Pregnancy Hypertension 17 (2019) 144–147

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Maternal preeclampsia and the risk of pediatric gastrointestinal diseases of the offspring: A population-based cohort study☆

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ARTICLE INFO

Keywords:
Hypertension
Intrauterine growth restriction
Epigenetics

ABSTRACT

Objective: We aimed to study the long-term effect of preeclampsia on the risk for subsequent gastrointestinal morbidity of the offspring.
Study design: A population based cohort analysis comparing total and different subtypes of gastrointestinal related pediatric hospitalizations among offspring of preeclamptic mothers versus offspring of mothers without preeclampsia. The analysis included all singletons born between the years 1999–2014 at a single tertiary regional medical center. Gastrointestinal related morbidities included hospitalizations involving a set of ICD-9 codes, as recorded in hospital files. Infants with congenital malformations, multiple gestations, and perinatal deaths were excluded from the analysis. A Kaplan-Meier survival curve was used to compare the cumulative morbidity, and a Cox proportional hazards model was constructed to adjust for confounders.
Results: The study population included 239,687 newborns who met inclusion criteria; among them 2222 (0.93%) were born to mothers with severe preeclampsia or eclampsia, and 7279 (3.03%) were born to mothers with mild preeclampsia. Offspring of mothers with severe preeclampsia had significantly higher rates of gastrointestinal-related hospitalizations in comparison to offspring of mothers with mild preeclampsia and offspring of non-preeclamptic mothers (7.7% vs. 5.5% vs. 5.3%, respectively; $p < 0.001$). The association between exposure to severe preeclampsia and eclampsia and long-term gastrointestinal morbidity of the offspring remained significant and independent while adjusting for confounders (Adjusted HR = 1.2, 95% CI 1.0–1.4; p = 0.019).
Conclusion: Severe preeclampsia and eclampsia are independent risk factors for pediatric gastrointestinal morbidity of the offspring.

1. Introduction

Preeclampsia is a multisystem progressive disorder characterized by the new onset of gestational hypertension and proteinuria, or of hypertension and end-organ dysfunction, in the last half of pregnancy or postpartum [1]. In a systematic review, 4.6% of pregnancies worldwide were complicated by preeclampsia [2,3].

Pregnancies affected with preeclampsia are at increased risk for maternal and fetal mortality or serious morbidity [4,5]. Previous studies had shown higher rates of fetal and obstetrical complications in the short term, such as: growth restriction, preterm delivery and placental abruption [6–8]. In addition, women with preeclampsia are at an increased risk for future chronic hypertension, cardiovascular disease [9–11], diabetes and stroke [12,13].

Several mechanisms were proposed to explain the adverse pregnancy and neonatal outcomes associated with preeclampsia. Shallow placentation and thus failure to establish an adequate uteroplacental blood flow can result in a state of oxidative stress in the placenta [14]. These may lead to under development of the feto-placental vasculature and abnormal vascular reactivity, which contribute to maternal and fetal adverse effects.

However, the long-term effects on offspring health were not thoroughly studied. It was shown that offspring of preeclamptic mothers are at risk for higher blood pressure and obesity [15–17]. To the best of our knowledge, the effect on the risk for long-term gastrointestinal morbidity was not investigated. We hypothesize that compromised environment in utero may lead to a subtle reduction in intestinal perfusion in order to preserve fetal blood flow to other vital organs. Therefore, we aimed to investigate whether prenatal exposure to preeclampsia is an independent risk factor for long-term gastrointestinal

☆ Will be presented in part at the SMFM **39th Annual Meeting,** February 11–16, 2019, Las-Vegas, Nevada.

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https://doi.org/10.1016/j.preghy.2019.06.005
Received 16 January 2019; Received in revised form 30 May 2019; Accepted 18 June 2019
Available online 19 June 2019

morbidity in the offspring.

2. Methods

Our study is a population-based retrospective cohort study. Included in the analysis were all singletons born between the years 1999–2014 at the Soroka University Medical Center (SUMC), the sole tertiary medical center in the region of southern Israel, serving 14.4% of Israel's population [18]. The exposure was defined as either severe preeclampsia or eclampsia or mild preeclampsia. Severity of preeclampsia was classified according to the guidelines of the Working Group of the National High Blood Pressure Education Program [19]. The comparison group included offspring of mothers with no hypertensive disorders. Exclusion criteria were: newborns with congenital malformations, multiple gestations, perinatal deaths and mothers with chronic hypertension or lack of prenatal care.

We studied the long-term gastrointestinal morbidity among offspring of mothers with preeclampsia or eclampsia in comparison to offspring of mothers without hypertensive disorders. The outcome assessed included hospitalizations with different subtypes of gastrointestinal morbidity in the offspring up to the age of 18 years, involving a pre-defined set of ICD-9 codes (detailed in the Supplemental Table).

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. Otherwise, follow up was censored in case of death or at age 18 years.

For the analyses two databases were cross-linked and merged: the computerized hospitalization database of SUMC ("Demog-ICD9") and the computerized perinatal database of the Obstetrics and Gynecology department. The perinatal database consists of information recorded immediately following delivery by an obstetrician and includes perinatal assessments, maternal morbidities and maternal and fetal outcome and complications. Skilled medical secretaries routinely review the information before entering it into the database. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations at SUMC. Records were anonymized prior to analysis. The study received the approval of the Institutional Review Board Committee of the Soroka University Medical Center (SUMC IRB).

Statistical analysis was performed using the SPSS package 23rd ed. (IBM/SPSS, Armonk, NY). Statistical significance in categorical data was assessed by chi-square for general association and ANOVA test was used for continuous variables with normal distribution.

Kaplan-Meier survival curves were used to compare cumulative gastrointestinal related hospitalization incidences over time according to preeclampsia exposure. The differences between the cumulative morbidity curves were assessed using the log-rank test.

A Cox proportional hazards model analysis was used to establish an independent association between exposure to eclampsia and preeclampsia during pregnancy and future gastrointestinal morbidity while controlling for potential confounders. All analyses were two-sided and a p value of less than 0.05 was considered statistically significant.

3. Results

The study population included 239,687 newborns which met inclusion criteria; among them 2222 (0.9%) were born to mothers with severe preeclampsia or eclampsia, and 7279 (3.0%) were born to mothers with mild preeclampsia. Table 1 presents a comparison between the clinical characteristics of pregnancies, including maternal and fetal characteristics, with varying degrees of preeclampsia. Maternal age at delivery was higher in the groups of mothers exposed to preeclampsia.

Pregnancies in the preeclampsia groups were significantly more likely to be affected by prematurity. Offspring of preeclamptic mothers had higher probability of low birth weights. Offspring gender distribution was similar between groups.

The long-term gastrointestinal morbidity of the offspring and the different subgroups of morbidities are presented in Table 2. A significant linear association was noted between the severity of preeclampsia (severe preeclampsia or eclampsia, mild preeclampsia and no hypertension) and the rate of gastrointestinal related hospitalizations [7.7 vs. 5.5 vs. 5.3, respectively; $p < 0.001$]. Specifically, children exposed in utero to preeclampsia had significantly higher rates of esophageal morbidity [0.5 vs. 0.3 vs. 0.2, respectively; $p = 0.037$], hernias [3.3 vs. 1.5 vs. 1.4, respectively; $p < 0.001$] and functional colonic morbidity [0.4 vs. 0.2 vs. 0.2, respectively; $p = 0.046$]. Kaplan -Meier curves for the cumulative incidence of long-term gastrointestinal morbidity of the offspring in each study group presented in Fig. 1 (log-rank p value < 0.001).

We used a Cox proportional hazard regression model to control for maternal age and gestational age at delivery. Maternal severe preeclampsia or eclampsia were found to be independent risk factors for long-term gastrointestinal disease of the offspring (adjusted HR 1.2 [1.0–1.4]; p-value 0.019). Nevertheless, mild preeclampsia was not found as an independent risk factor (adjusted HR 0.9 [0.9–1.1]; p-value 0.428) (Table 3).

4. Discussion

Our population-based study of offspring followed up to 18 years, showed an increased risk for pediatric gastrointestinal related hospitalizations in offspring exposed to preeclampsia. The association remained significant for severe preeclampsia or eclampsia while controlling for potentially important confounders. The confounders controlled for were gestational age and maternal age at delivery, which was higher in the groups of mothers exposed to preeclampsia. However, mild preeclampsia was not shown to be an independent risk factor for childhood gastrointestinal morbidities. To the best of our knowledge, this is the first study suggesting a possible association between maternal preeclampsia and long-term pediatric gastrointestinal morbidities.

One theory that can explain these findings is the "predictive adaptive response" theory proposed in 2006 by Glickman et al. [20]. This theory suggests that compromised fetal environment may cause fetal programming, in which variations in the supply of nutrients to the baby, permanently alters gene expression. These alterations could contribute to childhood and adulthood disease if these adaptions are mismatched with later environments. Epigenetic mechanisms, which allow for physiological plasticity and expression of different phenotypes from a given genotype, serve as possible underlying bases of the theory [21,22].

It is known that defects in spiral artery remodeling and trophoblast invasion are characteristic of hypertensive disorders of pregnancy [23,24]. These processes result in impaired placentation and placental ischemia, which may lead to placental release of soluble factors that cause systemic endothelial dysfunction [25–27]. Placental hypoxia increases placental necrosis and apoptosis, which releases cell-free DNA into the maternal circulation. Placental DNA released into the maternal circulation could play a role in driving the systemic inflammatory response of preeclampsia [28].

In addition, placental bed biopsies from preeclamptic women have revealed increased dendritic cell infiltration in decidual tissue [29]. It has been hypothesized that increased number of dendritic cells may result in alteration in presentation of maternal and fetal antigens at the decidual level, leading to either abnormal implantation or altered maternal immunologic response to fetal antigens.

Our hypothesis was that compromised environment in utero might lead to a subtle reduction in intestinal perfusion in order to preserve fetal blood flow to other vital organs. The resultant bowel injury may be notable only later in life. Nevertheless, this hypothesis remains to be investigated in following studies.

This study has few points of strength. The main advantage relates to the large cohort size and long follow up time. In addition, due to the

Table 1
Maternal, pregnancy, and neonatal characteristics in study groups.

	Severe preeclampsia or eclampsia % (n = 2222)	Mild preeclampsia % (n = 7279)	No hypertension % (n = 230186)	P Value
*Follow-up time (years, median, [*min, max*])*	11.1, [0,18]	11.4, [0,18]	10.2, [0, 18]	< 0.001
Maternal characteristics				
Age at delivery (years, mean ± SD)	29.0 ± 6.9	28.7 ± 6.3	28.1 ± 5.8	< 0.001
Parity				
1	43.4 (964)	39.2 (2854)	23.0 (52934)	
2–4	29.6 (657)	39.9 (2903)	51.8 (119217)	< 0.001
5+	27.0 (601)	20.9 (1520)	25.2 (57985)	
Fetal and delivery characteristics				
Gender				
Male	49.6 (1103)	51.1 (3716)	50.8 (117010)	0.496
Female	50.4 (1119)	48.9 (3563)	49.2 (113176)	
Gestational age (weeks, mean ± SD)	36.7 ± 3.0	38.7 ± 1.8	39.2 ± 1.8	< 0.001
Preterm labor (< 37 Weeks)	43.4 (965)	9.6 (701)	6.0 (13821)	< 0.001
Birth weight < 2500 gr	46.2 (1026)	10.6 (770)	5.8 (13399)	< 0.001
Apgar 1 min < 7	15.8 (352)	4.8 (349)	4.7 (10881)	< 0.001
Apgar 5 min < 7	1.6 (36)	0.6 (44)	1.8 (4212)	< 0.001

Table 2
Gastrointestinal morbidity in the offspring in all groups.

Cardiovascular Disease	Severe preeclampsia or eclampsia (n = 2222)	Mild preeclampsia (n = 7279)	No hypertension (n = 230186)	P value
Esophageal	0.5% (10)	0.3% (19)	0.2% (486)	0.037
Gastroduodenal	0.5% (11)	0.5% (39)	0.5% (1233)	0.966
Functional	0 (0)	0.02% (2)	0.01% (17)	0.152
Appendix	0.9% (19)	0.5% (36)	0.6% (1394)	0.150
Hernia*	3.3% (73)	1.5% (110)	1.4% (3242)	< 0.001
Inflammatory bowel disease	1.8% (39)	1.8% (134)	1.7% (3906)	0.633
Vascular	0.1 (2)	0 (0)	0 (10)	< 0.001
Colonic – functional	0.4% (8)	0. 2% (12)	0.2% (352)	0.046
Hepatitis	0 (1)	0.1% (5	0.1% (219)	0.578
Surgical**	0.1% (38)	0.2% (12)	0.1% (299)	0.718
Cholecystitis-lithiasis	0.1% (2)	0.04% (3)	0.03% (77)	0.339
Celiac	0.2% (5)	0.5% (33)	0.4% (888)	0.308
Gastrointestinal hospitalizations, total	7.7% (172)	5.5% (402)	5.3% (12285)	< 0.001

* Inguinal, umbilical and abdominal wall hernia.
** Obstruction, intussusception, volvulus, perforation.

fact that SUMC is the sole tertiary hospital in the entire Negev region and the fact that this area is characterized by positive immigration, loss to follow up and selection bias are probably minimal. Also, broad inclusion criteria and limited exclusion criteria in our study produce a study population that is more representative of the target population.

However, this study has also few limitations. The main limitation lies within its retrospective design. As a population-level analysis, our study can provide evidence only of association and not of causation. Nevertheless, there seems to be a biological plausibility for the observed association. Another limitation relates to the fact that many of the investigated gastrointestinal related morbidities are usually managed in an ambulatory setting and therefore not accounted for. Several potentially important covariates were not available for analysis, such as parental gastrointestinal morbidity, childhood exposures, and socioeconomic status. These important points remain to be investigated in future studies.

In conclusion, in this large population-based study, exposure to severe maternal preeclampsia was found to be an independent risk factor for long-term gastrointestinal morbidity in the offspring. This association has a preventive, medical and educational role. Further research is warranted from community databases, and should focus on the genetic base and environmental exposures during childhood. Also,

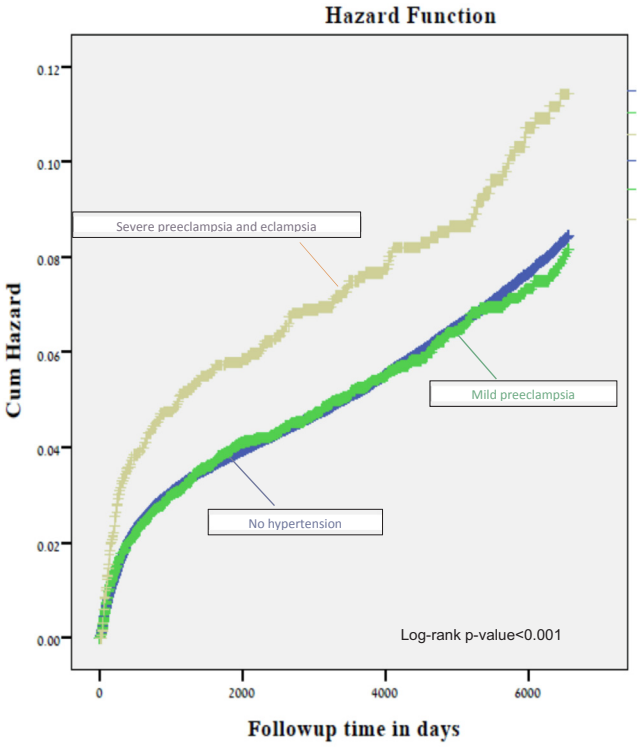

Fig. 1. A Kaplan-Meier cumulative hazard function of gastrointestinal morbidity in all groups.

Table 3
Cox proportional hazards model for the association between maternal preeclampsia or eclampsia and total gastrointestinal morbidity in the offspring.

Variable	Adjusted HR (95% CI)	P value
Mild preeclampsia	0.96 (0.87–1.06)	0.428
Severe preeclampsia or eclampsia	1.19 (1.03–1.39)	0.019
No preeclampsia	1 (reference)	
Maternal age (years)	0.99 (0.98–0.99)	< 0.001
Gestational age (weeks)	0.94(0.93–0.94)	< 0.001

surveillance strategies for offspring delivered following severe pre-eclampsia should be considered and remain to be further studied.

Acknowledgments/Disclosure

The authors report no conflict of interest.

Funding/Support

This study was not funded. b. Financial Disclosures: No financial disclosures. c. Leybovitz-Haleluya Noa, MD wrote the first draft of the manuscript. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript. d. This is a database study and as such has no clinical trial registration number.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.06.005.

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