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Gestational Diabetes and risk of cryptorchidism and hypospadias

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To the Editor

Gestational diabetes mellitus is the onset of glucose intolerance during pregnancy. Pregnancies complicated with diabetes are at increased risk for many maternal and fetal complications, including cesarean delivery, macrosomia, neonatal hypoglycemia, stillbirth, shoulder dystocia and congenital malformations.¹ However, few epidemiologic studies have evaluated associations between gestational diabetes and risk of cryptorchidism (failure of one or both testicles to descend into the scrotum) or hypospadias (urethral opening on the ventral side of the penis). Shared risk factors for cryptorchidism and hypospadias include intrauterine growth restriction (small for gestational age), low birth weight, preterm delivery and concomitant genital abnormalities. These two defects are commonly associated with testicular cancer risk in adult life²; thus, gaining a better understanding of their etiology may provide new means of identifying men at risk of developing testicular cancer.

In Israel, universal gestational diabetes screening is conducted in accordance with American Diabetes Association guidelines, and almost 90% of the pregnancies in the Maccabi Healthcare Services healthcare maintenance organization (HMO) between 2000 and 2010 were screened.³ Using administrative and clinical data, we conducted a population-based retrospective cohort study in this HMO to evaluate the association between gestational diabetes and two common male congenital anomalies, cryptorchidism and hypospadias, in male offspring.

Details of the study methods and characteristics of the study cohort are provided in the eAppendix and the eTable. Associations between gestational diabetes and the risk of cryptorchidism and hypospadias were estimated separately, using unconditional logistic regression analyses adjusting for year of birth, maternal age at oral glucose tolerance test, maternal birthplace, socioeconomic status, history of infertility, use of in vitro fertilization, and history of polycystic ovarian syndrome.

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The study included 150,144 mother-infant pairs. The frequency of diabetes was 40.3 per 1,000 pregnancies; 3,649 cases of cryptorchidism (24.2 per 1,000 male births) and 2,342 cases of hypospadias (15.6 per 1,000 male births) were identified. Maternal diabetes was not associated with cryptorchidism (odds ratio = 0.93 [95% confidence interval = 0.77–1.10] or hypospadias (0.83 [0.66–1.04]) (Table). Furthermore, among male children of mothers with gestational diabetes (n=5,497), neither the number of abnormal glucose-tolerance-test values or the use of insulin during pregnancy was associated with the risk of either anomaly (Table).

The current retrospective cohort study does not support an association of gestational diabetes with cryptorchidism or hypospadias. Consistent with our study, a Swedish registry-based study (1973–1982) reported no association between gestational diabetes and cryptorchidism.⁴ In contrast, one case-control study reported a positive association between gestational diabetes, diagnosed based on medical record reports of diet-controlled diabetes or abnormal glucose tolerance test, and cryptorchidism.⁵ However, that study was based on relatively small numbers (125 cases), and only 30% of cases and 22% of controls had a glucose tolerance test during pregnancy. In the current study, all pregnancies included in the analysis were screened for GDM and almost 90% of pregnancies in the MHS HMO during the study time period were screened.³ We are aware of three previous studies that have evaluated the association of gestational diabetes with hypospadias and, consistent with our results, all reported a null association.^{6–8}

An important strength of the current study is the direct ascertainment of gestational diabetes based on laboratory glucose tolerance tests, avoiding issues concerning self-report and inconsistent diagnostic criteria. Additional strengths of the study include its large size, retrospective cohort design, and the systematic and comprehensive collection of personal data. The study adds persuasive evidence that gestational diabetes is not associated with risk of cryptorchidism or hypospadias.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Risk of cryptorchidism or hypospadias in male children of 150,144 mothers who were tested for gestational diabetes mellitus between 1 January 1999 and 31 December 2008, Maccabi Healthcare Services.

Table

Clinical Characteristics	Cryptorchidism			Hypospadias		
	Yes No. (%)	No No. (%)	OR (95% CI) ^a	Yes No. (%)	No No. (%)	OR (95% CI) ^a
Gestational diabetes mellitus						
No ^b	3,518 (96.4)	140,794 (96.1)	1.00	2,265 (96.7)	142,047 (96.1)	1.00
Yes	131 (3.6)	5,701 (3.9)	0.93 (0.77–1.10)	77 (3.3)	5,755 (3.9)	0.83 (0.65–1.04)
Number of abnormal Oral Glucose Tolerance Tests (OGTT) among women diagnosed with gestational diabetes ^c						
2 ^b	82 (66.7)	3,788 (70.5)	1.00	59 (79.7)	3,811 (70.3)	1.00
3 or 4	41 (33.3)	1,586 (29.5)	1.18 (0.80–1.72)	15 (20.3)	1,612 (29.7)	0.61 (0.34–1.08)
Insulin use among women diagnosed with gestational diabetes ^c						
No ^b	115 (87.8)	5,010 (87.9)	1.00	69 (89.6)	5,056 (87.9)	1.00
Yes	16 (12.2)	691 (12.1)	1.04 (0.61–1.77)	8 (10.4)	699 (12.1)	0.91 (0.43–1.91)

^a adjusted for year of birth, and the following characteristics of the mother: birthplace, socioeconomic status, age at GDM testing, history of infertility treatment, use of in vitro fertilization treatment, and history of polycystic ovarian syndrome.

^b Reference category

^c GDM cases that were identified based on insulin therapy alone were excluded (n=335).