Is stillbirth associated with long-term atherosclerotic morbidity?

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OBJECTIVE: The purpose of this study was to investigate whether women who experienced at least 1 stillbirth are at increased risk for subsequent maternal long-term atherosclerotic morbidity.

STUDY DESIGN: We conducted a population-based study that compared the incidence of long-term atherosclerotic morbidity in a cohort of women with and without previous stillbirth. Deliveries occurred during a 25-year period. Patients with known cardiovascular or renal disease before the index pregnancy were excluded from the study. Kaplan-Meier survival curves were used to estimate the cumulative incidence of cardiovascular- and renal-related hospitalizations. Cox proportional hazards models were used to estimate the adjusted hazards ratio for cardiovascular- and renal-related hospitalizations.

RESULTS: Of 99,280 deliveries that met the inclusion criteria, 1879 deliveries (1.9%) occurred in patients who had had at least 1 stillbirth. After stillbirth, patients had a significantly higher cumulative incidence of cardiovascular and renal morbidity (Kaplan-Meier survival curve). During the follow-up period, patients with at least 1 stillbirth had higher rates of total cardiovascular and renal hospitalizations and had higher rates of simple and complex cardiovascular events. A significant stepwise increase was found between the number of stillbirths and future risk for cardiovascular morbidity. In a Cox proportional hazards model that was adjusted for confounders, previous stillbirth was associated independently with atherosclerotic morbidity.

CONCLUSION: Stillbirth is an independent risk factor for long-term maternal atherosclerotic morbidity. The risk is higher for patients with recurrent episodes of stillbirth.

Key words: atherosclerosis, long-term, maternal, morbidity, stillbirth

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Stillbirth is a major cause of perinatal death[1] and is known to account for >50% of all perinatal deaths in developed countries.[2] In Israel, *stillbirth* is defined as the delivery of a dead fetus after 24 completed weeks of gestation, which is a definition that is in accordance with the formal definition of the World Health Organization for stillbirth.[3,4] The reported incidence of stillbirth varies from 3–7.4 per 1000,[1,5-7] and there are reports of an increased incidence in recent years.[4] Although stillbirth without overt identifiable cause remains one of the most contributing factors to stillbirth,[4,8-9] several factors have been associated with the occurrence of stillbirth. Al Kadri and Tamim[10] showed a 25-fold increased risk of stillbirth with the occurrence of placental abruption, 10-fold with the occurrence of intrauterine growth restriction and 3-fold with the presence of hypertensive disorder in pregnancy. Other frequently described risk factors for stillbirth are obesity, advanced maternal age, and smoking, all of which are known to be risk factors of atherosclerosis.[11-13]

In recent years, there has been a growing body of evidence regarding the link between pregnancy complications and future risk for maternal atherosclerotic morbidity. Preeclampsia, gestational diabetes mellitus, placental abruption, delivery of a small-for-gestational-age (SGA) neonate, and preterm delivery were all shown to be associated with a future risk of cardiovascular morbidity and death.[14-18] Cardiovascular disease is a significant public health problem in Israel and in the western world. It is the second leading cause of death in women, with a mortality rate that exceeds the limit of 1400-100,000 among women >75 years old.[19] Therefore, methods that are used to screen populations that are at risk can be used to reduce the burden of cardiovascular morbidity and death. Moreover, the American Heart Association 2011 update guidelines[20] for the prevention of cardiovascular diseases include screening women for obstetric histories, especially preeclampsia, SGA, gestational diabetes mellitus, and preterm birth.

Because other perinatal morbidities that are associated with abnormal placentation are associated with long-term cardiovascular morbidity, we hypothesized that stillbirth, which is another condition with significant placental disease, would be associated similarly with later cardiovascular and renal disease.

The present population-based cohort study was aimed to investigate the risk of

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subsequent atherosclerotic morbidity in women with stillbirth during a follow-up period of more than a decade.

Materials and Methods

Study design

A retrospective population-based study was conducted. The primary exposure was ≥1 stillbirth. The main outcome was subsequent maternal cardiovascular and renal morbidity. *Stillbirth* was defined as the delivery of a dead fetus after 24 completed weeks of gestation, in accordance with the World Health Organization definition of stillbirth.[3] A comparison was performed between patients who had experienced at least 1 stillbirth and those who had not. For patients who experienced at least 1 stillbirth, the first event of stillbirth was chosen as the index pregnancy. For patients who had not experienced stillbirth, the index pregnancy was selected randomly. Deliveries occurred at the Soroka University Medical Center; these patients were observed retrospectively until 2012. Data were collected from 2 databases. The first database was the computerized perinatal database that consists of information recorded directly after delivery by an obstetrician. Skilled medical secretaries examine the information routinely before entering it into the databases. Coding was done after assessment of the medical prenatal care records and the routine hospital documents. These procedures assure maximal completeness and accuracy of the databases. Prepregnancy body mass index was based on the patient's files, because it was taken routinely as part of the first trimester follow-up evaluation. Gestational age was determined according to the last menstrual period, corrected to the first ultrasound scan, which usually was done at the first or early second trimester examination. *Postpartum anemia* was defined by the hemoglobin level of all patients at their second postpartum day. *SGA* was defined as a weight <10th percentile for the gestational age according to local charts.

The second database was the computerized hospitalization database of the Soroka University Medical Center, the Demog-ICD9 database, which includes demographic and medical diagnoses during hospitalization, with medical diagnoses drawn directly from the medical records. All diagnoses are classified according to the *International Classification of Diseases, 9th revision* (ICD-9). *Cardiovascular* and/or *renal morbidity* was defined as hospitalization for any cardiovascular or renal indication at the first cardiovascular hospitalization at the Soroka University Medical Center. The diagnoses codes captured the primary discharge diagnoses that were coded during hospitalization. Cardiovascular complications were further categorized into 4 subcategories according to type and severity, which 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 most serious diagnosis was chosen as the event for patients who were in >1 category for cardiovascular or renal disease. The exact ICD-9 codes for each subtype of cardiovascular and renal morbidity are presented in the Appendix, Supplementary Tables 1 and 2.

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

Study population

The study population was composed of singleton pregnancies of all of the women who delivered between the years 1988-2012. The study was conducted at Soroka University Medical Center, the sole hospital in the Negev, the southern region of Israel, which occupies 60% of the land of Israel, serving the entire population in this region, approximately 14.5% of the population in Israel.[21]

Thus, the study is based on a nonselective population data. Exclusion criteria from the study were patients with known cardiovascular (rheumatic heart disease unspecified: ICD-9 code 398.90, n = 60; other chronic pulmonary heart disease: ICD-9 code 416.8, n = 50) and renal disease (nephrotic syndrome with unspecified pathological lesion in kidney: ICD-9 code 581.9, n = 20; nephritis/nephritic acute or chronic glomerulonephritis not otherwise specified: ICD-9 code 583.9, n = 15) before or during the index pregnancy and patients with known congenital cardiac (congenital cardiovascular disorders of the mother: ICD 9 code 648.51, n = 179) or renal malformations (other specified congenital anomalies of kidney: ICD-9 code 753.3, n = 53). Women with missing data on key variables (lack of prenatal care: ICD-9 code v23.7, n = 23,505) were also excluded from the analysis.

Statistical analysis

Statistical analysis was performed with the SPSS software package (version 17; SPSS Inc, Chicago, IL). Statistical significance was calculated with the chi-square test for differences in qualitative variables and the Student *t* test for differences in continuous variables. The association between the number of previous events and the risk for subsequent atherosclerotic cardiovascular hospitalizations was evaluated with the chi-square 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, 99280 deliveries met the inclusion criteria; 1879 deliveries (1.9%) occurred in patients who had at least 1 previous stillbirth.

Table 1 summarizes the characteristics of patients with and without a diagnosis of stillbirth. Patients who experienced at least 1 stillbirth were significantly older and of higher parity than the comparison group. In addition, patients with a history of stillbirth had higher rates of other pregnancy complications such as SGA and placental abruption. Patients with a history of stillbirth had lower rates of gestational diabetes mellitus.

Table 2 presents a comparison of cardiovascular and renal hospitalizations during the follow-up period. Patients