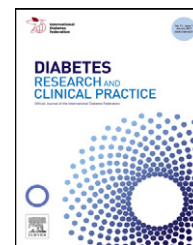




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Brief report

Atrial Natriuretic Peptide (ANP) in early pregnancy is associated with development of preeclampsia in type 1 diabetes

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ABSTRACT

The vasoactive markers of cardiac overload Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) are elevated in preeclampsia. This study documents higher ANP concentrations as early as at 9 weeks in type 1 diabetic women subsequently developing preeclampsia suggesting that preeclampsia is associated with cardiovascular changes in early pregnancy.

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1. Introduction

The vasoactive markers of cardiac overload Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) are synthesized in cardiac tissue in response to volume expansion and ventricular pressure overload [1,2]. In non-diabetic women

ANP and BNP concentrations are increased when preeclampsia is diagnosed [3–5]. As diabetic women are at particular risk of developing preeclampsia [6], we investigated whether higher concentrations of ANP and BNP are present in early pregnancy in women with type 1 diabetes subsequently developing preeclampsia.

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Abbreviations: ANP, Atrial Natriuretic Peptide; BNP, Brain Natriuretic Peptide; CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio; SMPG, self-monitored plasma glucose; UAE, Urinary Albumin Excretion.
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2. Materials and methods

As part of another study [7] we consecutively included 84 women with type 1 diabetes referred to Center for Pregnant Women with Diabetes, Rigshospitalet, before 14 completed weeks with a single living fetus, from September 2004 to April 2006.

The regional ethics committees approved the research protocol.

Blood sampling was performed at median 9 (range 6–13), 14 (12–16), 21 (20–23), 27 (25–29) and 33 (31–34) weeks. Plasma concentrations of ANP and BNP were determined by commercially available immunoradiometric assay kits (Shionoria, Osaka, Japan). In non-pregnant subjects, reference interval for ANP was 3.6 ± 1.4 pmol/l and for BNP 2.3 ± 1.7 pmol/l using the same laboratory as in [2].

Goals for self-monitored plasma glucose (SMPG) were 4.0–6.0 mmol/l preprandial, 4.0–8.0 mmol/l 90-min postprandial, 6.0–8.0 mmol/l pre-bedtime and $HbA_{1c} \leq 5.6\%$, in late pregnancy [7].

Presence of diabetic retinopathy at inclusion was routinely assessed by photo screening evaluated by one experienced ophthalmologist [8].

Based on 24-h Urinary Albumin Excretion (UAE) at inclusion, the women were classified as having normoalbuminuria (UAE < 30 mg/24 h), microalbuminuria (UAE 30–299 mg/24 h) or diabetic nephropathy (UAE \geq 300 mg/24 h). Preeclampsia in women with normoalbuminuria or microalbuminuria was defined as blood pressure >140/90 mmHg accompanied by proteinuria (\geq 1+ on sterile urine) using dip-stick (Uristix®, Bayer Diagnostics, Bridgend, UK) or proteinuria \geq 300 mg/24 h

later than 20 weeks. In women with diabetic nephropathy, the diagnosis was based on the same findings accompanied by a sudden increase of $\geq 15\%$ in systolic or diastolic blood pressure. Antihypertensive therapy, mainly with methyldopa, was initiated if blood pressure $\geq 135/85$ mmHg and/or UAE ≥ 300 mg/24 h [9].

2.1. Statistical analysis

Data are given as median (range) or numbers (%). Differences between groups were compared by Fisher's exact test (categorical variables) or non-parametric tests (continuous variables) when appropriate. Log-linear correlation analyses were performed using Pearson's coefficient, denoted *r*.

After logarithmic transformation, repeated measurements were analysed by a variance component model with ANP and BNP concentrations as dependent variable, "week" and "group" (preeclampsia yes/no) as discrete covariates and with random woman effect as a measure of each woman's level of ANP and BNP, respectively, during pregnancy.

Univariate logistic regression analysis was conducted with preeclampsia as dependent variable and ANP and BNP concentrations as independent continuous variables.

Statistically significant differences were defined as $p < 0.05$.

3. Results

Preeclampsia developed at median 34 (range 33–35) weeks in six women (7%) characterized by higher ANP concentrations at

Table 1 – Baseline data and pregnancy outcomes in 84 women with type 1 diabetes according to development of preeclampsia during pregnancy. Number (%) or median (range). Baseline data at 9 weeks are given unless otherwise stated. ANP: Atrial Natriuretic Peptide; BNP: Brain Natriuretic Peptide.

| | 78 women without preeclampsia | 6 women developing preeclampsia | <i>p</i> value |
|---|-------------------------------|---------------------------------|----------------|
| Maternal age (years) | 31 (21–42) | 32 (25–39) | 0.64 |
| Duration of diabetes (years) | 15 (1–31) | 23 (10–32) | 0.06 |
| HbA _{1c} (%) | 6.7 (4.9–10.5) | 6.6 (5.7–7.1) | 0.55 |
| Insulin dose (U/kg) | 0.75 (0.3–1.7) | 0.67 (0.6–1.1) | 0.86 |
| BMI before pregnancy (kg/m ²) | 24.3 (17.3–43.8) | 25.2 (21.8–32.4) | 0.45 |
| Diabetic retinopathy ^a | 41 (55%) | 6 (100%) | 0.04 |
| Microalbuminuria/diabetic nephropathy | 8 (10%)/3 (4%) | 0/3 (50%) | 0.009 |
| Systolic blood pressure (mmHg) | 120 (88–150) | 116 (100–150) | 0.76 |
| Diastolic blood pressure (mmHg) | 70 (55–86) | 71 (60–80) | 0.97 |
| Antihypertensive therapy | 8 (10%) | 3 (50%) | 0.03 |
| Plasma ANP (pmol/l) | 2.9 (0.7–7.8) | 6.0 (1.6–7.8) | 0.02 |
| Plasma ANP at 33 weeks (pmol/l) | 3.4 (1.0–8.7) | 5.2 (1.3–10.5) | 0.09 |
| Plasma BNP (pmol/l) | 3.6 (0.5–11.2) | 5.1 (2.0–16.7) | 0.18 |
| Plasma BNP at 33 weeks (pmol/l) | 2.2 (0.2–11.3) | 1.7 (0.6–28.1) | 0.89 |
| Plasma creatinine (μmol/l) | 51 (33–79) | 54 (42–95) | 0.50 |
| Nulliparous | 40 (51%) | 4 (67%) | 0.68 |
| Gestational age at birth (days) | 266 (220–276) | 254 (248–262) | 0.001 |
| Preterm delivery (<37 gestational weeks) | 11 (14%) | 5 (83%) | <0.0001 |
| Birth weight (g) | 3504 (2040–4900) | 2878 (2070–3850) | 0.02 |
| Small for gestational age infants (<10th centile) | 1 (1%) | 2 (33%) | 0.01 |
| Large for gestational age infants (>90th centile) | 35 (45%) | 2 (33%) | 0.69 |

^a Data are available in 75 women without development of preeclampsia.

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