

# Premature cardiovascular disease following a history of hypertensive disorder of pregnancy<sup>☆</sup>



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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 SYndrome) 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

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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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 SYndrome) 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/m<sup>2</sup> 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  $p \leq 0.05$  were considered statistically significant.

## 3. Results

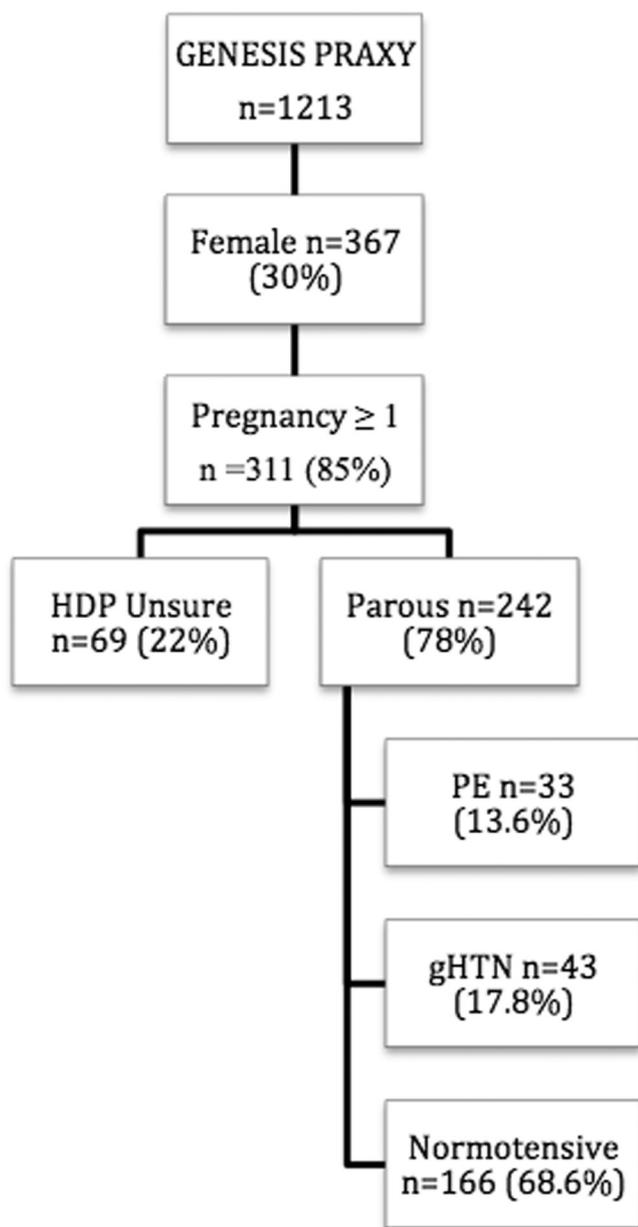
### 3.1. Establishment of the study cohort

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 preeclampsia 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



**Fig. 1.** Genesis of the PRAXY cohort. HDP=hypertensive disorder of pregnancy, PE=preeclampsia, gHTN=gestational hypertension

with prior normotensive pregnancies (Table 1). Sixty-nine women who were unsure about a history of HDP were excluded from analysis; in terms of baseline demographics they most resembled women with a history of normotensive pregnancies.

### 3.3. Differences in angiographic findings

On coronary angiography, women with prior gestational hypertension were equally likely to have high-risk coronary anatomy as women with prior normotensive pregnancy (34.9% vs. 25.9%,  $p = 0.24$ ). The same was true when comparing prior preeclamptic to normotensive pregnancies (21% vs. 25.9%,  $p = 0.57$ ). All groups of women had similar mean SYNTAX scores, a measure of CAD complexity, (11.3 vs. 11.5,  $p = 0.89$  for gestational hypertension vs. normotensive and 10.9 vs. 11.5,  $p = 0.70$  for preeclampsia vs. normotensive).

For the most part, the type of coronary lesion did not differ significantly by category of hypertension in pregnancy (Table 2). However, in unadjusted analyses there was more thrombus formation on

**Table 1**

Baseline characteristics of women with and without a history of a hypertensive disorder of pregnancy.

Characteristic	Normotensive pregnancy (n = 166)	Gestational hypertension (n = 43)	Preeclampsia (n = 33)
<b>Demographics</b>			
Age, median (IQR), years	50 [6]	48 [8]*	47.5 (9.5)*
Race (Caucasian)	149 (89.8)	37 (86.1)	28 (84.9)
>12 years of formal education	86 (51.8)	26 (60.5)	23 (71.9)*
<b>Medical characteristics</b>			
Hypertension	63 (40.0)	35 (81.4)*	29 (87.9)*
Dyslipidemia	83 (50.0)	24 (55.8)	22 (66.7)
Diabetes mellitus	30 (18.1)	17 (39.5)*	8 (24.2)
History of CAD	70 (42.4)	25 (58.1)	14 (42.4)
BMI > 30 kg/m <sup>2</sup>	60 (37.3)	29 (70.7)*	15 (48.4)
BMI, mean (sd), kg/m <sup>2</sup>	28.7 (7.4)	32.7 (6.0)*	32.3 (10.3)*
Smoker (ever)	68 (41.0)	16 (37.2)	13 (39.4)
Menopausal at presentation	97 (58.3)	22 (51.2)	12 (36.4)*
<b>Pregnancy characteristics</b>			
<b>Parity</b>			
1 child	42 (25.0)	14 (32.6)	12 (36.6)
≥2 children	124 (74.7)	29 (67.4)	21 (63.6)
Gestational diabetes	11 (6.6)	10 (23.3)*	7 (21.2)*
Late fetal loss	19 (11.5)	6 (14.0)	7 (21.2)

All data are shown as a number (%) unless otherwise indicated.

CAD (coronary artery disease), BMI (body mass index).

\*  $p$ -Value  $\leq 0.05$  on univariate analysis, compared to women without a history of hypertensive disorder of pregnancy.

angiography at the time of ACS in women with prior preeclampsia compared to women with prior normotensive pregnancy (57.7% vs. 32.9%,  $p = 0.05$ ).

In multivariate analyses (Table 3), neither gestational hypertension nor preeclampsia was associated with high-risk coronary anatomy (aOR 1.40, 95% CI 0.60–3.26 for gestational hypertension and aOR 0.63, 95% CI 0.23–1.74 for preeclampsia). Women with gestational hypertension did not have an increased risk of thrombus formation at the time of coronary catheterization compared to those with prior normotensive pregnancies (aOR 0.58, 95% CI 0.21–1.55). Comparatively, the trend for coronary thrombus among those with prior preeclampsia seen on univariate analysis failed to reach statistical significance after adjustment for type of ACS in addition to the other covariates (aOR 2.07, 95% CI 0.73–5.85). STEMI at presentation was not associated with a history of gestational hypertension (aOR 1.11, 95% CI 0.50–2.45) but was significantly associated with prior preeclampsia after adjustment (aOR 3.12, 95% CI 1.22–8.01).

### 3.4. Interpretation

In this cohort of women presenting with premature ACS, we found that a significant proportion (nearly a third of women) had a history of HDP. This is in contrast to population level data showing that HDP affects 2–8% of pregnancies [29,30]. We found that women with gestational hypertension were younger at presentation and had a higher burden of traditional atherosclerotic risk factors. Women with preeclampsia were also significantly younger at presentation, and more likely to be chronically hypertensive at the time of ACS. Despite this we were unable to demonstrate an increased prevalence of so-called higher risk coronary anatomy. Women with a history of preeclampsia had more thrombus formation on coronary catheterization and were three times more likely to have STEMI at presentation.

A number of studies have demonstrated a strong epidemiological link between HDP and the future development of cardiovascular risk factors and disease, including mortality [21]. It has also been shown that there is a persistence of the metabolic syndrome following an episode of HDP [12,13], and possibly a persistence of markers of endothelial dysfunction [14–19,31,32].

**Table 2**  
Angiographic findings of women with and without a history of hypertensive disorder of pregnancy.

Angiographic findings	Normotensive pregnancy (n = 166)	Gestational hypertension (n = 43)	Preeclampsia (n = 33)
Coronary anatomy			
SYNTAX score (sd)	11.54 (7.8)	11.34 (7.2)	10.9 (7.5)
High risk <sup>a</sup>	43 (25.9)	15 (34.9)	7 [21]
Proximal LAD	89 (53.6)	27 (64.0)	27 (54.5)
Left main	9 (5.5)	4 (11.0)	0 (0)
Multivessel	51 (30.7)	17 (39.5)	10 (30.3)
Single vessel	81 (48.8)	21 (50.0)	19 (57.6)
Coronary lesion <sup>b</sup>			
Thrombus formation	48/146 (32.9)	11/38 [29]	15/29 (57.7)*
Normal coronaries	23/154 [15]	3/40 (7.5)	1/30 (3.3)
Coronary dissection	18/152 (11.8)	2/39 (5.1)	3/30 (10.0)
Fibromuscular dysplasia	20/156 (12.8)	1/41 (2.4)	3/30 (10.0)
Coronary vasospasm	4/150 (2.7)	0/39 (0)	0/30 (0)
Type of ACS			
STEMI	75 (45.2)	21 (48.8)	20 (60.6)*
NSTEMI/unstable angina	85 (51.2)	22 (51.2)	12 (36.4)

All data are shown as a number (%) unless otherwise indicated.

SYNTAX (Synergy between percutaneous coronary intervention with TAXus and cardiac surgery); STEMI (ST-elevation myocardial infarction); LAD (left anterior descending); NSTEMI (non-ST-elevation myocardial infarction) \*vs. women without a history of hypertensive disorder of pregnancy.

†Adjusted for age, smoking, dyslipidemia, obesity, race, chronic hypertension, diabetes; thrombus model also adjusted for type of ACS.

ACS (acute coronary syndrome).

\* p-Value  $\leq 0.05$  on univariate analysis, compared to women without a history of hypertensive disorder of pregnancy.

<sup>a</sup> Defined as the presence of either 3-vessel, left main coronary artery or proximal left anterior descending coronary artery stenosis  $>50\%$ .

<sup>b</sup> Missing data; denominators included.

The pathophysiology of CVD following HDP is complex, multifactorial, and not yet completely elucidated [33–35]. There are two views regarding the development of CVD following HDP. The first relates to women with a history of gestational hypertension or mild preeclampsia, who are thought to have more traditional cardiovascular risk factors, such as hypertension, diabetes, and obesity (as was the case in our study). This in turn reflects HDP as a manifestation of a maternal phenotype that was already predisposed to, or was in the earlier stages of CVD, at the time when HDP developed [36].

This second view relates to a demonstrable imbalance of angiogenic factors and has emerged as one of the most important factors in the pathogenesis of preeclampsia [33,37]. Some studies have shown that although many of the acute symptoms of preeclampsia resolve with the delivery of the placenta, endothelial dysfunction that occurs as a result of poor placentation may persist [18,20]. Persistent endothelial damage over time may contribute to the development of CVD via a different pathogenesis than CVD developing in the context of traditional cardiovascular risk factors. The two mechanisms described are not necessarily mutually exclusive and in many women may co-exist.

We demonstrated that women with STEMI were significantly more likely to have a history of preeclampsia but not necessarily gestational hypertension, in support of different pathophysiological pathways for

the development of CVD in these two similar, but discrete, pregnancy-related disorders. This finding would align with the hypothesis that persistent endothelial dysfunction with ensuing hemostatic perturbation follows pregnancy complicated by preeclampsia [38]. We considered a high coronary thrombus burden as possibly a reflection of endothelial dysfunction; this is akin to patients with stable CAD who have developed coronary thrombosis as a result of demonstrable imbalances in angiogenic factors measured at the time of ACS [39]. These patients have high residual platelet reactivity and significantly impaired endothelial function [39,40]. It may be that the trend towards more thrombus formation on coronary catheterization in women with a history of preeclampsia is in keeping with observed higher odds of STEMI.

### 3.5. Limitations

Our study has several limitations. HDP was self-reported and a significant number of women reported being unsure if they had a history of HDP. These women were excluded from final analyses. However, the women who were excluded most resembled women with a history of normotensive pregnancy in terms of demographics. A sensitivity analysis was performed whereby women who were unsure about a history of HDP were analyzed along with women with a history of normotensive pregnancies and results did not change significantly. Several studies have examined women's accuracy of recollection of a history of HDP and results are conflicting [41–43]. Most studies show that the specificity of recall of preeclampsia is very high but the sensitivity is only moderately high [41,43]. However, available studies demonstrate that recall may not be differential between women with and without a future pathological outcome [44,45]. It is possible that some women in the "unsure" category actually had preeclampsia or gestational hypertension, were excluded from our analysis, and thereby limited the power of the study to observe a detectable difference between women with high-risk coronary anatomy; the null results of this study must be interpreted cautiously.

We did not capture the timing and severity of HDP, or if a history of hypertension or diabetes preceded HDP or not. Preeclampsia is a collection of conditions that share symptoms but are likely etiologically distinct. Preeclampsia arising later in pregnancy is potentially more likely to be associated with maternal factors such as pre-gestational hypertension, diabetes and obesity (prevalent in this study population), whereas early-onset preeclampsia is typically related to placental factors. We attempted to address this issue by performing separate analyses for gestational hypertension and preeclampsia.

## 4. Conclusions and future directions

Women with a history of HDP were more likely to have a higher burden of traditional risk factors for the development of CVD compared to women with prior normotensive pregnancies, and were more likely to present with ACS at a younger age. This study reinforces that in women with cardiovascular disease care providers should question a history of HDP, given the strong association. We found that women with STEMI were three times more likely to have a history of preeclampsia, and postulate that this is perhaps secondary to persistent

**Table 3**  
Multivariable analyses of primary outcomes.

Outcome	Normotensive pregnancy (n = 166)	Gestational hypertension (n = 43)	Adjusted odds ratio (95% CI)	Preeclampsia (n = 33)	Adjusted odds ratio (95% CI)
Thrombus no. (%)	48/146 (32.9)	11/38 (29.0)	0.58 (0.21–1.55)	15/29 (57.7)	2.07 (0.73–5.85)
High risk anatomy no. (%)	43/166 (25.9)	15/43 (34.9)	0.63 (0.23–1.74)	7/33 [21]	1.40 (0.60–3.26)
ACS type* no. (%)	75/166 (45.2)	21/43 (48.8)	1.11 (0.50–2.45)	20/33 (60.6)	3.12 (1.22–8.01)

\* ACS (acute coronary syndrome): ST vs. non-ST elevation myocardial infarction.

endothelial dysfunction. These findings would need to be replicated prior to making new recommendations about the long-term management of women following preeclampsia, including routine use of antiplatelet agents, statins or other targeted prevention therapies.

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### Role of the sponsor

The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

### Conflict of interest

The authors report no conflicts of interest.

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