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Cardiovascular biomarkers in the years following pregnancies complicated by hypertensive disorders or delivered preterm

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ABSTRACT

Background: Women with a history of hypertensive disorders of pregnancy and preterm delivery have an increased risk of cardiovascular disease (CVD). Chronic inflammation, endothelial dysfunction, and dyslipidemia may link pregnancy outcomes with CVD.
Objective: We evaluated whether women with a history of HDP or normotensive preterm delivery had adverse CVD biomarker profiles after pregnancy.
Study design: We identified parous women from the Nurses' Health Study II with C-reactive protein (CRP; n = 2614), interleukin-6 (IL-6; n = 2490), glycated hemoglobin (n = 885), intracellular adhesion molecule-1 (n = 1231), high density lipoprotein cholesterol (n = 931), low density lipoprotein cholesterol (n = 931), triglycerides (n = 1428), or total cholesterol (n = 2940) assessed in stored blood samples. Multivariable-adjusted robust linear regression models evaluated percent differences and 95% confidence intervals (CIs) in each biomarker associated with a history of HDP or preterm delivery.
Results: Ten percent of women had a history of HDP, while 11% with normotensive pregnancies had at least one preterm delivery. Median time from first pregnancy to blood draw was 17 years (interquartile range: 12, 22). Plasma levels of CRP and IL-6 were 34.4% (95% CI: 17.2, 54.1), and 11.6% higher (95% CI: 2.1, 21.9) respectively, among women with a history of HDP compared to those with only normotensive pregnancies. Altered CVD biomarker levels were otherwise not present in women with a history of HDP or preterm delivery.
Conclusion: CRP and IL-6, but not other CVD biomarkers, were elevated in women with a history of HDP in the years following pregnancy, suggesting inflammation may be a pathway linking HDP with future CVD risk.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in women [1]. The American Heart Association's guidelines for CVD prevention in women identify preeclampsia, gestational hypertension, and gestational diabetes as CVD risk factors [2]. Pregnancy may act as a "stress test" that unmasks subclinical cardiovascular risk, providing early insight into a woman's cardiovascular health [3–5].

Pregnancy complications, including preeclampsia, preterm delivery, gestational diabetes, and low birth weight, will impact approximately 20% of women [5]. Women with a history of a hypertensive disorder of pregnancy (HDP; gestational hypertension and preeclampsia) or preterm delivery are at nearly two-fold higher risk of CVD than women without these complications [6–14]. However, research evaluating mechanisms that link these conditions is limited and primarily focused on postpartum development of clinical CVD risk factors (e.g. chronic hypertension) [13,15–17]. Preeclampsia and preterm delivery have been linked to elevated inflammatory biomarkers and alterations in

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lipid levels during pregnancy [18–24], providing biological plausibility for persistent changes after pregnancy. Therefore, elevated inflammatory, endothelial, and lipid biomarkers may provide insight into the development of CVD risk after complicated pregnancies. However, studies that have investigated the relationship between HDP, preterm delivery, and CVD biomarkers have produced inconsistent results, and suffer from small sample sizes or short follow-up after pregnancy [25–30].

We evaluated the associations between HDP, preterm delivery, and CVD biomarkers 1–34 years after pregnancy in the Nurses' Health Study II (NHSII), a cohort in which we have demonstrated associations of these pregnancy complications with increased risk of chronic hypertension, type 2 diabetes, dyslipidemia, and CVD events [14,31,32]. We hypothesized that women with a history of HDP or preterm delivery would have adverse CVD biomarker profiles in the years following pregnancy.

2. Materials and methods

2.1. Study population

The study population consisted of participants in the NHSII, a longitudinal cohort of 116,429 female U.S. registered nurses between aged 25 and 42 years at baseline in 1989. Participants completed biennial questionnaires that assessed health-related behaviors, medication use, reproductive history, and incident disease. Women who responded to the 1995 questionnaire and had not previously reported a cancer diagnosis were invited to provide blood samples (n = 92,888). Between 1996 and 2001, 29,611 women provided a blood sample. Our analysis was restricted to parous women whose blood sample had been analyzed for a previous sub-study (nested case-control studies of chronic diseases or cohort studies of lifestyle exposures). The NHSII was approved by the Partners Human Research Committee (Institutional Review Board) of Brigham and Women's Hospital. Questionnaire return was considered informed consent.

2.2. Exposure assessment

2.2.1. Hypertensive disorders of pregnancy

On the 2009 questionnaire, women self-reported whether each pregnancy lasting at least 20 weeks was complicated by 'preeclampsia/toxemia' or 'high blood pressure' (i.e. gestational hypertension). If a woman reported either of these conditions in any pregnancy prior to her blood draw, she was considered to have a history of HDP.

2.2.2. Gestational length

In 2009, women self-reported gestation length for all pregnancies in the following categories: < 8, 8–11, 12–19, 20–27, 28–31, 32–36, 37–39, 40–42, and 43+ weeks. For this analysis, these were collapsed into term (≥37 weeks), moderate preterm (≥32 to < 37 weeks), and very preterm (≥20 to < 32 weeks). Pregnancies lasting < 20 weeks were not included. For women who had more than one birth, gestation length category was determined by the shortest length of all reported births prior to blood draw. Since HDP is an indication for preterm delivery [33], and because we hypothesized HDP to be associated with the CVD biomarkers of interest, primary analyses of gestation length focused on women with no history of HDP to isolate the preterm-CVD biomarker relationship.

2.2.3. Exposure validity

We assessed the validity of self-reported preeclampsia and gestation length in a subset of participants who reported preeclampsia between 1991 and 2001. Among 462 women with complete medical records, the positive predictive value for preeclampsia was 89%. Gestation length validity was evaluated using a 3-category exposure (term, moderate preterm, very preterm) for 403 participants, yielding a Kappa statistic of 0.74.

2.3. Biomarker assessment

Participants returned blood samples to the laboratory by overnight courier for processing and storage at ≤130° Celsius, as described elsewhere [34,35]. Our analysis consists of women who had at least one of the following established CVD biomarkers [36–38] assayed: C-reactive protein (CRP), interleukin-6 (IL-6), glycated hemoglobin (HbA_{1C}), intracellular adhesion molecule-1 (ICAM-1), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, or triglycerides; 78% of these samples were provided after fasting for ≥8 h. These biomarkers have been evaluated and shown to be stable within 36 h of transport [39]. Assays used to measure each biomarker are presented in Supplemental Table 1. Most assays were conducted at the laboratory of Dr. Nader Rifai at Boston Children's Hospital and Harvard Medical School. Intra-assay coefficients of variation (CVs) from replicate, blinded, quality-control samples ranged from 0.3% to 15.3%, with 92% of laboratory batches yielding CVs < 10% (Supplemental Table 1).

2.4. Covariates

Covariates were chosen *a priori* either because they were matching factors used to select controls in the nested case-control studies or were hypothesized as potential confounders of the pregnancy history-CVD risk association. The following matching factors were included as covariates: menopausal status (pre, post, or unknown/missing), current smoking, alcohol intake (none, moderate (< 1 drink/day), or heavy consumption (≥1 drink/day) in the month before blood draw), current post-menopausal hormone (PMH) use, and history of infertility at blood draw. We considered a woman to have a history of infertility if she reported trying to become pregnant for more than one year without success. Age and parity at blood draw, race/ethnicity, and pre-pregnancy body mass index (BMI, kilograms per meter^2; < 18.5, 18.5 to < 25, 25 to < 30, ≥30), diet (Alternative Healthy Eating Index-2010 (AHEI) [40] in quintiles), and strenuous physical activity (never, 1–3, 4–6, 7–9, 10–12 months per year) were considered potential confounders.

2.5. Exclusions

Our analytic sample included women who provided a blood sample, completed the 2009 pregnancy history questions, were parous before blood draw, and were ≥18 years old at first birth (Fig. 1). For each biomarker analysis, we excluded women who did not have the biomarker of interest measured or who self-reported use of cholesterol-lowering or diabetes medication before blood draw. We also excluded women whose blood sample had been chosen for analysis because they were cases in CVD-related nested case-control studies (i.e. hypertension, diabetes, stroke, and myocardial infarction cases) due to known relationships between our pregnancy exposures, CVD biomarkers, and these diseases. While we did not exclude non-CVD related cases (e.g. Barrett's esophagus cases), as a sensitivity analysis, we excluded all samples selected as cases for biomarker case-control studies. In the CRP analysis, we additionally excluded women with CRP values > 10 mg/L, a clinical cutoff used to denote acute infection. Sample sizes differ for each biomarker analysis, ranging from 885 to 2940 women, since they are composed of different sub-studies (based on which biomarkers were assayed).

2.6. Statistical analysis

Biomarkers were log-transformed to improve normality. To reduce the potential for laboratory drift, we adjusted for batch using a method described by Rosner [41]. Multivariable adjusted robust regression models were used to estimate the percent differences in post-pregnancy CVD biomarker levels and 95% confidence intervals (CI) by history of