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Prenatal exposure to preeclampsia as an independent risk factor for long-term cardiovascular morbidity of the offspring☆

Kira Nahum Sacks[a], Michael Friger[a], Ilana Shoham-Vardi[a], Efrat Spiegel[b], Ruslan Sergienko[a], Daniella Landau[c], Eyal Sheiner[b,*]

[a] Department of Public Health, Faculty of Health Sciences, Ben Gurion University of the Negev, Israel
[b] Department of Obstetrics and Gynecology, Faculty of Health Sciences, Soroka University Medical Center, Ben-Gurion University of the Negev, Israel
[c] Department of Pediatrics, Faculty of Health Sciences, Soroka University Medical Center, Ben-Gurion University of the Negev, Israel

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ABSTRACT

Introduction: Preeclampsia is a leading cause of maternal and fetal morbidity and mortality. Regarding the offspring, little is known about the long-term complications. The objective of the current study is to assess whether in utero exposure to preeclampsia increases the risk of long-term cardiovascular morbidity in the offspring.

Materials and methods: A population-based cohort study compared the incidence of cardiovascular disease between singletons exposed and unexposed to preeclampsia. Deliveries occurred between 1991 and 2014 in a regional tertiary medical center. A Cox proportional hazard model was used to control for confounders.

Results: During the study period 231,298 deliveries met the inclusion criteria; 4.1% of the births were to mothers diagnosed with preeclampsia, of which 3.2% with mild preeclampsia (n = 7286), 0.9% with severe preeclampsia (n = 2174) and 0.03% with eclampsia (n = 73). A significant linear association was noted between preeclampsia (no preeclampsia, mild preeclampsia, severe preeclampsia and eclampsia) and cardiovascular disease of the offspring (0.24%, vs. 0.33% vs. 0.51% vs. 2.73% respectively, $p < 0.001$ using the chi-square test for trends). In the offspring born at term, severe preeclampsia was found to be an independent risk factor for cardiovascular morbidity (adjusted HR = 2.32; 95% CI 1.15–4.67). In offspring born preterm, neither severe preeclampsia (adjusted HR = 1.36; 95% CI 0.53–3.48) nor mild preeclampsia (adjusted HR = 0.37; 95% CI 0.52–2.71) were associated with cardiovascular morbidity of the offspring.

Conclusion: Exposure to severe maternal preeclampsia is an independent risk factor for long-term cardiovascular morbidity in the offspring born at term.

1. Introduction

Preeclampsia is a disease characterized by gestational hypertension and proteinuria that effects 2–8% of pregnancies worldwide [1]. In 2010, the rate of preeclampsia in the Unites States was 3.8%: an increase from 2.5% in 1987 [2], and in Canada the incidence of pre-eclampsia has increased from 26.4 per 1000 deliveries in 1989, to 50.6 in 2012 [3]. This increase is disturbing since pre-eclampsia has a substantial impact on the intrauterine environment and is a leading cause of maternal and fetal mortality and morbidity [4–6]. Regarding the offspring, previous studies have mainly addressed the immediate adverse outcomes, such as the increased the risk of fetal growth restriction [7], perinatal death [8] and severe neonatal morbidity [9,10].

While there are studies on the long-term neurological effects of preeclampsia on the offspring [11,12], less data exists regarding the long-term cardiovascular effect, even though there is evidence of both congenital cardiovascular predispositions [13–15] and a higher incidence of cardiovascular risk factors amongst children prenatally exposed to preeclampsia [16,17]. The congenital cardiovascular predispositions found in children exposed in utero to preeclampsia include congenital heart defects [13], smaller hearts [14], increased heart rate [14], and higher pulmonary artery pressure [15], and cardiovascular risk factors amongst children prenatally exposed to preeclampsia include a higher blood pressure, a higher weight and a higher BMI

Abbreviations: AHA, American heart association; CVD, cardiovascular disease; GEE, generalized estimating equation; HR, hazard ratio; IUGR, intrauterine growth restriction; SUMC, Soroka University Medical Center

☆ The study was conducted in Beer Sheva, Israel.

* Corresponding author at: Department of Obstetrics and Gynecology, Soroka University Medical Center, POB 151, Beer-Sheva 84101, Israel.
E-mail address: sheiner@bgu.ac.il (E. Sheiner).

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Table 1
Cohort characteristics by exposure to maternal preeclampsia.

Characteristics		No Preeclampsia (n = 221765)	Mild Preeclampsia (n = 7286)	Severe Preeclampsia (n = 2174)	Eclampsia (n = 73)	P value[a]
Maternal Characteristics						
Maternal age, y (mean ± SD)		28.22 ± 6	28.66 ± 6	29.03 ± 7	25.37 ± 8	< 0.001
Maternal obesity (%)		1.0%	1.6%	1.0%	1.4%	< 0.0001
Maternal diabetes (%)		5.3%	9.4%	10.8%	4.1%	< 0.0001
Pregnancy Characteristics						
Birth order (%)	1	23.9%	40.0%	43.9%	60.3%	< 0.001
	2–4	52.2%	40.1%	31.7%	17.8%	
	5+	23.8%	19.9%	24.4%	21.9%	
IUGR[b]		1.8%	3.5%	17.0%	12.3%	< 0.001
Gestational age at birth, wk (mean ± SD)		39.16 ± 2	38.68 ± 2	36.39 ± 3	37.30 ± 3	< 0.001
Offspring Characteristics						
Gender of offspring (%)	Male	51.2%	51.5%	50.3%	65.8%	0.06
	Female	48.8%	48.5%	49.7%	34.2%	
Weight at birth, grams (mean ± SD)		3222 ± 493	3140 ± 532	2498 ± 772	2701 ± 713	< 0.001
Obesity of the offspring (%)		0.2%	0.4%	0.4%	1.4%	< 0.001

[a] Data evaluated with Pearson test or One-way Anova accordingly.
[b] Abbreviations: IUGR, Intrauterine growth restriction; SD, Standard deviation.

[16,17].

These predispositions may represent the first signs of a pathological cardiovascular system, which will eventually manifest as end-point cardiovascular morbidity. The objective of the present population-based study is to investigate whether prenatal exposure to preeclampsia is an independent risk factor for long-term cardiovascular morbidity in the offspring. We also aim to investigate the association between the severity of the preeclampsia and offspring morbidity, while addressing term and preterm labor separately.

2. Methods

2.1. Setting

The study was conducted at the Soroka University Medical Center (SUMC), a tertiary hospital that serves the entire population of southern Israel. Thus, the study is based on a nonselective population data. The institutional review board (in accordance with the Helsinki declaration) approved the study (# SOR-0236-13 approved on November 2013).

2.2. Study population

The study population included all patients who delivered between the years 1991–2014 and their offspring. Perinatal deaths, multiple gestations, mothers with chronic hypertension or lack of prenatal care, and children with congenital malformations were excluded from the study.

2.3. Study design

We conducted a population-based cohort study. The primary exposure was having been prenatally exposed to preeclampsia. Severity of preeclampsia was diagnosed by a trained obstetrician, according to the guidelines of the Working Group of the National High Blood Pressure Education Program [18,19]. A retrospective follow-up of cardiovascular morbidity of the offspring up to 18 years of age was performed.

The main outcome was defined as cardiomyopathy, hypertension, pulmonary heart disease, arrhythmia or heart failure (Supplement Table 1), documented during any of the offspring's hospital admissions. These cardiovascular morbidities were chosen because they cover both a wide range of clinical presentation and a wide range of etiologies. Most importantly, these conditions were selected due to the associations that have already been found between cardiovascular conditions and in utero exposure to preeclampsia [13–17].

Primary and secondary diagnoses were analyzed so that cardiovascular morbidity could be detected, even if it was not the primary cause for hospitalization. All hospitalizations were analyzed so that multiple diagnoses could be given to a single child. The date of the first hospitalization for any single cause was used to calculate time-to-event.

Data were collected from two databases that were cross-linked and merged: the computerized perinatal database and the computerized hospitalization 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 before entering it into the database. The hospitalization database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalization.

2.4. Statistical analysis

Statistical analysis was performed with the SPSS software (version 21; SPSS Inc, Chicago, IL). Statistical significance was calculated using Pearson x^2 test and One-way Anova accordingly. A Kaplan Meier survival curve was used to compare the cumulative incidence of pediatric morbidity. In the multivariate analysis “Severe Preeclampsia” and “Eclampsia” were analyzed as one group, and models were performed on term and preterm deliveries separately. Both a cox proportional hazard analysis, and a multivariate generalized estimating equation (GEE) logistic regression model analysis were used to control for confounders and for maternal clusters. A probability value of < 0.05 was considered statistically significant.

3. Results

During the study period the births of 320,875 children were documented. After excluding perinatal deaths (n = 2491), multiple gestations (n = 23,797), chronic hypertension (n = 12,203), lack of prenatal care (n = 22,510), and congenital malformations (n = 27,501), the remaining 231,298 deliveries were included in our analysis. Of the 231,298 deliveries, 4.1% of the births were to mothers diagnosed with preeclampsia or eclampsia (n = 9533), in accordance with the current literature [1–3]. Of these mothers, 3.2% were diagnosed with mild preeclampsia (n = 7286), 0.9% with severe preeclampsia (n = 2174) and 0.03% with eclampsia (n = 73).

Table 1 presents a comparison between the clinical characteristics of pregnancies with varying degrees of preeclampsia. In comparison to the no preeclampsia group, Mothers in the preeclampsia groups were significantly more likely to be primiparous, and pregnancies in the