The relationship between fetal renal size and function in early childhood within the NextGen birth cohort

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BACKGROUND

The global prevalence of youth-onset type 2 diabetes (T2D) has increased significantly over the last 20 years, with the greatest impact on youth of racial minorities and/or poor socioeconomic settings. If current trends continue, there is estimated to be a five-fold increase in disease prevalence in Canadian youth by the year 2030. Youth of First Nations heritage have the greatest burden of illness of youth-onset T2D compared to other ethnic groups. Youth-onset T2D commonly targets the kidneys early on in the disease, making screening for nephropathy, starting at the time of diagnosis, of utmost importance. To detect potential disease-related nephropathy, regular screening guidelines include measurements of blood pressure and urine albumin-creatinine ratios (ACRs) at the time of T2D diagnosis and then annually. Maternal diabetes in pregnancy is known to be a major risk factor for the development of youth-onset T2D and exposure to T2D in utero shortens the length of time before the development of T2D in children. While the exact pathophysiology of this earlier age at diagnosis remains unclear, it raises suspicion about the potential fetal origins of childhood disease. However, the relationship between in utero exposure to diabetes mellitus and fetal kidney size remains unknown.

OBJECTIVE

To determine the relationship between mid-gestation fetal renal size and albuminuria in early childhood.

METHODS

This was a historic cohort study of offspring from the NextGeneration longitudinal birth cohort (NextGen cohort), which is the largest prospective birth cohort of First Nations children with diabetes in Canada. We included offspring of mothers with T2D born since 2005 (to coincide with earliest year of stored fetal ultrasound images) until the latest available date (2018). All children with stored ACR measurements taken between age 1 and 6 were eligible for inclusion. Subjects were excluded if there were no stored fetal ultrasound images available for review from a mid- gestation anatomy scan performed between 18 to 24 weeks' gestation. Subjects were also excluded if they were born outside of Manitoba. Because of the small numbers of mothers with GDM or healthy controls in the larger birth cohort, the analysis was restricted to offspring exposed to T2D in utero only. Post-processing review of stored fetal ultrasound images was performed by two blinded, independent observers using a standardized technique. From routine transverse images of the fetal abdomen, the width and thickness of the fetal kidneys were measured. Fetal renal width and thickness were recorded as continuous measurements separately and as a mean when both kidneys were visible. For each fetus, the mean renal diameter overall was also calculated by averaging the width and thickness, given that the dimensions are equivalent in both planes up to 25 weeks' gestation. Additional fetal biometry (head circumference, biparietal diameter, abdominal circumference, femur length, and estimated fetal weight) from mid-gestation were also included to evaluate their relation to childhood renal function. Fetal ultrasound data were then linked to existing maternal, neonatal, and childhood variables within the NextGen data repository.

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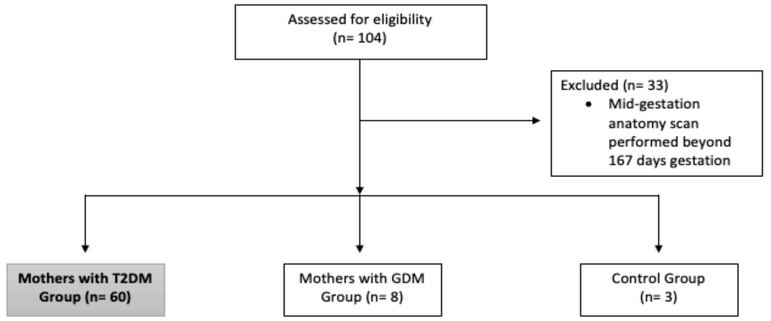

Figure 1. Flow diagram.

RESULTS

There were 104 offspring of mothers with T2D with stored ACRs eligible for this study. 33 offspring were excluded as they did not have a mid-gestation anatomy scan available for review. Of the remaining 71 mother-child dyads, analysis was restricted to the 60 children with exposure to maternal T2D in utero. Median kidney width and thickness were 10.8 mm [IQR 9.2-12.3] and 11.2 [IQR 9.8-12.5], and the mean kidney diameter was 11.5 mm (SD 2.8). Good inter-observer reliability was achieved (r=0.792; p<0.0001).
At the time of delivery, mean maternal age was 25.1 years (SD 7.0) and most were multiparas (68.3%). The mean pre-pregnancy weight was 77.4 kg (SD 19.3); however in the third trimester, mean weight was 90.9 kg (SD 20.5), with over half of mothers classified as obese (51.7%) compared to 38.3% of normal weight, and 10% that were considered lean. The average HbA1C value was 7.9% (SD 2.1). For the 30 mothers with available data about smoking status, 70% were smokers. The mean gestational age at birth was 36 weeks 3 days gestation (SD 1w6d). The median birthweight was 3538 grams [IQR 2821 to 3937]. 47.2% of deliveries were spontaneous vaginal delivery and another 47.2% were Cesarean section. Almost 1 in 10 children (9.6%) in the NextGen cohort included in this analysis had abnormal ACRs by age 6 years. However, there was no obvious difference in fetal kidney size at mid-gestation between those with normal versus abnormal ACRs (11.4 mm (SD 2.8) versus 11.8 mm (SD 3.2); p=0.791), nor any direct correlation between renal diameter and continuous ACRs (r=0.102; p=0.356). There was no difference in fetal renal size between males and females (11.1 mm [IQR 9.9 to 12.5] for males and 11.0 mm [IQR 9.8 to 11.7] for females; p=0.961. Regarding HNF-1α status, over half of the children were heterozygous (S/G genotype) (51.7%), while 40% were wild-type (G/G), and only 8.3% were homozygous for the S/S affected variant. There was also no statistically significant difference in kidney size by HNF-1α genotype, but there was a trend towards smaller kidneys in those with the S/S variant, although numbers in that group were small: median kidney diameter for the wild-type (G/G genotype) was 11.1 mm [IQR 10.6 to 12.1], 11.5 mm [IQR 10.8 to 12.6] for heterozygous (S/G genotype), and 10.7 mm [IQR 9.6 to 11.9] for affected/ variant (S/S genotype), p=0.054 .

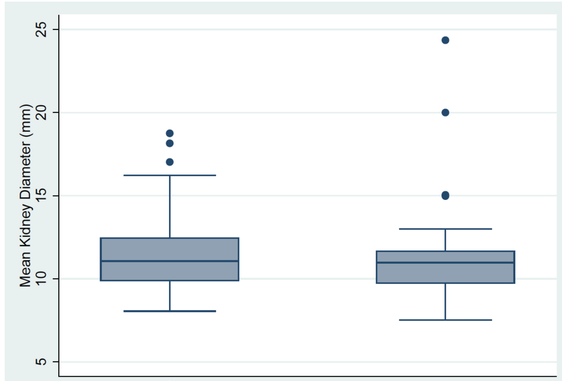

Figure 2. Mean kidney diameter by ACR measurement (normal= 0/ abnormal =1).

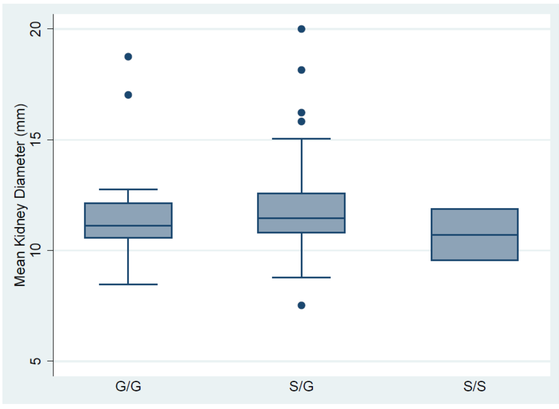

Figure 3. Mean kidney diameter by HNF-1α genotype (Wildtype (G/G); Heterozygous (S/G); Variant (S/S))

CONCLUSION

While there was no obvious relationship between fetal renal size and albuminuria in early childhood, **~1 in 10 children** at high-risk for future T2D and renal disease had **abnormal ACRs already by age 6 years**. There was also a trend towards smaller renal size amongst those with the S/S variant of the HNF-1α gene. Ongoing work is urgently needed to identify early predictors of childhood renal disease and develop effective prevention strategies to improve outcomes.