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Premature cardiovascular disease following a history of hypertensive disorder of pregnancy^{*}



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ABSTRACT

Background: Following an episode of hypertensive disorder of pregnancy (HDP) women have an increased risk of cardiovascular disease over their lifetime. At the time of acute coronary syndrome we compared clinical information between women with and without a history of hypertension in pregnancy to gain further insight into the pathophysiology of cardiovascular disease in this population.

Methods: GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond—PRemature Acute Coronary SYdrome) is a prospective multicenter study, with recruitment between January 2009 and April 2013, including 242 parous women with premature acute coronary syndrome.

Results: The median age was 50 years (IQR 6) and HDP was common; 43 (17.8%) women had prior gestational hypertension, 33 (13.6%) preeclampsia and 166 (68.6%) a prior normotensive pregnancy. Women with a history of HDP commonly had chronic hypertension and diabetes and those presenting with ST-elevation myocardial infarction were more likely to have a history of preeclampsia (aOR 3.12, 95% CI 1.22–8.01) than were women with prior normotensive pregnancies. Neither gestational hypertension (aOR 1.40, 95% CI 0.60–3.26) nor preeclampsia (aOR 0.63, 95% CI 0.23–1.74) was associated with a higher composite risk of three-vessel, left main or proximal left anterior descending coronary disease.

Conclusion: In this study of women with premature cardiovascular disease, ST-elevation myocardial infarction was associated with a history of preeclampsia possibly because of persistent endothelial dysfunction. High-risk coronary lesions on angiography did not appear to have an association with preeclampsia or gestational hypertension despite a high burden of traditional risk factors.

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1. Introduction

Cardiovascular disease (CVD) remains a leading cause of death among women in North America [1], accounting for 51.7% of female deaths in the US in 2008 [2]. Traditional CVD risk factors, such as family history, smoking, hypertension, and diabetes, do not account for the total observed burden of CVD in women [3,4]. There is acceptance that complications occurring during pregnancy, such as gestational hypertension and preeclampsia, independently predict the later development of CVD in women [5–10], conferring a two-fold increased risk of major CVD outcomes [11]. Women with preeclampsia have a higher prevalence of metabolic syndrome both following the index delivery, and

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longer-term [12,13]. Moreover, preeclampsia is a complex clinical syndrome characterized by disordered maternal endothelium [14–18], which may persist following delivery [19,20]. Persistent abnormal vasculature following HDP may in part explain the higher incidence of CVD and partially account for poorer outcomes in young women with acute coronary syndrome (ACS) as compared to their male counterparts [21].

Many studies reporting on the association between HDP and CVD have used administrative database linkage [22–24], or have reported on the predicted risk of future CVD [25]. We aren't aware of any published studies reporting on the impact of prior HDP on the clinical presentation of ACS later in life. Direct correlation with coronary findings in women with and without a history of HDP could contribute information towards the mechanism for increased risk of CVD. An improved understanding of this mechanism would help to establish management and surveillance guidelines for young women following an episode of hypertension in pregnancy.

In a contemporary cohort of women hospitalized with premature ACS, we compared angiographic findings among women with and without a history of HDP. We investigated whether ST-elevation myocardial

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² This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

infarction (STEMI) was more common after a pregnancy complicated by HDP reflecting persistently impaired endothelium. We compared various features of high-risk coronary anatomy such as involvement of the left main coronary artery, proximal left anterior descending (LAD), or three-vessel disease between groups. We hypothesized that women with features of high-risk coronary anatomy would have a greater prevalence of HDP and an associated long duration of CVD risk factors culminating in ACS.

2. Methods

2.1. Study design

GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond—PRemature Acute Coronary SYdrome) is a multicenter, prospective study of patients hospitalized with premature ACS. Recruitment took place between January 2009 and April 2013 and involved 24 Canadian centers, 1 center in the United States and 1 in Switzerland. The methods and design of the study have been previously described [26].

2.2. Study population and data sources

Eligible patients were adults aged 18 to 55 years, with fluency in either English or French and who were able to provide informed consent upon admission to the hospital for ACS. A research nurse approached each eligible patient within 24 h of recruitment once admitted to the coronary care unit. Each participant completed a self-administered questionnaire and anthropometric measurements were obtained. The patient's medical history, procedure data and information related to the ACS were collected and reviewed by a research nurse.

2.3. Demographic and clinical characteristics

Participants' demographics and clinical characteristics were derived from a combination of chart review and self-report. Prior CVD events included myocardial infarction (MI), peripheral artery disease, stroke, coronary artery bypass grafting and percutaneous coronary intervention (PCI). Body mass index (BMI) was calculated from index height (m) and weight (kg) at the time of event. Obesity was defined as a BMI of 30 kg/m² or more.

2.4. Exposure to hypertension in pregnancy

We ascertained prior pregnancy if women reported at least one previous pregnancy, at least one biological child, and/or a history of stillbirth. A history of preeclampsia was determined either if women answered yes to preeclampsia, or yes to hypertension in pregnancy in addition to proteinuria in pregnancy. Women were categorized as having had gestational hypertension if they answered yes to hypertension in pregnancy, no to preeclampsia, and no to proteinuria during pregnancy. Women were otherwise characterized as having had a normotensive pregnancy. Women who were unsure about a history of preeclampsia or of gestational hypertension were initially excluded from the analysis.

2.5. Ascertainment of angiographic findings

All patients underwent PCI at the time of ACS; angiograms were reviewed by two independent, blinded study interventional cardiologists, who confirmed the findings documented in the original catheterization report, and calculated the severity of coronary lesions using the SYNTAX score [27]. The SYNTAX score is based on qualitative and quantitative characterization of CAD by including 11 angiographic variables that take into consideration lesion location and characteristics. This score has been shown to be an effective tool to risk-stratify patients with complex CAD undergoing PCI in the landmark SYNTAX trial, as well as in other clinical settings [27].

2.6. Angiographic outcomes

The main outcomes of interest were (i) high risk coronary anatomy including either three-vessel, left main coronary artery or proximal left anterior descending coronary artery stenosis >50%, (ii) type of coronary lesion on catheterization leading to ACS, and (iii) for atherosclerotic disease, STEMI versus other type of ACS (NSTEMI or unstable angina).

2.7. Statistical analyses

We compared baseline characteristics including prevalence of traditional cardiovascular risk factors, angiographic findings and severity and type of ACS (STEMI versus NSTEMI/unstable angina) between three groups of women: those with a history of gestational hypertension, and those with a history of preeclampsia and those with a history of normotensive pregnancies (the referent group). We included women with either gestational hypertension or preeclampsia to encompass any HDP [28].

Continuous variables were compared using 2-sample *t*-tests or Wilcoxon tests, as appropriate. Dichotomous variables were evaluated using a chi-square test, with normotensive pregnancy women as the referent. In separate analyses, multivariable logistic regression was performed to compare women with either preeclampsia or gestational hypertension to those with a normotensive pregnancy, on their odds of high-risk coronary anatomy, coronary thrombosis, and type of ACS at presentation. In each model, we adjusted, a priori, for age, race, obesity, hypertension, diabetes, dyslipidemia, and smoking status at the time of the index ACS. In the analysis of coronary thrombosis as the outcome, we also adjusted for type of ACS, as thrombus was highly correlated with STEMI.

All statistical analyses were performed using SAS version 9.2 (Cary, North Carolina). Statistical tests were two-sided; differences with $p \le 0.05$ were considered statistically significant.

3. Results

3.1. Establishment of the study cohort

The GENESIS-PRAXY population consisted of 1213 patients of which 367 (30%) were women, and 311 (26%) reported at least one pregnancy. Since 69/311 (22%) women were unsure about a history of preeclampsia or of gestational hypertension, they were excluded from analysis. Thus our cohort comprised 242 parous women hospitalized for ACS at a young age. Hypertensive disorders of pregnancy were common in this population, with 33/242 (13.6%) reporting a prior history of pre-eclampsia and 43/242 (17.8%) reporting prior gestational hypertension. Only 166/242 (68.6%) women had no prior history of HDP (Fig. 1).

3.2. Patient characteristics

At the time of ACS, women with prior HDP differed from women with prior normotensive pregnancy on a number of important clinical characteristics.

As compared to normotensive pregnancy, women with a history of gestational hypertension were younger at presentation (median age 48 vs. 50, p = 0.05), more likely to have a diagnosis of hypertension at the time of ACS (81.4% vs. 40%, p < 0.0001), diabetes mellitus (39.5% vs. 18.1%, p = 0.003), a history of gestational diabetes (23.3% vs. 6.6%, p = 0.001), and more of these women were obese (70.7% vs. 37.3%, p = 0.0001). Women with a history of preeclampsia were also more likely to present with ACS at a younger age (median 47.5 vs. 50, p = 0.03), to have hypertension (87.9% vs. 40%, p = 0.0001), and a history of gestational diabetes (21.2% vs. 6.6%, p = 0.008) than were women

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