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Preeclampsia and cardiovascular disease risk assessment – Do arterial stiffness and atherosclerosis uncover increased risk ten years after delivery?

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ABSTRACT

Objectives: Epidemiological studies associate preeclampsia with increased risk of premature cardiovascular disease (CVD) later in life. This study aims to make a comprehensive CVD risk assessment comparing women with previous preeclamptic pregnancies to women with previous normotensive pregnancies 10 years after index pregnancy.
Study design: A nested, matched, observational cohort study.
Main outcome measures: Markers of arterial stiffness, aortic pulse wave velocity (aPWV) and augmentation index (AIx-75), and markers of atherosclerosis, carotid intima-media thickness (cIMT) and carotid plaque presence. Traditional CVD risk factors and 10-year and 30-year Framingham CVD risk scores were also assessed.
Results: Women were included from April 2014 to October 2014 at a tertiary referral hospital in Denmark. Twenty-one exposed women with a history of preeclampsia and 21 unexposed with a history of normotensive pregnancies were included. Ten years after delivery, significantly more exposed women suffered from hypertension and received antihypertensive treatment and significantly more fulfilled the hypertension-definition at screening. Previously preeclamptic women also tended to have more unfavorable CVD risk estimates. The Framingham risk scores seemed to extend the unfavorable CVD risk. The exposed women tended to have a higher aPWV compared to unexposed women, ($P = 0.057$). No differences were shown in the other examined arteriosclerotic or atherosclerotic variables.
Conclusions: Ten years after delivery, we found increased risk of hypertension and trend toward unfavorable CVD risk profile in 40-year-old previously preeclamptic women. However, arterial stiffness and atherosclerosis did not uncover any additional CVD risk information at this time point.

1. Introduction

Preeclampsia is a syndrome defined as new-onset hypertension and proteinuria after 20 weeks of gestation [1]. Preeclampsia represents not only a maternal risk during pregnancy, but epidemiological studies also show increased risk of premature cardiovascular disease (CVD) after delivery [2,3]. Systematic reviews support the epidemiological findings and demonstrate an

Abbreviations: CVD, cardiovascular disease; aPWV, aortic pulse wave velocity; AIx-75, augmentation index adjusted for heart rate; cIMT, carotid intima-media thickness; MAP, mean arterial blood pressure; BMI, body mass index.

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approximately doubled risk of ischemic heart disease, cerebrovascular incidents and mortality of CVD after preeclampsia [4,5].

In 2011, American Heart Association changed their recommendations regarding women's CVD risk. Preeclampsia was included as an independent factor heralding special attention. However, American Heart Association did not specify how and when the CVD risk of previously preeclamptic women should be assessed.

Still, the association between preeclampsia and premature CVD is incompletely understood. Studies have established that preeclampsia is a vascular disease related to traditional CVD risk factors such as hypertension, dyslipidemia and obesity. Prepregnancy CVD risk factors increase the risk of subsequent preeclampsia [6,7]. Moreover, traditional CVD risk factors are more prevalent after preeclampsia [8,9]. If preeclampsia itself additionally affects CVD risk is more uncertain. Indicating an additional intrinsic preeclamptic effect, studies found significantly more pronounced CVD risk in the combined presence of traditional risk factors and history of preeclampsia [3,10].

Despite the established relation to traditional risk factors and a possible intrinsic effect, the value of a traditional CVD risk assessment including markers of arterial stiffness and atherosclerosis in women 10 years after preeclampsia remains unclear.

The primary objective of our study was to elucidate if an increased CVD risk can be detected as early as 10 years after preeclampsia. Therefore, the aim was to complete a comprehensive CVD risk assessment including markers of arterial stiffness, atherosclerosis and Framingham risk scores comparing women with previous preeclamptic pregnancies to women with previous normotensive pregnancies 10 years after delivery.

2. Methods

The source population for this observational study was a cohort comprised of approximately 1600 pregnant women studied at the tertiary referral hospital, Randers, Denmark in the period 2001–4 [11].

For the present study women were excluded if they were currently pregnant, breastfeeding, or living more than 100 km away from the hospital. Exposure was defined as having one preeclamptic pregnancy 2001–4. Preeclampsia diagnosis was defined as new-onset hypertension (systolic blood pressure $\geqslant$ 140 mmHg and/or diastolic blood pressure $\geqslant$ 90 mmHg) and proteinuria ($\geqslant$300 mg/24 h or $\geqslant$ 30 mg/mmol albumin:creatinine random urine or $\geqslant$1+ on repeat dipstick). Details regarding exposure based on medicals records were retrieved from the former study. Unexposed women had pregnancies 2001–4 not complicated by gestational hypertension, preeclampsia, HELLP syndrome or eclampsia. However, unexposed women who experienced hypertensive disorder of pregnancy before or after 2001–4 were excluded. Eligible unexposed women matched on age (±2 years) and time since delivery (±1 year) were identified for each exposed woman.

All eligible women exposed to preeclampsia (n = 29) as well as randomly selected eligible matched unexposed women in the source population were invited to participate in the current study by mail.

The study protocol was approved by the local Medical Ethics Committee and The Danish Data Protection Agency and carried out according to the Declaration of Helsinki Principles. The study was registered at: www.clinicaltrials.gov as NCT02337049. Verbal and written informed consent was obtained from each participant.

All participants underwent standardized interviews providing self-reported information regarding for example current medication and tobacco use. Height (m) and body weight (kg) were measured. Body mass index (BMI) was calculated by dividing body weight (kg) by squared height (m). Waist and hip circumferences were measured in accordance with the WHO recommendations [12]. Insulin resistance was estimated using the interactive homeostasis model assessment (HOMA2-IR) downloaded from: https://www.dtu.ox.ac.uk/homacalculator/download.php. The metabolic syndrome was defined according to the internationally accepted criteria specified by the International Diabetes Federation [13].

A venous blood sample was taken at the level of the antecubital vein and handled and analyzed according to standard laboratory protocols.

Arterial blood pressure was measured after 10 min rest in seated position using a fully automatic oscillometric device (Omron MIT Elite; Omron Healthcare Co; Kyoto; Japan). Initially, appropriate cuff size was decided. If an interarm difference of 10 mmHg or more was detected, the arm showing the highest blood pressure was preferred. A minimum of three measurements at 3-min intervals was performed. The mean value of the last two measurements was used in the analysis. If the two last measurements differed more than 5 mmHg, measurements were repeated.

Arterial stiffness was measured by two independent markers: Aortic pulse wave velocity (aPWV) and central augmentation index adjusted for heart rate (AIx-75). Both parameters were obtained using the operator-independent, oscillometric Arteriograph device (TensioMed, Budapest, Hungrary). The procedure is described elsewhere [14]. However, aPWV and AIx-75 are presented as mean values of three recordings.

Atherosclerosis was evaluated by carotid intima-media-thickness (cIMT) and carotid plaque presence. Both markers were obtained performing carotid ultrasonography using a B-mode ultrasound system with a 9 MHz linear transducer (GE Vivid E9, GE Healthcare). The ultrasonography procedure followed the 2011 Mannheim Carotid Intima-Media Thickness and Plaque Consensus using semi-automated edge detection software providing up till 250 measurements on a 10-mm segment [15]. The average of mean cIMT obtained from two different angels (anterior, lateral or posterior) was calculated on each side. The entire carotid system was surveyed bilaterally for the presence of plaque. Presence of plaque was defined as a focal increase in cIMT above 1.5 mm and needed to be seen in both in longitudinal and cross-sectional views.

All carotid ultrasound examinations were performed by the same assessor. Evaluating the reliability of carotid examinations, we used intra-class correlation coefficient (ICC) [16]. ICC > 0.8 indicates almost perfect agreement. Quantifying the intra-examiner (test-retest) reliability, our assessor attained ICC = 0.93 examining ten women at two separate occasions. Quantifying the inter-examiner reliability, a trained assessor (more than 250 carotid ultrasound scans) examined the same ten women. The comparison resulted in ICC = 0.89.

Framingham risk scores are based on gender-specific multivariable risk factor algorithms. Besides gender, permanent variables are: Age, systolic blood pressure, anti-hypertensive treatment, current smoking and diabetes mellitus. In the present study, the 10-year Framingham risk scores were calculated with the 'Cardiovascular disease (10-year risk)' model adding either BMI or lipids (HDL and total cholesterol) to the permanent variables [17]. The 30-year Framingham risk scores were calculated with the 'Cardiovascular disease (30-year risk)' model also adding BMI or lipids [18]. Both the 10-year and 30-year risk scores included coronary death, myocardial infarction, coronary insufficiency, angina, ischemic or hemorrhagic stroke, transient ischemic attack, peripheral artery disease or heart failure.

We performed all statistical analyses using Stata software (version 13.1, StataCorp, College Station, Texas, USA). Normally distributed continuous variables were reported as mean ± standard deviation and otherwise as median (inter-quartile range). Binary variables were reported as absolute value (percentage). The