Pregnancy Hypertension xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Microvascular disease during pregnancy in type 1 diabetes is associated with ambulatory arterial stiffness

Ingvild Holm Tjessem[a,*], Hanine Fadel Mustafa Al-Far[a], Jens Fuglsang[b], Finn Friis Lauszus[a,b]

[a] Department of Obstetrics/Gynecology, Herning, Herning Hospital, Gl. Landevej 61, DK-7400 Herning, Denmark
[b] Department of Obstetrics/Gynecology, Aarhus, Aarhus University Hospital, Nørrebrogade 44, DK-8000 Aarhus C, Denmark

ARTICLE INFO

Keywords:
Hypertension
Pregnancy
Arterial stiffness index
Type 1 diabetes
Microvascular disease

ABSTRACT

Objectives: The objective of this study was to evaluate the association between the ambulatory arterial stiffness index (AASI) and markers of microvascular disease during pregnancy in women with type 1 diabetes.
Study design: A total of 151 women with type 1 diabetes mellitus were recruited for repeat 24-h BP recordings thrice during pregnancy and once three months post partum. Fifty women without diabetes served as controls. The AASI and pulse pressure (PP) were computed from blood pressure recordings. Repeated measures analysis of variance was used for comparison between groups during and after pregnancy. Linear regression analysis was performed with AASI and PP as dependent variables and albuminuria and retinopathy as independent variables.
Main outcome measures: AASI during diabetic pregnancy and association with microvascular disease.
Results: Micro- or macroalbuminuria was present in 23% of the women and 58% had either simplex or proliferative retinopathy. The AASI was inversely associated with the coefficient of determination, which means that the stiffer vascular wall the more random variability in BP.
Conclusion: AASI showed a strong association with microvascular disease during pregnancy in women with type 1 diabetes. Together with the flattened circadian rhythm this indicates a pregnancy-related functional change in the vascular bed.

1. Introduction

Pregnancy is associated with physiological vascular adaptations to accommodate to the needs of the maternal–fetal unit. However, these adaptations may challenge the maternal vascular system and metabolic homeostasis, and gestational hypertension and preeclampsia may develop. Monitoring blood pressure (BP) alterations poses a challenge in order to detect increased risks and treatment effects. Further, antihypertensive drug therapy has been found of questionable use during pregnancy. Despite reviewing trials including more than 4700 women, no evidence was found of a difference in the risk of preeclampsia and no clear effect on the risk of neonatal demise, being delivered preterm or at small-for-gestational-age [1]. In non-pregnant women with type 1 diabetes mellitus minute increases in BP and albuminuria are forerunners for incipient and overt nephropathy. Antihypertensive treatment may conserve renal function, decreasing the risk of renal insufficiency. During pregnancy, renal insufficiency may lead to termination of pregnancy and it carries a risk of up to 50% for developing hypertensive complications including preeclampsia [2]. We believe that BP evaluation for diagnosis and monitoring the changes based on reliable measurements is invaluable. Nevertheless, a majority of BP monitors used in obstetric wards are non-validated, semi-automatic BP monitors [3]. Monitoring nocturnal BP values may give some indications of whether treatment goals and compliance is at set levels.

The benefits of treating hypertension are lost when basic rules for validating methodology for optimizing sensitivity and specificity are discarded for quick solutions, which dilute intuitively right concepts. From the diurnal BP an ambulatory arterial stiffness index (AASI) can be calculated that predicts cardiovascular death and stroke more precisely than classical risk factors [3–5]. The ambulatory arterial stiffness index is proposed as an indirect measure of arterial wall elasticity associated with target organ damage in individuals with arterial hypertension, i.e., left ventricular hypertrophy, carotid artery abnormalities and reduced renal function [5–8].

The AASI correlates with pulse wave velocity and has been used to detect arterial dysfunction at a younger age than was achievable by pulse pressure (PP) [9]. AASI and PP have been proposed as a novel indirect measure of arterial stiffness [3,4,6,7,9].

Several studies have been performed on AASI in high-risk subpopulations like women with pre-gestational hypertension, gestational

* Corresponding author at: Dept. of Gynecology and Obstetrics, Sykehuset Innlandet HF, Lillehammer, Anders Sandvigs gate 17, NO-2609 Lillehammer, Denmark.
E-mail address: ingvild.holm.tjessem@sykehuset-innlandet.no (I.H. Tjessem).

https://doi.org/10.1016/j.preghy.2017.11.011
Received 5 June 2017; Received in revised form 19 November 2017; Accepted 22 November 2017

diabetes, and twin pregnancies [10–12]. These reports showed a strong association of AASI with metabolic syndrome after pregnancy and insulin requirement during pregnancy. Hence, pregnancy may be a window for assessing the risk and prognosis of a woman's future risk of metabolic and cardiovascular disease [13]. We therefore found interest in further evaluating the use of AASI and PP as it carries the potential to detect risks and outcomes for mothers with type 1 diabetes mellitus.

We present results from a cohort of pregnant women with type 1 diabetes in which AASI and PP were analyzed during pregnancy and were compared to women without diabetes. We evaluated the AASIs during pregnancy and investigated the association between AASI and markers of microvascular disease, i.e. albuminuria grade and retinopathy. Furthermore, the association to PP and diurnal variation patterns in BP was scrutinised. Pre-pregnant and post partum measurements were then compared to pregnancy values in the women with type 1 diabetes. We hypothesized that the dynamic changes in the stiffness of the arterial wall would depict the biological characteristics of vasculopathy during pregnancy. The association between AASI and preeclampsia will be reported elsewhere (manuscript in writing).

2. Methods

In total, 151 women with type 1 diabetes were consecutively recruited for repeat 24-h ambulatory BP recordings 3 times during pregnancy and once 3 months post partum. No exclusion of any woman took place unless BP failed. The women with diabetes were recruited before pregnancy when possible and attended the maternity ward for visits every second week during pregnancy until week 32 and hereafter weekly. BP was measured using a portable oscillometry monitor providing more than 60 readings per person per 24 h (SpaceLab 90207, Redmond, WA, USA). The details on validation of monitors, the recommended clinical setting, and the timing during the day of BP are found on the British Hypertension Society's homepage [3,14]. After demonstration of equipment, three auscultatory BP were measured in the supine position with use of a random zero sphygmomanometer (Hawksley, Lancing, U.K.). The average of these three auscultatory measurements was termed the clinical BP. The women with type 1 diabetes had measurement of BP performed in gestational week 13, 25, and 33 and 3 months post partum. The control women were recruited at their second visit to Obstetric ward for ultrasound in week 18 and those who accepted participation had a further BP measurement in week 33 with the same monitors as the women with T1DM. No matching took place (age, BMI, parity) and no exclusion due to previous hypertension or preeclampsia was performed. Only women with previous and current gestational diabetes were excluded. One of the non-diabetic women had gestational hypertension and further two women subsequently developed preeclampsia.

2.1. Blood pressure evaluation

The regression slope of diastolic on systolic BP from unedited 24-h recordings was computed for each participant in every trimester (Fig. 1). The AASI was defined as one minus the regression slope (α) of diastolic BP on systolic BP from the diurnal recording [16]. The regression line for AASI was not forced through zero. Thus, the stiffer the arterial tree, the closer the regression slope approaches zero and AASI consequently approaches one. The variation of the AASI measurements was evaluated with the square of the regression coefficients, known as the 'coefficient of determination', CoD, from the calculation of diastolic BP on systolic BP. It estimates the proportion of the variability accounted for by the linear relationship between systolic and diastolic BP. CoD is a statistical measure of how close the data are to the fitted regression line (Fig. 1). If the CoD approached 1 the diastole on systole BP has a solid linear association and if it approaches zero the relation of diastolic with systolic BP is random and highly variable [5,15].

The PP was calculated by subtraction of the diastolic value from the systolic value and a relative PP was set to the systolic and diastolic value, respectively. Circadian BP was evaluated for systolic and diastolic BP with night/day ratio (ND-ratio) calculated as a mean night BP/mean day BP. Night time was defined from 11 p.m. until and including 6 a.m. An activity diary accompanied the monitor and women with night work and inverse sleeping rhythms were excluded before further calculations.

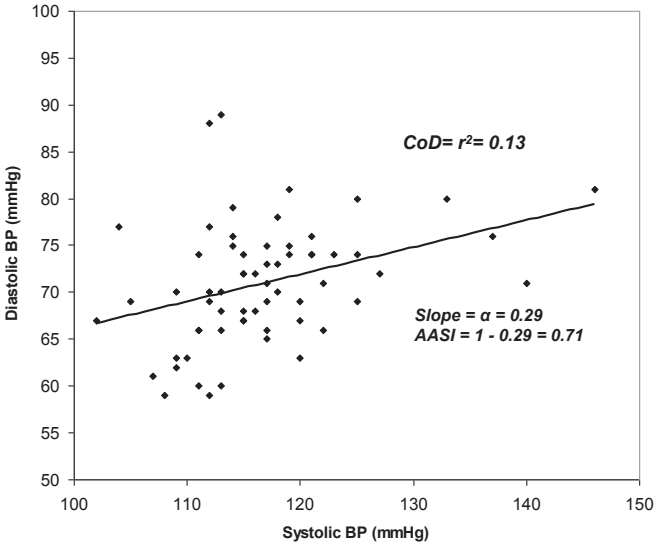

Fig. 1. 24-h blood pressure in 1st trimester in a woman with type 1 diabetes. Regression line shown on diastolic BP = α * systolic BP + β: AASI calculation = 1 − slope (α): 1 − 0.29 = 0.71, CoD: Coefficient of determination: 0.13. Mean diurnal BP 117/71 mmHg.

Women were identified as chronic hypertensive if pre-gestational or first trimester BP confirmed a BP of at least 140 mmHg systolic or 90 mmHg diastolic in diurnal BP based on 50–60 readings. Preeclampsia was defined as systolic/diastolic BP of 140/90 mmHg or greater for individuals that were normohypertensive before week 20 and, simultaneously, albuminuria in excess of 300 mg per day in previously normoalbuminuric women. Pregnancy-induced hypertension was hypertension without signs of preeclampsia. Albumin excretion rate (AER) was measured by 24-h collection of urine. AER was divided in normo-, micro- and macroalbuminuria groups if albumin excretion was < 30 g, 30–299 g, and ≥300 g/24-h. A birth weight ratio was computed by dividing the observed birth weight with the expected birth weight for the same gestational age and gender. The expected weights were calculated and distributed by the Danish Health and Medicines Authority based on the work of Marsál et al. [16].

The women were scheduled for ophthalmologic examination before pregnancy, once in each trimester, and 4 months after birth. Before and after pregnancy 44 women (29%) and 90 (60%), respectively, had an ophthalmologic examination. All 151 women had at least three fundus examinations during pregnancy except from 43 who had less than three. These 43 women displayed no retinopathy.

The study was performed in concordance with the Helsinki II declaration and all women gave their informed consent. The study was part of an evaluation of morbidity in diabetic pregnancy with respect to nephropathy and retinopathy approved by the local Ethical Committee (jr.nr.1992/2523, 1998/4147, and 2026-99) and by the Danish Data Protection Agency (no. 1-16-02-92-16).

2.2. Statistical evaluation

The BP data were either initially stored to a data file or manually re-entered from a paper output and further statistically processed. The sample size of 50 control women was calculated from the mean ± SD diurnal systolic BP of 120 ± 11 mmHg in the diabetic sample of 150