDs and non-normally distributed data as medians with ranges. Shapiro–Wilk's *W*-test was used in testing for normality. For continuous variables, the non-parametric Mann–Whitney *U*-test and Kruskal–Wallis one-way ANOVA on ranks with multiple comparison *Z*-value tests were used to compare groups. For categorical data Fisher's Exact test was used to compare groups. Correlations were performed by using Pearson's correlation method. In logistic regression analysis we examined clinical factors (FABP4 at 24 and 32 weeks of gestation, FABP4 difference, hs-CRP at 24 and 32 weeks of gestation, hs-CRP difference, testosterone at 24 and 32 weeks of gestation, age at 24 weeks of gestation, pre-pregnancy BMI, weight gain during pregnancy, fP-glucose and ISI at 24 weeks of gestation, SBP after 10 min standing, ΔSBP), and PIH was used as the dependent variable. Variables were selected as they were known risk factors of pre-eclampsia (pre-pregnancy BMI), factors associated with pre-eclampsia (hs-CRP, systolic blood pressure) and our hypothetical factors associated with pre-eclampsia (FABP4, testosterone, ISI). Multiple regression analysis was performed using PIH as the dependent variable. Probability values of <0.05 were considered statistically significant in all analyses.

3. Results

3.1. Baseline and metabolic characteristics of the study groups

The clinical characteristics of the study groups are summarized in Table 1 according to pregnancy outcome. There were no significant differences between the groups in maternal age, weight, BMI before pregnancy, weight gain during pregnancy, BMI at the time of delivery, or smoking (Table 1). All women were normotensive in the first trimester, but women who developed PIH had significantly higher SBPs and DBPs from the 1st to the 3rd trimesters of pregnancy compared with women who stayed normotensive (Table 1). All 12 women with preeclampsia had late-onset disease (gestational weeks ≥ 34, data not shown). Three women with preeclampsia fulfilled the criteria for severe hypertension. Three women with preeclampsia and 1 woman with non-proteinuric PIH received antihypertensive medication (data not shown). Weeks of gestation at delivery and birth weight did not significantly differ between the groups (Table 1). At 24 weeks, there were no differences in lipid levels between the study groups (data not shown). Whole-body ISI and HOMA-IR at 24 weeks and fasting blood glucose at 32 weeks were the same in the two groups, irrespective of subsequent hypertension (data not shown).