

ORIGINAL ARTICLE

# Long-term maternal atherosclerotic morbidity in women with pre-eclampsia

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## ABSTRACT

**Objective** To investigate whether severe and recurrent pre-eclampsia increase the risk for long-term maternal atherosclerotic disease.

**Study design** A population-based study compared the incidence of long-term atherosclerotic morbidity in a cohort of women who delivered in the years 1988–2012. The exposure variable was pre-eclampsia. Mean follow-up duration was 11.2 years. Kaplan–Meier survival curves were used to estimate cumulative incidence of simple, complex (ie, angina pectoris and congestive heart failure, respectively) cardiovascular-related and renal-related hospitalisations. Cox proportional hazards models were used to estimate the adjusted HRs for cardiovascular and renal morbidity.

**Results** During the study, 96 370 patients met the inclusion criteria; 7824 (8.1%) in patients who were diagnosed at least once with pre-eclampsia. Patients with pre-eclampsia had higher rates of cardiovascular morbidity including cardiac non-invasive (OR 1.4; 95% CI 1.1 to 1.7;  $p=0.005$ ) and invasive diagnostic procedures (OR 1.7; 95% CI 1.2 to 2.3;  $p=0.001$ ), simple (OR 1.5; 95% CI 1.2 to 1.8;  $p=0.001$ ), as well as complex cardiovascular events (OR 2.4; 95% CI 2.2 to 2.8;  $p=0.001$ ) and renal (OR 3.7; 95% CI 2.2 to 6.0;  $p=0.001$ ) hospitalisations. A significant linear association was noted between the severity of pre-eclampsia (no pre-eclampsia, mild pre-eclampsia, severe pre-eclampsia and eclampsia) and cardiovascular (2.7% vs 4.5% vs 5.2% vs 5.7%, respectively;  $p=0.001$ ), as well as renal disease (0.1% vs 0.2% vs 0.5% vs 1.1%, respectively;  $p=0.001$ ). Likewise, a linear association was found between the number of previous pregnancies with pre-eclampsia (no pre-eclampsia, one event and  $\geq 2$  events of pre-eclampsia) and risk for future simple cardiovascular disease (1.2% vs 1.6% vs 2.2%, respectively;  $p=0.001$ ), complex cardiovascular disease (1.3% vs 2.7% vs 4.6%, respectively;  $p=0.001$ ) and total cardiovascular hospitalisations (2.7% vs 4.4% vs 6.0%, respectively;  $p=0.001$ ). Using a Kaplan–Meier survival curve, patients with pre-eclampsia had significantly higher cumulative incidence of atherosclerotic-related hospitalisations. In a Cox proportional hazards model, adjusted for confounders such as maternal age, parity, diabetes mellitus and obesity, pre-eclampsia remained independently associated with atherosclerotic hospitalisations.

**Conclusions** Previous pregnancy with pre-eclampsia is an independent risk factor for long-term maternal atherosclerotic morbidity. The risk is more substantial for patients with severe and recurrent episodes of pre-eclampsia.

## INTRODUCTION

The incidence of hypertensive disorders such as pre-eclampsia and eclampsia in pregnancy is relatively high worldwide. These disorders are considered among the main obstetrical causes for maternal death during pregnancy.<sup>1 2</sup> There are several proposed mechanisms regarding the pathogenesis of pre-eclampsia, most of them involve the placenta as a central organ for the development of this disorder with placental-derived soluble factor that influence the systemic vascular system.<sup>3 4</sup> In recent years, there is a growing interest regarding the link between pre-eclampsia and future risk for atherosclerotic morbidity including both cardiovascular<sup>5–11</sup> and renal<sup>12–14</sup> morbidity.

Previous studies have described the link between a history of pre-eclampsia and future risk of cardiovascular morbidity and mortality.<sup>5–7 9</sup> This evidence led the American Heart Association to include a history of pre-eclampsia as a risk factor in the guidelines for the preliminary risk evaluation for cardiovascular disease (CVD) in women.<sup>15</sup>

Data regarding the link between pre-eclampsia and future risk for renal morbidity are not that well established.<sup>13 14</sup> Also, it is not clear whether a ‘dose–response’ association exists between the severity of the condition and the number of episodes of pre-eclampsia and the risk for CVD and renal morbidity later in the non-pregnant life.

The objective of the present population-based study was to investigate whether a history of pre-eclampsia is an independent risk factor for subsequent long-term atherosclerotic morbidity (cardiovascular and renal) in women. We also wanted to investigate whether this risk is increased if a patient had a history of several episodes of pre-eclampsia or had more severe disease.

## MATERIALS AND METHODS

### Setting

The study was conducted at the Soroka University Medical Center, the sole hospital of the Negev, the southern region of Israel, serving the entire population in this region and where all deliveries take place (the annual average of deliveries during the study period was approximately 12 000–15 000 deliveries).

### Study population

The study population comprised all patients who delivered between the years 1988 and 2012; follow-up period in non-pregnant life was until 2012. Patients with multiple pregnancies, with known cardiovascular and renal disease before or

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## Cardiac risk factors and prevention

**Table 1** Characteristics of patients with and without a history of pre-eclampsia at the index birth

Characteristics	Pre-eclampsia (n=7824)	No pre-eclampsia (n= 88 546)	p Value
Maternal age (years±SD)	28.3±6	28.8±6	0.001
Postpartum anaemia (haemoglobin<10 g/dL)	34.9%	28.3%	0.001
Diabetes mellitus (gestational and pre-gestational)	8.6%	5.8%	0.001
Small for gestational age	9.4%	4.7%	0.001
Antepartum fetal death	1.1%	0.6%	0.001
Placental abruption	1.8%	0.6%	0.001
Obesity (pre-gestational BMI>30 kg/m <sup>2</sup> )	1.1%	0.9%	0.018
Parity, median (mode)	5.4±3	5±3	0.015
Mean number of years (±SD) from index pregnancy to hospitalisation	11.6±6.3	12.7±6.1	0.001

BMI, body mass index.

during the index pregnancy, and patients with known congenital cardiac or renal malformations were excluded from the study.

### Study design

A population-based retrospective cohort study was conducted. The primary exposure was having had at least one pregnancy complicated with pre-eclampsia, all other patients served as the comparison group. A retrospective follow-up of hospitalisations due to atherosclerotic morbidity up to 24 years after the index birth was performed. Atherosclerotic morbidity was defined as the first hospitalisations for any cardiovascular and renal indication at Soroka University Medical Center. Cardiovascular morbidity was divided into four categories according to severity and type, including simple and complex cardiovascular events (eg, angina pectoris and congestive heart failure, respectively), and invasive and non-invasive cardiac procedures (eg, insertion of a stent and a treadmill stress test, respectively). The International Classification of Diseases (ICD) codes for each subtype of cardiovascular and renal morbidity are presented in the online supplementary tables S1 and S2.

Data were collected from two databases that were cross-linked and merged: the computerised perinatal database and the computerised hospitalisation database of the Soroka University Medical Center. The perinatal database consists of information recorded directly after delivery by an obstetrician. Skilled medical secretaries routinely review the information prior to entering it into the database. Coding was performed after assessing medical prenatal care records together with the routine hospital documents. The hospitalisation database includes demographic information and ICD 9 codes for all medical diagnoses made during hospitalisations.

### Statistical analysis

Statistical analysis was performed using the SPSS package 17 edition (SPSS, Chicago, Illinois, USA). Statistical significance was calculated using  $\chi^2$  test for differences in qualitative variables and Student t test for differences in continuous variables. The association between the number and severity of previous events and the risk for subsequent atherosclerotic cardiovascular hospitalisations was evaluated using  $\chi^2$  test for trend (the linear-by-linear association test).

Kaplan–Meier survival curves were used to compare cumulative incidence of cardiovascular hospitalisations. Cox proportional hazards models were used to estimate the adjusted HRs and 95% CIs for long-term cardiovascular hospitalisations.  $p<0.05$  was considered statistically significant.

### RESULTS

During the study period, 96 370 parturient met the inclusion criteria; 7824 (8.1%) occurred in women who were diagnosed at least once with pre-eclampsia.

Table 1 summarises characteristics of the patients with and without a diagnosis of pre-eclampsia. At the index birth, patients in the pre-eclampsia group were significantly older, had a higher birth order and were more likely to be obese and had higher rates of other pregnancy complications such as diabetes mellitus, postpartum anaemia, small for gestational age, antepartum fetal death and placental abruption. The mean number of years of follow-up to the atherosclerotic hospitalisation was significantly shorter in the pre-eclampsia group compared with the comparison group.

Table 2 presents a comparison of cardiovascular and renal morbidity and hospitalisations during the follow-up period. Patients with pre-eclampsia had higher rates of renal morbidity in addition to cardiovascular morbidity, including cardiac

**Table 2** Incidence of cardiovascular and renal-related morbidity and hospitalisations during the follow-up period in patients with and without a history of pre-eclampsia

	Pre-eclampsia (n=7824) (%)	No pre-eclampsia (n=88 546) (%)	p Value*
Cardiac non-invasive diagnostic procedures	1.3	0.9	0.036
Cardiac invasive diagnostic procedures	0.6	0.3	0.004
Simple cardiovascular events	1.7	1.2	0.001
Complex cardiovascular events	3.0	1.3	0.001
Total cardiovascular hospitalisations	4.6	2.7	0.001
Renal morbidity	0.3	0.1	0.001

\*Log-rank test.

**Table 3** A comparison of the incidence of cardiovascular-related and renal-related hospitalisations and morbidity between patients with a history of two or more pregnancies with pre-eclampsia to patients with just one pregnancy with pre-eclampsia and no pregnancy with pre-eclampsia

	No pre-eclampsia (n=88 546) (%)	A single occurrence of pre-eclampsia (n=6642) (%)	≥2 pre-eclampsia (n=1182) (%)	p Value*
Cardiac non-invasive diagnostic procedures	0.9	1.2	1.7	0.030
Cardiac invasive diagnostic procedures	0.3	0.6	0.6	0.012
Simple cardiovascular events	1.2	1.6	2.2	0.001
Complex cardiovascular events	1.3	2.7	4.6	0.001
Total cardiovascular hospitalisations	2.7	4.4	6.0	0.001
Renal-related hospitalisations	0.1	0.3	0.2	0.001

\*Log-rank test.

invasive and non-invasive diagnostic procedures, simple as well as complex cardiovascular events, and hospitalisations due to cardiovascular causes.

Table 3 presents a comparison between the incidence of renal and cardiovascular morbidity in women with no history of pre-eclampsia to women with a history of one pregnancy with pre-eclampsia and women with two or more pregnancies with a diagnosis of pre-eclampsia. The risk for renal-related and cardiovascular-related hospitalisations including total cardiovascular hospitalisations increased linearly and with statistically significance with the number of past events.

Table 4 presents a comparison between the incidence of renal and cardiovascular morbidity according to the severity of pre-eclampsia. The risk for future renal and cardiovascular morbidity including cardiac invasive and non-invasive diagnostic procedures, simple as well as complex cardiovascular events, and hospitalisations due to cardiovascular causes increased linearly with the severity of the disease (mild pre-eclampsia vs severe pre-eclampsia vs eclampsia).

Figure 1 presents Kaplan–Meier survival curves for the cumulative incidence of cardiovascular (a) and renal (b) hospitalisations following the index birth in both study groups (pre-eclampsia and no pre-eclampsia). Patients with a history of pre-eclampsia had a significantly higher risk for cumulative cardiovascular and renal events during the whole follow-up period.

Cox proportional hazards models were used to estimate the adjusted HRs and 95% CI for long-term cardiovascular (table 5) and renal hospitalisations (table 6). After controlling for maternal age, parity and recognised confounders related to the metabolic syndrome such as diabetes and obesity, pre-eclampsia remained independently associated with cardiovascular-related and renal-related hospitalisations.

## DISCUSSION

The results of the current study further establish the association between a history of pre-eclampsia and future risk for renal as well as

cardiovascular-related morbidity and hospitalisations. Furthermore, a significance linear association exists between the number of past pre-eclampsia episodes and in addition the severity of the disease to the appearance of CVD and renal morbidity later in life.

The results of our study add to the data from other studies regarding the relationship between pre-eclampsia and future risk for cardiovascular morbidity.<sup>5–7 9</sup> Irgens *et al*<sup>5</sup> studied a registry of 626 727 births and compared mothers with and without a history of pre-eclampsia. They found women with a history of pre-eclampsia to be at higher risk for cardiovascular-related mortality.<sup>5</sup> Shalom *et al*<sup>6</sup> found a history of pre-eclampsia to be a significant risk factor for long-term morbidity such as chronic hypertension and general hospitalisations.<sup>6</sup> Likewise, Mangos *et al*<sup>7</sup> studied patients with a history of pre-eclampsia or gestational hypertension and found biochemical evidence predisposing them to later cardiovascular complications.<sup>7</sup> Hashemi *et al*<sup>9</sup> studied a cohort of 226 patients with a history of hypertensive disorders of pregnancy and 226 matched women. They found patients with a history of pre-eclampsia to be at increased risk for hypertension, diabetes mellitus and dyslipidemia later in non-pregnant life.<sup>9</sup> In the current study, we performed further categorisation of the cardiovascular complications according to ICD codes. This analysis emphasises the importance of a previous history of pre-eclampsia as a risk factor for not only the end point of cardiovascular-related hospitalisations, but also for simple as well as complex morbidity and diagnostic procedures.

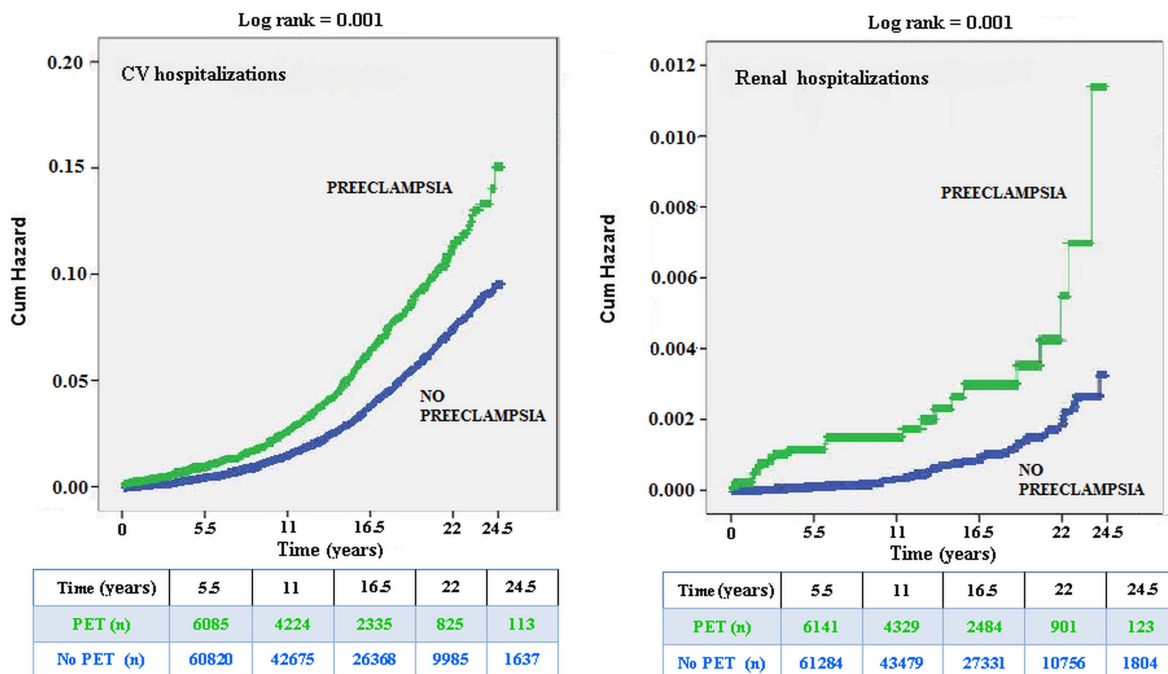
In addition, to the best of our knowledge, this is the first study to investigate not only the relationship between a previous diagnosis of pre-eclampsia but also whether a correlation exists between the number of events or severity of the disease to the future risk for cardiovascular-related morbidity and hospitalisations. Future risk for atherosclerotic morbidity is increased linearly with the number of past pregnancies with a diagnosis of pre-eclampsia and also with the severity of the disease. This information is of major importance when counselling future risk

**Table 4** Incidence of cardiovascular-related and renal-related hospitalisations and morbidity by pre-eclampsia severity

	No pre-eclampsia (n=88 546) (%)	Mild pre-eclampsia (n=6018) (%)	Severe pre-eclampsia (n=1719) (%)	Eclampsia (n=87) (%)	p Value*
Cardiac non-invasive diagnostic procedures	0.9	1.2	1.6	0.0	0.015
Cardiac invasive diagnostic procedures	0.3	0.6	0.5	0.0	0.008
Simple cardiovascular events	1.2	1.8	1.5	2.3	0.001
Complex cardiovascular events	1.3	2.8	3.4	4.6	0.001
Total cardiovascular hospitalisations	2.7	4.5	5.2	5.7	0.001
Renal-related hospitalisations	0.1	0.2	0.5	1.1	0.001

\*Log-rank test.

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**Figure 1** Cumulative incidence of cardiovascular (CV) (A) and renal hospitalisations (B).

for cardiovascular and renal morbidity in patients with previous episodes of pre-eclampsia.

Furthermore, in our study, we investigated the link between pre-eclampsia and future risk for renal-related hospitalisations. Previous published data regarding the association between pre-eclampsia and long-term renal morbidity are relatively scarce and the studies are limited by the low prevalence of renal disorders and thus small sample size. In a review by McDonald *et al*,<sup>13</sup> only seven cohort studies with a total of 273 patients were found. Patients with a history of pre-eclampsia were found to be at an eightfold increased risk for microalbuminuria.<sup>13</sup> Recently, Wu *et al*<sup>14</sup> studied a database of 13 633 women with a maximum follow-up of 11 years and found 46 women with a diagnosis of end-stage renal disease. The authors found patients with a history of pre-eclampsia to be at 10 times greater risk for end-stage renal disease.<sup>14</sup> According to the results of our study, patients with a previous diagnosis of pre-eclampsia were at a higher risk for renal-related hospitalisations even after controlling for maternal age and other confounders known to be related to the metabolic syndrome. Furthermore, a linear correlation was noted between renal morbidity and the number of past events as well as the severity of the disease (same as with CVD).

**Table 5** Cox multivariable regression model for the risk of cardiovascular hospitalisation

	Adjusted HR	95% CI	p Value
Pre-eclampsia	1.7	1.6 to 1.9	0.001
Maternal age (years)	1.056	1.048 to 1.064	0.001
Parity at index pregnancy	1.123	1.107 to 1.139	0.001
Gestational diabetes mellitus	1.7	1.5 to 1.9	0.001
Obesity (pre-gestational BMI >30 kg/m <sup>2</sup> )	1.9	1.5 to 2.5	0.001
Smoking	2.0	1.4 to 2.8	0.001

BMI, body mass index.

In a study by Heidrich *et al*,<sup>16</sup> the authors performed a survey to assess physicians' knowledge regarding the long-term risk for CVD after pre-eclampsia. The authors concluded that while the majority of physicians were aware of the risk, weaknesses existed in the follow-up and consultations of these patients.<sup>16</sup> In another study by Cusimano *et al*,<sup>17</sup> women with common obstetric complications were referred to a clinic for complete lifetime risk assessment for CVD. The authors suggest that this assessment identifies postpartum patients susceptible for CVD and may be effective for primary prevention strategy.<sup>17</sup>

The main strength of the present study lies in the fact that our hospital is the sole hospital serving the entire population of southern Israel. The hospital provides both maternity services and tertiary cardiovascular and renal medical services, thus as long as patients live in the area they would only use this hospital. However, the ascertainment of cardiovascular events, which occurred outside of the hospital, could not be accomplished. It is therefore possible that some cardiovascular/renal events were missed, but there is no reason to suspect differential rates of outcome ascertainment in the two study groups.

In conclusion, our results establish that pre-eclampsia is an independent risk factor for subsequent long-term atherosclerotic complications including cardiovascular and renal complications requiring hospitalisations.

**Table 6** Cox multivariable regression model for the risk of renal-related hospitalisation\*

	Adjusted HR	95% CI	p Value
Pre-eclampsia	3.7	2.3 to 6.0	0.001
Maternal age (years)	1.053	1.009 to 1.098	0.018
Parity at index pregnancy	1.154	1.069 to 1.247	0.001
Gestational diabetes mellitus	1.9	1.1 to 3.2	0.030

\*The model also controlled for obesity and smoking.

The risk is more substantial for patients with severe and recurrent episodes of pre-eclampsia. In general, most women are usually screened only when born, during pregnancy and later in life when diagnosed with a chronic disease. Atherosclerotic risk assessment and counselling for women is suboptimal and pregnancy should be viewed by physicians as not only a stress test that might be used for risk assessment but also as an opportunity to counsel women regarding specific surveillance and lifestyle modifications recommended.

### Key messages

#### What is already known on this subject?

There is a link between a history of pre-eclampsia and future risk of cardiovascular morbidity and mortality.

#### What might this study add?

This study further establishes this link and in addition shows that there is a 'dose-response' association between the severity of pre-eclampsia (no pre-eclampsia 2.7% vs mild pre-eclampsia 4.5% vs severe pre-eclampsia 5.2% and eclampsia 5.7%, respectively;  $p=0.001$ ) and the number of episodes of pre-eclampsia (no pre-eclampsia 2.7% vs one event of pre-eclampsia 4.4% vs  $\geq 2$  events 6.0%, respectively;  $p=0.001$ ) to this future risk. Furthermore, this study helps to establish a new link between pre-eclampsia and future risk for renal morbidity.

#### How might this impact on clinical practice?

By establishing pre-eclampsia as an independent cardiovascular risk factor, the study shows that this risk is more substantial for patients with severe and recurrent episodes of pre-eclampsia and suggests an additional association to renal morbidity. This may help when performing risk assessment for future cardiovascular and renal morbidity for women, and also serve as an opportunity to recommend women regarding specific surveillance and lifestyle modifications.

**Competing interests** None.

**Ethics approval** The Institutional Review Board (in accordance with the Helsinki declaration) approved the study.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**Heart**

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