An association between preterm delivery and long-term maternal cardiovascular morbidity

Roy Kessous, MD; Ilana Shoham-Vardi, PhD; Gali Pariente, MD; Gershon Holcberg, MD; Eyal Sheiner, MD, PhD

OBJECTIVE: The purpose of this study was to investigate whether a history of preterm delivery (PTD) poses a risk for subsequent maternal long-term cardiovascular morbidity.

STUDY DESIGN: A population-based study compared the incidence of cardiovascular morbidity in a cohort of women who delivered preterm (<37 weeks' gestation) and those who gave birth at term at the same period. Deliveries occurred during the years 1988-1999 with follow up until 2010. Kaplan-Meier survival curves were used to estimate cumulative incidence of cardiovascular hospitalizations. Cox proportional hazards models were used to estimate the adjusted hazard ratios for cardiovascular hospitalizations.

RESULTS: During the study period 47,908 women met the inclusion criteria; 12.5% of the patients (n = 5992) delivered preterm. During a follow-up period of >10 years, patients with PTD had higher rates of simple and complex cardiovascular events and higher rates of total cardiovascular-related hospitalizations. A linear association was found between the number of previous PTD and future risk for cardiovascular hospitalizations (5.5% for ≥2 PTDs; 5.0% for 1 PTD vs 3.5% in the comparison group; $P < .001$). The association remained significant for spontaneous vs induced PTD and for early (<34 weeks) and late (34 weeks to 36 weeks 6 days' gestation) PTD. In a Cox proportional hazards model that adjusted for pregnancy confounders such as labor induction, diabetes mellitus, preeclampsia, and obesity, PTD was associated independently with cardiovascular hospitalizations (adjusted hazard ratio, 1.4; 95% confidence interval, 1.2—1.6).

CONCLUSION: PTD is an independent risk factor for long-term cardiovascular morbidity in a follow-up period of more than a decade.

Key words: cardiovascular morbidity, hospitalization, long term, pregnancy, preterm delivery

Cite this article as: Kessous R, Shoham-Vardi I, Pariente G, et al. An association between preterm delivery and long-term maternal cardiovascular morbidity. Am J Obstet Gynecol 2013;209:368.e1-8.

Preterm delivery (PTD; <37 weeks' gestation) complicates 5-12.7% of deliveries worldwide.[1] In 2007, the rate of PTD in the United States was 12.7%; this is an increase of 20% from the 1990s and 36% from the 1980s. This increase is due to an increase in the number of indicated PTD rather than spontaneous PTD.[2] A similar increase can be seen in other industrial countries.[3] PTD is the leading cause of perinatal morbidity and death.[2]

★ EDITORS' CHOICE ★

The link between pregnancy complications and future risk for cardiovascular disease (CVD) has been studied previously,[4-7] with a specific focus on preeclampsia and gestational diabetes mellitus. Irgens et al[4] studied a registry of 626,727 births and compared mothers with and without a history of preeclampsia. They found women with a history of preeclampsia to be at higher risk for cardiovascular-related death. Recently, Shalom et al[5] found preeclampsia to be a significant risk factor for long-term morbidity such as chronic hypertension and hospitalizations. Likewise, Mangos et al[6] studied patients with a history of preeclampsia or gestational hypertension and found biochemical evidence predisposing them to later cardiovascular complications.

A similar trend was noted for gestational diabetes mellitus. Vrachnis et al[7] reviewed studies regarding gestational diabetes mellitus and future risk for CVD and concluded that these patients should be considered a population at risk for future CVD. This evidence led to recent recommendations published by the American Heart Association, which included preeclampsia and gestational diabetes mellitus in the guidelines for the preliminary risk evaluation for CVD in women.[8]

Data regarding other pregnancy complications such as PTD and future risk for CVD are not well established. The underlining cause and mechanism of PTD delivery is not yet completely understood. The main mechanisms that have been suggested are inflammation, infection, and vascular diseases.[9-11]

Several studies have investigated the association between PTD and subsequent risk for cardiovascular morbidity.[12-16] Nevertheless, it is not yet

From the Departments of Obstetrics and Gynecology (Drs Kessous, Parienta, Holcberg, and Sheiner) and Epidemiology and Health Services Evaluation (Dr Shoham-Vardi), Faculty of Health Sciences, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

Received Feb. 27, 2013; revised April 27, 2013; accepted May 22, 2013.

The authors report no conflict of interest.

Presented in oral format at the 33rd annual meeting of the Society for Maternal-Fetal Medicine, San Francisco, CA, Feb. 11-16, 2013.

Reprints: Eyal Sheiner, MD, PhD, Department of Obstetrics and Gynecology, Soroka University Medical Center, POB 151, Beer Sheva 84101, Israel. sheiner@bgu.ac.il.

0002-9378/free

http://dx.doi.org/10.1016/j.ajog.2013.05.041

For Editors' Commentary, see Contents

TABLE 1
Characteristics of patients with and without a history of preterm delivery

Characteristic	Preterm delivery (n = 5992)	No preterm delivery (n = 41,916)	*P* value
Maternal age at index birth, y[a]	28.1 ± 6	29.9 ± 6	.001
Ethnicity, %			.001
Jewish	52.6	70.4	
Bedouin	47.4	29.6	
Postpartum anemia: hemoglobin (<10 g/dL), %	23.8	18.2	.001
Diabetes mellitus: gestational and pregestational, %	8.3	8.2	.768
Obesity: pregestational body mass index >30 kg/m^2, %	1.1	2.0	.001
Parity at index birth, n[b]	3 (2)	3 (1)	.001
Years from index pregnancy to hospitalization[a]	9.3 ± 4.7	10.6 ± 4.8	.001

[a] Data are given as mean ± SD; [b] Data are given as median (mode).

Kessous. PTD and future risk for cardiovascular disease. Am J Obstet Gynecol 2013.

understood clearly whether there is a direct association between PTD and future risk for CVD or whether this increased risk is due to other comorbidities such as hypertensive disorders or growth restriction.[13]

The objective of the present population-based study was to investigate whether PTD is an independent risk factor for subsequent long-term cardiovascular morbidity during a follow-up period of more than a decade. We also wanted to investigate the association between spontaneous vs induced PTD, early vs late PTD, and the number of PTDs to long-term cardiovascular hospitalizations.

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, that serves the entire population in this region. Thus, the study is based on a nonselective population data. The institutional review board (in accordance with the Helsinki declaration) approved the study.

Study population

The study population was composed of all patients who delivered in the years 1988-1998; the follow-up period was until 2010. Patients with multiple pregnancies and with known CVD before or during the index pregnancy were excluded from the study.

Study design

We conducted a population-based retrospective cohort study. The primary exposure was having had at least 1 PTD. Patients who for the entire period of follow up did not experience PTD comprised the comparison group; the last delivery was used as the index birth. A retrospective follow up of hospitalizations because of cardiovascular morbidity 10-20 years after the index birth was preformed. *Cardiovascular morbidity* was defined as hospitalizations for any cardiovascular reasons at the first cardiovascular hospitalization at Soroka University Medical Center. Cardiovascular morbidity was divided into 4 categories according to severity and type that included simple and complex cardiovascular events (eg, angina pectoris and congestive heart failure, respectively), and invasive and noninvasive cardiac procedures (eg, insertion of a stent and a treadmill stress test, respectively). The exact *International Classification of Diseases*, 9th edition (ICD-9) codes for each subtype of cardiovascular morbidity are presented in the Appendix (Supplementary Table).

Data were collected from 2 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. Coding was performed after assessment of medical prenatal care records together with the routine hospital documents. The hospitalization database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations.

Statistical analysis

Statistical analysis was performed with the SPSS software (version 17; SPSS Inc, Chicago, IL). Statistical significance was calculated with the χ^2 test for differences in qualitative variables and the Student *t* test for differences in continuous variables. Stratified analysis was performed (the pooled odds ratio was calculated with the Mantel-Haenszel test) to investigate the association between spontaneous vs induced PTD, early vs late, PTD with and without preterm premature rupture of membranes, PTD with and without preeclampsia, and long-term CVD. The association between the number of PTDs and the risk for subsequent cardiovascular hospitalizations and morbidity was evaluated with the χ^2 test for trends (the linear-by-linear association test).

Kaplan-Meier survival curve was used to compare cumulative incidence of cardiovascular hospitalizations. Cox proportional hazards models were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for long-term cardiovascular hospitalizations. A probability value of $< .05$ was considered statistically significant.

Results

During the study period, there were 47,908 women who met the inclusion