Prenatal exposure to gestational diabetes mellitus as an independent risk factor for long-term neuropsychiatric morbidity of the offspring

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BACKGROUND: The reported rates of gestational diabetes mellitus are constantly escalating and little is known about long-term complications in the offspring. Evidence from the field of epigenetics strongly advocates the need for research on the neuropsychiatric complications in offspring prenatally exposed to gestational diabetes mellitus.

OBJECTIVE: We sought to assess whether in utero exposure to gestational diabetes mellitus increases the risk of long-term neuropsychiatric morbidity in the offspring.

STUDY DESIGN: A population-based cohort study compared the incidence of hospitalizations due to neuropsychiatric disease between singletons exposed and unexposed to gestational diabetes mellitus. Deliveries occurred in the years 1991 through 2014 in a regional tertiary medical center. Perinatal deaths, multiple gestations, mothers with pregestational diabetes or lack of prenatal care, and children with congenital malformations were excluded from the study. A multivariate generalized estimating equation logistic regression model analysis was used to control for confounders and for maternal clusters.

RESULTS: During the study period 231,271 deliveries met the inclusion criteria; 5.4% of the births were to mothers diagnosed with gestational diabetes mellitus (n = 12,642), of these 4.3% had gestational diabetes type A_1 (n = 10,076) and 1.1% had gestational diabetes type A_2 (n = 2566). During the follow-up period, a significant linear association was noted between the severity of the gestational diabetes (no gestational diabetes, gestational diabetes mellitus A_1, gestational diabetes mellitus A_2) and neuropsychiatric disease of the offspring (1.02% vs 1.36% vs 1.68%, respectively, $P < .001$). A Kaplan-Meier curve demonstrated that children born to women with gestational diabetes mellitus had higher cumulative incidence of neuropsychiatric morbidity. Using a generalized estimating equation multivariable logistic regression model, controlling for time-to-event, maternal age, gestational age at delivery, maternal obesity, maternal preeclampsia and fertility treatments, maternal gestational diabetes mellitus was found to be an independent risk factor for long-term neuropsychiatric disease of the offspring (gestational diabetes mellitus A_1 [adjusted odds ratio, 1.83; 95% confidence interval, 1.53—2.19] and gestational diabetes mellitus A_2 [adjusted odds ratio, 1.64; 95% confidence interval, 1.18—2.27]). Within the limits of our database, our findings also point to a possible association between in utero exposure to gestational diabetes mellitus and autistic spectrum disorder of the offspring (adjusted odds ratio, 4.44; 95% confidence interval, 1.55—12.69), which was found significant also after controlling for time-to-event, maternal age, gestational age at delivery, and offspring weight at birth.

CONCLUSION: Exposure to maternal gestational diabetes mellitus is an independent risk factor for long-term neuropsychiatric morbidity in the offspring.

Key words: autistic disorder, gestational diabetes mellitus, long-term effects, neuropsychiatric disorders, offspring, prenatal exposure

Introduction

The reported rates of gestational diabetes mellitus (GDM), defined as glucose intolerance that begins or is first recognized during pregnancy,[1] are constantly escalating. GDM occurs in approximately 7% of pregnancies and this number is expected to double due to the increasing prevalence of obesity and new diagnostic criteria.[2,3]

Most of the current literature has addressed adverse pregnancy outcomes such as macrosomia, shoulder dystocia, and preeclampsia,[4] and short-term neonatal complications such as hypoglycemia, hyperbilirubinemia, and respiratory distress syndrome.[5,6] Scarce information exists regarding long-term complications of the offspring. Recent studies have shown that in utero exposure to GDM is associated with a higher blood pressure and a predisposition to obesity and metabolic syndrome.[7,8] Data regarding other long-term complications such as neuropsychiatric morbidity are not well established, and evidence from the field of epigenetics strongly advocates the need for such research.[9-13]

In contrast to the relative lack of information on long-term outcomes of GDM, more is known about long-term morbidity in children exposed in utero to pre-GDM. Some studies have addressed glycemic regulation or lipid metabolism as a common pathology in both GDM and pregestational diabetes. Two such studies found significantly lower intelligence quotient and worse motor proficiency in children whose mothers showed higher levels of lipid metabolism.[14,15] These studies suggest an association between neuropsychiatric morbidity and in utero exposure to any type of diabetes.

Although cohort studies have shown evidence of this associations between neuropsychiatric morbidity and maternal diabetes,[16-19] many of these studies lacked details regarding GDM exposure. The objective of the present population-based study is to investigate whether in utero exposure to GDM is an independent risk factor for long-term

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TABLE 1
Cohort characteristics by exposure to maternal gestational diabetes mellitus

Characteristics	No GDM n = 218,629	GDM A_1 n = 10,076	GDM A_2 n = 2566	*P* value[a]
Maternal age, y, mean ± SD	27.93 ± 6	32.16 ± 6	33.82 ± 6	<.001
Birth order, %				<.001
1	23.9	20.7	12.9	
2–4	51.4	44.7	42.1	
≥5	24.7	34.5	45.0	
Gender of offspring, %				<.001
Male	51.1	52.8	52.5	
Female	48.9	47.2	47.5	
Gestational age at birth, wk, mean ± SD	39.09 ± 2	38.75 ± 2	37.6 ± 2	<.001
Maternal obesity, %	1.0	1.1	3.7	<.001
Obesity of offspring, %	0.2	0.5	0.8	<.001

GDM, gestational diabetes mellitus.

[a] Data evaluated with Pearson χ^2 test.

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neuropsychiatric morbidity in the offspring. The contribution of the current study is its specific focus on GDM, which is a far more common in utero exposure than pregestational diabetes.[20]

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, which serves the entire population in this region of Israel. Thus, the study is based on a nonselective population data. The institutional review board (in accordance with the Declaration of Helsinki) approved the study (no. SOR-0236-13 approved November 2013).

Study population

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

TABLE 2
Incidence rates for disease-specific hospitalization

	Cohort[a]			
Neuropsychiatric morbidity	No GDM n = 218,629	GDM A_1 n = 10,076	GDM A_2 n = 2566	*P* value[b]
Autistic spectrum disorders, n = 32	27 (0.01)	3 (0.02)	2 (0.07)	.007
Eating disorders, n = 486	437 (0.19)	42 (0.42)	7 (0.27)	<.001
Obstructive sleep apnea, n = 1347	1259 (0.58)	60 (0.60)	28 (1.09)	.003
Epilepsy or infantile seizures, n = 431	399 (0.18)	28 (0.27)	4 (0.16)	.089
Cerebral palsy, n = 138	130 (0.06)	6 (0.06)	2 (0.08)	.930
Total neuropsychiatric hospitalization, n = 2409	2228 (1.02)	138 (1.36)	43 (1.68)	<.001

GDM, gestational diabetes mellitus.

[a] Data are no. (%) unless otherwise indicated; [b] Data evaluated with χ^2 test for trends.

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Study design

We conducted a population-based cohort study. The primary exposure was defined as in utero exposure to either GDM A_1, defined as GDM controlled by diet and exercise, or GDM A_2, defined as GDM requiring insulin or oral hypoglycemic agents.[21] Children who were not exposed prenatally to GDM comprised the comparison group. The main outcome was defined as neuropsychiatric morbidity of the offspring that was documented in the hospitalization records. All encounters with the hospital were analyzed so that multiple neuropsychiatric 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.

Neuropsychiatric morbidity was defined as autistic spectrum disorder (ASD), disorders of eating, cerebral palsy (CP), obstructive sleep apnea (OSA), epilepsy, or infantile spasms (Supplemental Table 1). Autism spectrum disorder, previously known as the pervasive developmental disorders, includes a group of neurodevelopmental syndromes characterized by a wide range of impairments in social communication and restricted and repetitive behaviors.[22]

These neuropsychiatric morbidities were chosen because they cover both a wide range of clinical presentation and a wide range of topographic locations in the brain.[23-25] Most importantly, these conditions were selected due to the associations that have already been found between neuropsychiatric conditions and in utero exposure to GDM.[16,17,26]

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