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Placenta previa and long-term morbidity of the term offspring☆

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ABSTRACT

Objective: The long-term impact of placenta previa on term infants is unknown. We aimed to investigate whether abnormal placentation increases the risk for long-term morbidity of the term offspring.
Study design: A population-based cohort study compared the incidence of long-term hospitalizations up to the age of 18 due to cardiovascular, endocrine, neurological, hematological, respiratory and urinary morbidity of children born at term in pregnancies diagnosed with placenta previa and those without. Deliveries occurred between the years 1991–2013 in a tertiary medical center. Multiple pregnancies, and fetal congenital malformations were excluded. Kaplan–Meier survival curves were used to compare cumulative morbidity incidence over time. A multivariable generalized estimating equation (GEE) logistic regression model analysis was used to control for confounders and for maternal clusters.
Results: During the study period 233,123 term deliveries met the inclusion criteria; 0.2% (n = 502) of the children were born to mothers with placenta previa. During the follow-up period, children born to mothers with placenta previa did not have an increased risk for long-term cardiovascular, endocrine, hematological, neurological, respiratory, and urinary morbidity.
Conclusion: Term offsprings of mothers diagnosed with placenta previa do not appear to be at an increased risk for long-term morbidity up to the age of 18.

Introduction

Placenta previa, which refers to the presence of placental tissue covering the internal cervical os, occurs in roughly 4 per 1000 deliveries [1,2]. Reported risk factors include: previous placenta previa, previous cesarean delivery (CD), multiple gestation, multiparity, advanced maternal age, maternal smoking, and more [2–6]. Although relatively common, the pathogenesis of placenta previa remains largely speculative. Two major hypotheses dominate; one involves the possible presence of areas of suboptimal endometrium in different areas of the uterine cavity (due to previous surgery for example), which promote trophoblast implantation in the lower uterine cavity and cervical area [1,3,6,7]. The second hypothesis is based on placental response to reduced perfusion, which increases the likelihood that the placenta will encroach upon the cervical os. Several pregnancy complications have been associated with placenta previa, the most serious of which is placenta accreta [8]. Other well-documented immediate complications include severe bleeding, preterm delivery, fetal growth restriction and congenital anomalies [5]. Over time, neonatal morbidity rates in pregnancies complicated by placenta previa declined due to improved perinatal care, and evidently, the principal causes of neonatal morbidity and mortality are related to preterm delivery (which is still common), rather than growth restriction, hypoxia or anemia [9]. While the potentially devastating consequences of preterm delivery and growth restriction are well documented, the long-term impact of placenta previa on term infants was never systematically investigated. Infants born with growth-restriction, for example, are known to be at risk for significant long-term morbidity including not only growth abnormalities, but also coronary heart disease, hyperlipidemia, hypertension, and chronic kidney disease as adults [10–13].

In preterm survivors, long-term neurodevelopmental disability is the major cause of morbidity. In addition, chronic medical

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problems including respiratory abnormalities and poor growth are common in preterm children resulting in frequent hospitalizations. Preterm adults compared with those born full-term appear to have increases in insulin resistance and blood pressure, and a decrease in reproductive rate [14–18].

We aimed to investigate whether this is also true for infants born to women diagnosed with placenta previa, excluding pregnancies ending prematurely (<37 completed weeks of gestation). We hypothesize that since placenta previa may represent poor placentation and suboptimal intrauterine environment, it may impact on the child's future health.

Materials and methods

In this population-based cohort study we included all singleton pregnancies of women who delivered between January 1991 and December 2013. The study was conducted at the Soroka University Medical Center, the sole hospital in the Negev (southern Israel), which occupies 60% of the land of Israel, and is serving the entire population of the region (14.4% of Israel's population) [19]. Thus, the study is based on non-selective population data.

The institutional review board approved the study that has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (# SOR-0236-13 approved on November 20, 2013).

The primary exposure was a diagnosis of placenta previa during pregnancy. A diagnosis of placenta previa is routinely verified immediately prior to delivery by an ultrasound performed upon admission. Such a diagnosis includes complete, partial or marginal placenta previa as well as low-lying placenta (<20 mm from internal cervical os). Gestational age was determined using menstrual history and first trimester ultrasound. We excluded multiple pregnancies, preterm deliveries (occurring prior to 37 completed weeks of gestation), and fetuses with congenital malformations. A comparison was performed between children born at term to women diagnosed with placenta previa and those born at term without such diagnosis. Outcomes assessed included hospitalizations up to the age of 18 due to cardiovascular, endocrine, neurological, hematological, respiratory and urinary morbidity. This was defined as having one or more diagnosis from the list detailed in Supplement Table 1. Follow up terminated at the first hospitalization for each category of morbidity, or when hospitalization resulted in death, or when the child reached 18 years of age.

Data were collected from two databases that were cross-linked and merged: the computerized perinatal database of the obstetrics and gynecology department, and the computerized hospitalization database of the Soroka University Medical Center ("Demog-ICD9"). The perinatal database consists of information recorded immediately following delivery by an obstetrician. Medical secretaries routinely review the information prior to entering it into the database to insure its maximal completeness and accuracy. Coding is performed after assessing medical prenatal care records as well as routine hospital documents. The Demog-ICD9 database includes demographic information and ICD-9 codes for all medical diagnoses made during hospitalizations in the Soroka University Medical Center.

Statistical analysis

Statistical analysis was performed using the SPSS package 17 ed. (SPSS, Chicago, IL). Categorical data are shown in counts and percentages and the differences were assessed by chi-square for general association. The Student t test and Mann–Whitney U test were used for differences in continuous variables. Kaplan–Meier survival curves were used to compare cumulative morbidity incidences over time. The differences between the two morbidity curves were assessed using the log-rank test.

A multivariable generalized estimating equation (GEE) logistic regression model analysis was used to control for time-to-event, maternal age, and maternal clusters.

P value of <0.05 was considered statistically significant.

Results

During the study period 233,123 term deliveries met the inclusion criteria. Of those, 0.2% ($n = 502$) were diagnosed with placenta previa. Table 1 compares characteristics and outcomes of deliveries with and without a diagnosis of placenta previa. Pregnancies complicated with placenta previa were characterized by higher maternal age, higher parity, and the parturients were more likely to have had a previous CD compared with the comparison group (i.e. no placenta previa). The newborns were more likely to have been diagnosed with low birth weight (<2500 g) and less likely to weigh over 4000 g. No statistically significant difference was demonstrated in SGA (small for gestational age; weight < 5th percentile) or VLBW (very low birth weight) rates.

The long-term morbidity of the offsprings is presented in Table 2. Long-term respiratory morbidity necessitating hospitalization was evident in 5% of the placenta previa group and in 5.5% of the controls. This difference was not statistically significant. Other

Table 1
Pregnancy characteristics and delivery outcomes of children born at term to mothers with and without placenta previa.

	Placenta previa $n = 502$	No placenta previa $n = 232\,621$	Odds Rati (Confidence Interval)	*p* value
Maternal age at index birth (years ± SD)	32.6 ± 5.5	28.1 ± 5.7	–	<0.001
Parity at index pregnancy, (mean ± SD)	3.8 ± 2.5	3.4 ± 2.4	–	<0.001
Previous cesarean delivery (%)	27.3	12.0	2.7 (2.2–3.3)	<0.001
Mean gestational age at delivery (weeks ± SD)	38.07 ± 1.2	39.4 ± 1.2	–	<0.001
Gender (%)			0.995 (0.83–1.1)	0.955
Male	51.0	51.1		
Female	49.0	48.9		
Birthweight (g, mean ± SD)	3069.9 ± 403	3273.8 ± 438	–	<0.001
Birthweight				
SGA (%)	2.6	4.1	0.63(0.4–1.1)	0.09
<1500 g (%VLBW)	0	0.0001	–	0.77
<2500 g (%LBW)	7.2	2.7	2.78 (1.9–3.9)	
2500–3999 g (%)	90.8	92.1	–	<0.001
≥4000 g (%)	2.0	5.2	0.38 (0.2–0.7)	

SD – standard deviation, SGA – small for gestational age defined as the fifth percentile or less for the specific gestational age, VLBW – very low birth weight, LBW – low birth weight.