


ORIGINAL ARTICLE

Normal foetal kidney volume in offspring of women treated for gestational diabetes

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Abstract

Aims: The worldwide prevalence of gestational diabetes mellitus (GDM) is increasing. Studies in rodent models indicate that hyperglycaemia during pregnancy alters kidney development, yet few studies have examined if this is so in humans. The objective of this study was to evaluate the association of treated GDM with foetal kidney size.

Materials and Methods: Participants were recruited from an Australian tertiary hospital, and clinical data were collected from women without GDM and women diagnosed and treated for GDM and their offspring. Participants underwent an obstetric ultrasound at 32-34 weeks gestation for foetal biometry and foetal kidney volume measurement.

Results: Sixty-four non-GDM and 64 GDM women participated in the study. Thirty percent of GDM women were diagnosed with fasting hyperglycaemia, while 89%

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had an elevated 2-hour glucose level. Maternal age, weight and body mass index were similar in women with and without GDM. Estimated foetal weight, foetal kidney dimensions, total foetal kidney volume and birth weight were similar in offspring of women with and without GDM.

Conclusions: We conclude that a period of mild hyperglycaemia prior to diagnosis of GDM and treatment initiation, which coincides with a period of rapid nephron formation and kidney growth, does not alter kidney size at 32-34 weeks gestation.

KEYWORDS

foetal kidney volume, gestational diabetes, kidney development

1 | INTRODUCTION

The prevalence of gestational diabetes mellitus (GDM), defined as any degree of glucose intolerance with onset or first recognition during pregnancy,¹ is increasing,^{2,3} and affects up to 20% of pregnancies. Prevalence rates vary due to local screening practice and diagnostic criteria as well as population characteristics such as obesity, maternal age, Type 2 diabetes and ethnicity.⁴ GDM can have short- and long-term implications for both maternal and infant health.^{5,6}

In humans, kidney development begins around week 5 of gestation with the first nephrons formed at gestational week 9. Nephrogenesis continues until approximately 34-36 weeks gestation,⁷ generating the entire complement of nephrons for life. There is evidence that low nephron number is associated with renal disease in adulthood,⁸⁻¹¹ with a multitude of animal studies identifying that a 20%-30% reduction in nephron number is important.¹²⁻¹⁵ Precise and accurate estimation of nephron number by noninvasive methods is not currently feasible, although a direct relation between foetal weight and kidney size,¹⁶ birth weight and kidney function,^{17,18} and between kidney mass and total nephron number^{19,20} has been reported. As renal mass is proportional to renal volume in infants, kidney volume is currently considered a surrogate measure of nephron number.^{19,21} This concept is supported by findings that smaller foetal kidney size is associated with lower kidney function in school-aged children,²² that both low birth weight and Indigenous offspring, who are at increased risk of renal disease, present with lower kidney volumes at birth,²³⁻²⁵ and that lower childhood kidney volume is associated with reduced kidney function.²⁶⁻²⁸

Evidence from animal studies indicates that maternal hyperglycaemia can be detrimental to renal development and kidney function in exposed offspring.^{12,29,30} GDM is usually detected in mid-pregnancy (typically at 24-28 weeks gestation) by routine population screening.³¹ The period between onset, and diagnosis and treatment, coincides with a period of rapid nephron formation and kidney growth.^{32,33} In humans, renal dysfunction and disease have been reported in adults whose mothers had Type 1 or Type 2 diabetes.³⁴⁻³⁷ Despite the high prevalence of GDM, only a handful of studies have examined kidney development or renal function in offspring of women with GDM.

Available data from reports of kidney volume in offspring of mothers with GDM are extremely limited and contradictory. While one study found normal foetal kidney volume in diabetic pregnancies (pregestational diabetes and GDM pregnancies grouped together),³⁸ another found increased foetal kidney volume in pregnancies of women with GDM.³⁹ A third preliminary study reported reduced renal cortical volume and increased albumin excretion in 3-year-old children whose mothers had GDM, taken to suggest a reduction in nephron endowment and glomerular impairment.⁴⁰

Overall, evidence for the extent to which GDM affects developing human kidneys is not robust. It is unclear what effect a period of hyperglycaemia has on foetal kidney development and growth, and subsequent renal physiology and function. While treatment of GDM to control glucose levels can reduce the risk of some adverse perinatal and infant outcomes,⁴¹⁻⁴³ evidence of treatment benefits are often unsupported,^{43,44} and there is uncertainty regarding optimal diagnostic thresholds and optimal glycemic targets.⁴⁵ The objective of this study was to evaluate the association of treated GDM with foetal kidney size in late pregnancy.

2 | MATERIALS AND METHODS

2.1 | Study design and subject recruitment

This study was conducted between June 2013 and August 2016 at Monash Medical Centre, a large public university teaching hospital in metropolitan Melbourne, Australia, with over 4000 births annually. All procedures were approved by the Monash University Human Research Ethics Committee and the Monash Health Human Research Ethics Committee (13041B). Academic research staff attended on average one routine pregnancy clinic and one diabetic pregnancy clinic per week during the recruitment period. Four hundred and thirty-five women with a singleton pregnancy, aged 18-40 years and who spoke English were approached by academic research staff. Written informed consent was obtained from 169 women to measure foetal kidney volume at 32-34 weeks gestation by ultrasound. Consent was also sought to collect maternal information including: body weight and body mass index (BMI) at hospital booking (first antenatal appointment), age, self-reported ethnicity, parity, GDM test

results and treatment, pre-existing medical and obstetric conditions (eg pregnancy-induced hypertension, thyroid disorder), birth and neonatal outcomes (gestational age from early ultrasound estimates and date of last menstrual period, mode of birth, birth weight, birth centile, and 1 and 5 minute Apgar scores).

Of the 169 women recruited, 64 women without GDM and 64 women diagnosed with GDM participated. Overall, 24% (n = 41/169) of women enrolled in the study did not have an ultrasound at 32-34 weeks, most often due to scheduling issues. A summary of participant participation and data collection is presented in Figure 1. Women with pre-existing diabetes were excluded. No women had renal anomalies or kidney disease.

Gestational diabetes mellitus was diagnosed by a routine 75 g oral glucose tolerance test (OGTT) at 24-28 weeks gestation if fasting plasma glucose was ≥ 5.5 mmol/L and/or 2-hour plasma glucose was ≥ 8.0 mmol/L.⁴⁶ One abnormal value was sufficient for diagnosis. Women with normal OGTT values were considered not to have diabetes. Women with and without GDM received routine antenatal care. In addition to routine antenatal care, women diagnosed with GDM received specialist support for glucose monitoring, diet and exercise and were made aware of the risks associated with GDM. They were provided information on home glucose monitoring to be performed on 3-4 occasions per day. Women attended frequent clinic review with a diabetes physician and were typically seen every 1-2 weeks until birth, dependent on clinical indication. Insulin therapy was commenced if women reported more than one in three home postprandial blood glucose readings per day > 7.0 mmol/L or fasting blood glucose levels > 5.5 mmol/L (GDM-Insulin n = 24, 32%).⁴⁷

2.2 | Obstetric ultrasound

High-resolution obstetric ultrasound imaging was performed between 32 and 34 weeks gestation by qualified sonographers using a Philips iU22 xMatrix ultrasound system. As per standard Australian

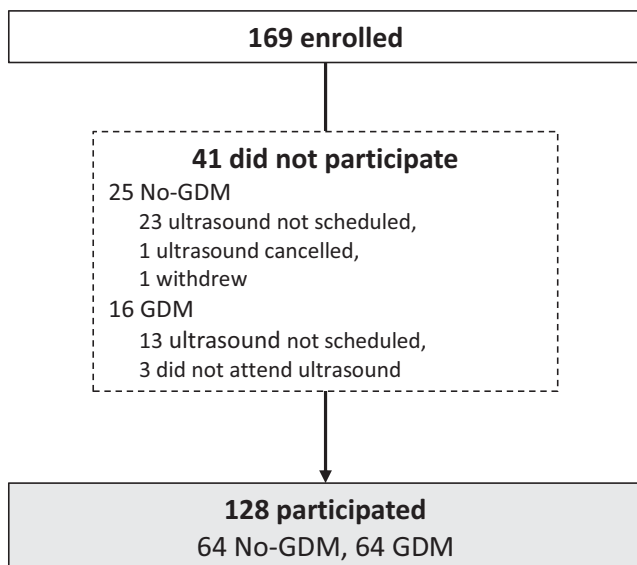


FIGURE 1 Participant flow diagram

practices, estimated foetal weight (EFW) was calculated from measurements of bi-parietal diameter, head circumference, abdominal circumference and femur length (Hadlock IV).⁴⁸ Umbilical artery pulsatility index, middle cerebral artery pulsatility index and amniotic fluid index were also recorded. Right and left foetal kidney dimensions (length, width [mediolateral diameter] and depth [anteroposterior diameter]) were measured (intra-observer variability 4.4%). Foetal kidney volume was calculated as the approximation of a prolate ellipsoid (volume = length \times width \times depth \times 0.523) and total (combined left and right) kidney volume determined.³⁸

2.3 | Statistical analyses

We considered a 20% difference in foetal kidney volume to be biologically relevant. Prior to the present study, a sample size calculation based on published values for male and female foetal kidney volume in late pregnancy (>25 weeks gestation)³⁸ was conducted. We calculated that 44 female and 54 male participants were required to detect a 20% difference in foetal kidney volume between groups, respectively. Power calculations conducted a posteriori on the kidney volume measurements obtained in the present study indicated a sample size of n = 50 in both groups was sufficient to detect a 20% difference ($1 - \beta = 0.8$). The 64 participants in each group were powered to 0.89 to detect a 20% difference in foetal kidney volume.

Data were analysed using STATA 15 statistical software.⁴⁹ Data were initially tested for normality using Shapiro-Wilk tests. Descriptive statistics were used to compare maternal and offspring characteristics of normal and GDM pregnancies: Wilcoxon rank-sum test or independent-samples t test was used to compare means, and chi-square test or test of proportions were used to compare proportions, as appropriate. To assess the role of GDM treatment type (diet and exercise alone, or diet and exercise with insulin therapy) as an indication of glycemic control on maternal, foetal and birth characteristics ANOVA with Tukey's post hoc test or Kruskal-Wallis rank test with Dunn's multiple comparisons test to compare means, or chi-square test to compare proportions were used as appropriate. Ultrasounds were performed slightly earlier in women receiving insulin therapy; analyses of foetal characteristics between No-GDM, GDM-Diet & Exercise and GDM-Insulin were therefore adjusted for gestational age using ANCOVA with Tukey's post hoc test. Unadjusted linear regressions were performed to assess relationships between total foetal kidney volume and maternal and foetal characteristics. Multiple regression analysis was also performed, adjusting for relevant potential confounders identified in the above group and correlation analyses. Multicollinearity was checked using variance inflation factor. $P < .05$ indicates statistical significance.

3 | RESULTS

3.1 | Maternal characteristics

Maternal characteristics of the total study cohort are presented in Table 1. As expected, women with GDM had significantly higher fasting and 2-hour glucose levels at their routine OGTT at 24-28 weeks

TABLE 1 Maternal characteristics and medical/obstetric complications

	No-GDM (n = 64)	GDM (n = 64)	P ^a	GDM-Diet & Exercise (n = 42)	GDM-Insulin (n = 22)	P ^b
Maternal characteristics						
OGTT fasting glucose, mmol/L	4.30 (0.32)	4.84 (0.71)	<.0001	4.62 (0.60)	5.28 (0.72)	<.0001 ^{†,‡,§}
OGTT 2-h glucose, mmol/L	5.69 (1.17)	8.84 (1.48)	<.0001	8.73 (1.23)	9.06 (1.89)	<.0001 ^{†,‡,§}
Weight at hospital booking, kg	66.4 (14.4)	65.3 (18.1)	.38	63.0 (11.5)	70.2 (26.2)	.23
BMI at hospital booking, kg/m ²	24.23 (4.5)	24.9 (6.5)	.90	24.2 (4.0)	26.5 (9.5)	.22
Age at conception, y	31.3 (4.5)	31.4 (4.7)	.62	31.9 (4.0)	30.1 (5.6)	.30
Nulliparous, n (%)	27 (42.2)	34 (53.1)	.22	21 (50.0)	13 (59.1)	.35
Caucasian ethnicity, n (%)	34 (53.1)	16 (25.0)	.001	12 (28.6)	4 (18.1)	.004
Maternal medical and obstetric complications						
History of GDM, n (%)	2 (3.1)	2 (3.1)	1.0	1 (2.4)	1 (4.5)	–
Pre-eclampsia, n (%)	2 (3.1)	1 (1.6)	–	1 (2.4)	0	–
Pregnancy-induced hypertension, n (%)	1 (1.6)	0	–	0	0	–
Pre-existing hypertension, n (%)	1 (1.6)	2 (3.4)	–	1 (2.4)	1 (4.5)	–
Polyhydramnios, n (%)	1 (1.6)	1 (1.6)	–	1 (2.4)	0	–
Polycystic ovarian syndrome, n (%)	2 (3.1)	1 (1.6)	–	1 (2.4)	0	–
Thyroid disorder, n (%)	8 (12.5)	4 (6.3)	.74	3 (7.1)	0	–

Note: Values are mean (SD) except where indicated otherwise.

Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test.

‘–’ indicates insufficient observations for analysis.

^aData analysed by Wilcoxon rank-sum test, independent-samples *t* test or chi-square test.

^bData analysed by one-way ANOVA with Tukey's post hoc test or chi-square test.

Bold values represent statistical significance.

[†] $P_{ANOVA} < .05$, No-GDM vs GDM-Diet & Exercise.

[‡] $P_{ANOVA} < .05$, No-GDM vs GDM-Insulin.

[§] $P_{ANOVA} < .05$, GDM-Diet & Exercise vs GDM-Insulin.

gestation as compared to nondiabetic women. Only 30% of GDM women (n = 19/64) were diagnosed with fasting hyperglycaemia; thus, the mean fasting glucose level for GDM women was below the diagnostic threshold. Eighty-nine percent (n = 57/64) had an elevated 2-hour glucose level (one abnormal OGTT value was deemed sufficient for diagnosis). There were no differences in maternal weight, BMI, age or parity between women with and without GDM, although fewer women with GDM were Caucasian. Overall, 91% of non-Caucasian women were of South-Asian, Southeast-Asian or East-Asian ethnicity. Previous GDM, pre-existing medical conditions and obstetric complications were uncommon and are presented in Table 1.

Comparison of maternal characteristics among GDM women requiring insulin therapy (GDM-Insulin; n = 22, 34%) to GDM women treated by diet and exercise alone (GDM-Diet & Exercise; n = 42, 66%) identified that women requiring insulin had higher fasting and 2-hour glucose levels during the OGTT (Table 1). Other maternal characteristics did not differ by treatment modality.

3.2 | Foetal biometry and foetal kidney size at 32-34 weeks

Foetal characteristics as measured by obstetric ultrasound at 32-34 weeks gestation are presented in Table 2. Foetal biometry, amniotic fluid index and umbilical artery pulsatility index were

similar among fetuses of women with and without GDM, as was gestational age at ultrasound (P = .25). Mean values of foetal middle cerebral artery pulsatility index were lower in GDM pregnancies, although all values were within the normal range. Left and right foetal kidney dimensions and volumes were similar in fetuses of pregnant women with and without GDM. There was no difference in total foetal kidney volume between groups, including after adjustment for EFW or foetal abdominal circumference. Estimated foetal weight (P = .18) and total kidney volume (P = .21) did not differ by sex.

Biometry and kidney size in fetuses of women with GDM by treatment method are also presented in Table 2. Ultrasounds were performed on average half a week earlier in GDM women requiring insulin therapy; analyses were therefore adjusted for gestational age. Middle cerebral artery pulsatility index was lower in GDM women treated by diet and exercise alone compared to nondiabetic pregnancies. All other biometry and kidney measurements were similar in fetuses of GDM women, irrespective of maternal treatment.

3.3 | Associations between total foetal kidney volume and maternal and foetal characteristics

Unadjusted regression coefficients for the entire sample are presented in Table 3. Maternal OGTT glucose levels were not associated

TABLE 2 Foetal biometry and foetal kidney size

	No-GDM (n = 64)	GDM (n = 64)	P ^a	GDM-Diet & Exercise (n = 42)	GDM-Insulin (n = 22)	P ^b
Foetal biometry						
Gestational age, wk	32.9 (0.7)	32.6 (0.7)	.25	32.9 (0.7)	32.4 (0.5)	.01 ^{‡,§}
Estimated foetal weight (EFW), g	2158.0 (248.5)	2093.2 (277.3)	.17	2154.0 (248.2)	1993.2 (234.4)	.27
EFW percentile, median (IQR)	55 (39-76)	45 (25-82)	.29	50 (26-83)	38 (23-62)	.23
Abdominal circumference (AC), cm	29.5 (1.4)	29.1 (1.7)	.17	29.5 (1.5)	28.4 (1.8)	.14
Amniotic fluid index	16.0 (3.7)	15.1 (3.8)	.09	15.4 (3.7)	14.6 (4.0)	.20
Umbilical artery pulsatility index	1.01 (0.28)	1.04 (0.37)	.76	1.04 (0.41)	1.04 (0.24)	.62
Middle cerebral artery pulsatility index	2.13 (0.40)	1.95 (0.33)	.007	1.93 (0.31)	1.99 (0.37)	.02[†]
Foetal kidney dimensions and volumes						
Right kidney length, cm	4.07 (0.53)	3.98 (0.55)	.55	4.06 (0.59)	3.89 (0.42)	.47
Right kidney width, cm	2.32 (0.38)	2.25 (0.37)	.24	2.26 (0.33)	2.23 (0.32)	.41
Right kidney depth, cm	2.24 (0.28)	2.17 (0.38)	.30	2.19 (0.38)	2.11 (0.48)	.31
Right kidney volume, cm ³	11.42 (4.31)	10.48 (4.02)	.20	10.78 (3.98)	9.96 (4.11)	.35
Left kidney length, cm	3.93 (0.48)	3.98 (0.44)	.31	4.01 (0.44)	4.00 (0.38)	.63
Left kidney width, cm	2.24 (0.37)	2.28 (0.39)	.43	2.16 (0.39)	2.24 (0.32)	.71
Left kidney depth, cm	2.18 (0.30)	2.19 (0.32)	.92	2.19 (0.34)	2.18 (0.30)	.89
Left kidney volume, cm ³	10.25 (3.43)	10.12 (3.50)	.80	10.17 (3.77)	10.00 (3.14)	.97
Total kidney volume, cm ³	21.28 (7.58)	20.47 (7.26)	.52	21.09 (7.22)	18.98 (7.52)	.79
Total kidney volume: EFW ratio (cm ³ /kg)	9.96 (3.38)	9.83 (3.45)	.84	9.66 (3.21)	10.38 (3.24)	.96
Total kidney volume: AC ratio (cm ³ /cm)	0.72 (0.25)	0.70 (0.24)	.78	0.71 (0.24)	0.73 (0.24)	.94

Note: Values are mean (SD) except where indicated otherwise.

^aData analysed by Wilcoxon rank-sum test or independent-samples *t* test.

^bData analysed by ANCOVA with Tukey's post hoc test, adjusting for gestational age.

Bold values represent statistical significance.

[†] $P_{ANOVA} < .05$, No-GDM vs GDM-Diet & Exercise.

[‡] $P_{ANOVA} < .05$, No-GDM vs GDM-Insulin.

[§] $P_{ANOVA} < .05$, GDM-Diet & Exercise vs GDM-Insulin.

with total foetal kidney volume. Kidney volume was positively associated with maternal Caucasian ethnicity, parity and foetal biometry measures. Multivariable regression analysis was performed relating total foetal kidney volume to maternal OGTT glucose levels and adjusting for maternal Caucasian ethnicity, parity and ultrasound-estimated foetal weight ($R^2 = .089$, $P = .006$, Table 4). Estimated foetal weight had a significant positive regression coefficient ($\beta = 0.210$, $P = .02$). Maternal characteristics did not contribute to the model.

3.4 | Birth outcomes

Birth outcomes are presented in Table 5. Birth weight trended lower in neonates of women with GDM ($P = .07$); women with GDM gave birth approximately 3-4 days earlier than nondiabetic women. There were no differences in the rate of labour induction ($P = .59$) or caesarean births between groups. The proportion of neonates with birth weights above the 90th centile (large for gestational age; LGA) or below the 10th centile (small for gestational age) were also similar. Male neonates were heavier than female neonates at birth (mean (SD): male 3397 (472) g; female 3208 (404) g; $P = .02$), although no

interaction effect between sex and GDM status on birth weight was identified ($P = .41$). Birth outcomes did not differ by GDM treatment mode (Table 5).

4 | DISCUSSION

The present study of pregnant women with and without GDM indicated that foetal kidney size was normal among foetuses of women with GDM. Our further analyses of foetal kidney development revealed no differences in kidney dimensions between foetuses of women with GDM who required insulin therapy and to those of nondiabetic women. By investigating the continuous relation between OGTT glucose profiles and total foetal kidney volume, we also observed that kidney volume was normal in foetuses of women who had higher glucose levels at diagnosis. Our findings suggest that exposure to a limited period of hyperglycaemia prior to diagnosis and treatment of GDM does not perturb foetal kidney size at 32-34 weeks of gestation, a favourable finding given the increasing number of women diagnosed with GDM.

It is important to note that the participating women in this study had relatively mild GDM, as few were diagnosed with fasting hyperglycaemia and few required insulin. The diagnosis of GDM at Monash Medical Centre was modified towards the end of the present study to incorporate the new guidelines for GDM diagnosis as recommended by The Australasian Diabetes in Pregnancy Society (fasting plasma glucose ≥ 5.1 mmol/L and/or 2-hour plasma glucose ≥ 8.5 mmol/L).⁵⁰ The data presented here describe women classified only by the original set of criteria (fasting plasma glucose ≥ 5.5 mmol/L or 2 hours plasma glucose ≥ 8.0 mmol/L). Interestingly, upon reclassification, none of the 64 control women would have been diagnosed with GDM, yet 27% of GDM mothers would no longer have been diagnosed as such if the new criteria were applied to our study, highlighting the fact that our cohort included a number of women with mild or 'borderline' dysglycemia. It should be noted that supplementary analyses following reclassification of participants with the new diagnostic criteria did not alter offspring outcomes or our findings (data not shown).

Overall, women identified as having GDM and who participated in this study were an engaged and motivated group who regularly attended clinic, and were typically seen by a diabetes physician every 1-2 weeks until birth, dependent on clinical indication. Post-treatment glucose profiles were monitored by clinicians but were not consistently reported in clinical notes. However, all GDM women were managed and treated to normalize their blood glucose levels and may be regarded as having generally well-controlled diabetes, with only one third requiring insulin. The effective management of GDM was further evident given the absence of foetal overgrowth, even after allowing for earlier delivery of mothers with GDM. This

TABLE 3 Unadjusted regressions between total foetal kidney volume and maternal and foetal characteristics

	Total foetal kidney volume
Maternal characteristics	
OGTT fasting glucose	-0.06
OGTT 2-h glucose	-0.15
Body weight at hospital booking	0.14
BMI at hospital booking	0.10
Parity	0.32***
Ethnicity (Caucasian)	0.23*
Foetal characteristics	
Estimated foetal weight (EFW)	0.27**
EFW percentile	0.20*
Abdominal circumference	0.27**
Total kidney volume	.

Note: Values are standardized regression coefficients (β). Abbreviations: BMI, body mass index; OGTT, oral glucose tolerance test.

Bold values represent statistical significance.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

study is therefore an important assessment of how mild treated GDM affects kidney size, rather than an assessment of GDM per se. Further studies assessing foetal kidney development in women with poorly controlled GDM or untreated GDM would be informative.

Women with and without GDM in our sample were broadly comparable to other obstetric cohorts reported at Monash Medical Centre with regards to age, BMI and ethnicity.^{47,51} We recognize that there were ethnic differences between women with and without GDM in our cohort, which reflects the ethnically diverse population receiving pregnancy care at Monash Medical Centre (where up to 60% of births are to women born outside Australia)⁵² and the increased prevalence of GDM in women from South Asia and Southeast Asia.^{53,54} In general, Asian women have a lower BMI and have neonates with lower birth weights and fewer LGA infants than Caucasian women.^{55,56} Ethnic differences may in part account for why elevated maternal BMI, foetal weight and birth weight values were not observed in GDM pregnancies in the present study. Other than ethnicity, most GDM women did not have recognized risk factors associated with GDM. Nor were there many women with medical and obstetric complications that may have influenced the current results.

Surprisingly, only two studies have previously reported foetal kidney volume in women with GDM. Neves et al³⁹ serially measured kidney volume between 22 and 38 weeks gestation in 339 women without diabetes and 92 women with GDM. Foetal kidney volume was higher in GDM pregnancies throughout gestation (22-38 weeks). Excessive kidney growth was observed prior to GDM diagnosis and subsequently, despite the fact that approximately 80% of GDM women achieved glycemic control. However, although 339 women were included in the study, sample sizes at individual time points were low with n ranging from 2 to 26 in the GDM group, and maternal characteristics, glucose profiles, treatment modality and foetal and birth weight outcomes were not reported. In a second study, Verburg et al³⁸ assessed the effect of various maternal and foetal factors on foetal kidney volume in 1215 pregnancies. Maternal diabetes (pre-existing and GDM combined) was not associated with

TABLE 4 Multivariable regression of total foetal kidney volume and maternal and foetal characteristics

	Total foetal kidney volume		
	B	B SE	β
OGTT 2-h glucose	-0.197	0.350	-0.053
Parity	1.861	1.309	0.129
Ethnicity (Caucasian)	2.155	1.387	0.147
Estimated foetal weight	0.006	0.002	0.210*
Adjusted R^2	0.089**		

Abbreviations: B, unstandardized regression coefficient; B SE, standard error of coefficient; β , standardized regression coefficient; OGTT, oral glucose tolerance test.

Bold values represent statistical significance.

* $P < .05$.

** $P < .01$.

TABLE 5 Birth outcomes

	No-GDM (n = 64)	GDM (n = 64)	P ^a	GDM-Diet & Exercise (n = 42)	GDM-Insulin (n = 22)	P ^b
Birth outcomes						
Birth weight, g	3373 (488)	3221 (388)	.07	3224 (384)	3214 (405)	.16
Gestational age, wk	39.5 (1.3)	39.1 (1.2)	.07	39.1 (1.1)	39.2 (1.3)	.26
Birth weight percentile, median (IQR)	50 (24-76)	40 (15-72)	.25	30 (15-77)	40 (23-55)	.47
Caesarean birth, n (%)	17 (26.5)	21 (32.8)	.67	14 (33.3)	7 (31.8)	.71
Apgar score, 1 min	8.5 (1.4)	8.3 (1.3)	.12	8.3 (1.4)	8.5 (0.9)	.63
Apgar score, 5 min	8.9 (0.7)	8.9 (0.5)	.99	8.9 (0.5)	9.0 (0.0)	.61
Male, n (%)	31 (48.4)	30 (46.9)	.91	18 (42.9)	11 (50.0)	.84
Large for gestational age (>90th centile), n (%)	8 (12.5)	5 (7.8)	.79	3 (7.1)	2 (9.1)	.67
Small for gestational age (<10th centile), n (%)	9 (14.0)	10 (15.6)	.92	8 (19.0)	2 (9.1)	.56
Low birth weight (<2500 g), n (%)	2 (3.1)	1 (1.6)	-	1 (2.4)	0	-
Macrosomia (birth weight > 4500 g), n (%)	1 (1.6)	0	-	0	0	-

Note: Values are mean (SD) except where indicated otherwise.

'-' indicates insufficient observations for analysis.

^aData analysed by Wilcoxon rank-sum test, independent-samples t test or chi-square test.

^bData analysed by Kruskal-Wallis rank test with Dunn's multiple comparisons test, one-way ANOVA with Dunn's multiple comparisons test or chi-square test.

foetal kidney volume at 30 weeks gestation, although only 16 cases of maternal diabetes were reported among these 1215 pregnancies. In contrast to these two previous studies, the current study presents data for a larger sample of 64 diabetic women, and outcomes are reported for women with GDM only, rather than combining potentially confounding results from women with GDM and pre-existing diabetes. We report data for a range of maternal and foetal characteristics, and analysed kidney size by assessing left and right kidney dimensions and volumes, as well as total kidney volume and total volume adjusted for foetal size.

We are aware of just two studies that assess postnatal kidney size in infants or children of diabetic mothers. Bos et al⁵⁷ measured kidney length in 20 healthy newborn controls and 20 infants born to women with Type 1 diabetes. As in our study, diabetic mothers were tightly controlled and no differences in infant left or right kidney lengths were reported. Conversely, Cappuccini et al⁴⁰ reported reduced renal cortical volume and microalbuminuria in 3-year-old children of women with pre-existing diabetes (n = 13) and GDM (n = 29), compared to 21 children whose mothers had not had diabetes. It is possible that women who had GDM in the latter study had greater levels of hyperglycaemia than women in the present study, as 86% of their participants required insulin. However, maternal glucose profiles were not reported.

In conclusion, our findings indicate that a period of mild hyperglycaemia prior to GDM diagnosis and treatment does not alter kidney volume at 32-34 weeks gestation. Further studies to assess kidney size and function in children and adults of both well controlled and poorly controlled (or untreated) GDM are warranted to validate the effectiveness of GDM treatment protocols—an important area of research given the limited number

of studies in this field and the increasing number of women diagnosed with GDM.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors participated in review of the manuscript and the data shown and have read and approved the final version of the manuscript. Specifically: Study design (LAC-M, VP, JI, MJB, DR, PC, CA, JAA, JB, EW); participant recruitment (SH, NNdZ, BC, VA); acquisition of data (SH, NNdZ, BC, VA, CE); data analysis and interpretation (SH, JB, LAC-M); preparation of manuscript (SH, NdZ, JB, LAC-M); review of manuscript (all authors).

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

Data available on request from the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

- Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. *Diab Care*. 1998;21:B161-B167.
- Chamberlain C, Banks E, Joshy G, et al. Prevalence of gestational diabetes mellitus among Indigenous women and comparison with non-Indigenous Australian women: 1990–2009. *Aust N Z J Obstet Gynaecol*. 2014;54:433–440.
- Correa A, Bardenheier B, Elixhauser A, Geiss LS, Gregg E. Trends in prevalence of diabetes among delivery hospitalizations, United States, 1993–2009. *Matern Child Health J*. 2015;19:635–642.
- Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to Type 2 diabetes: a global perspective. *Curr Diab Rep*. 2016;16:7.
- Catalano PM, McIntyre HD, Cruickshank JK, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diab Care*. 2012;35:780–786.
- The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008;358:1991–2002.
- Cullen-McEwen L, Sutherland MR, Black MJ. Chapter 3 - The human kidney: parallels in structure, spatial development, and timing of nephrogenesis. In: Little MH, ed. *Kidney Development, Disease, Repair and Regeneration*. San Diego, CA: Academic Press; 2016:27–40.
- Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med*. 2003;348:101–108.
- Hughson MD, Douglas-Denton R, Bertram JF, Hoy WE. Hypertension, glomerular number, and birth weight in African Americans and white subjects in the southeastern United States. *Kidney Int*. 2006;69:671–678.
- Luyckx VA, Bertram JF, Brenner BM, et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet*. 2013;382:273–283.
- Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? *Am J Hypertens*. 1988;1:335–347.
- Chen Y-W, Chenier I, Tran S, Scotcher M, Chang S-Y, Zhang S-L. Maternal diabetes programs hypertension and kidney injury in offspring. *Pediatr Nephrol*. 2010;25:1319–1329.
- Nehiri T, Duong Van Huyen J-P, Viltard M, et al. Exposure to maternal diabetes induces salt-sensitive hypertension and impairs renal function in adult rat offspring. *Diabetes*. 2008;57:2167–2175.
- Cullen-McEwen LA, Kett MM, Dowling J, Anderson WP, Bertram JF. Nephron number, renal function, and arterial pressure in aged GDNF heterozygous mice. *Hypertension*. 2003;41:335–340.
- Stelloh C, Allen KP, Mattson DL, Lerch-Gaggl A, Reddy S, El-Meanawy A. Prematurity in mice leads to reduction in nephron number, hypertension, and proteinuria. *Transl Res*. 2012;159:80–89.
- Diehm CJ, Lumbers ER, Weatherall L, et al. Assessment of fetal kidney growth and birth weight in an Indigenous Australian cohort. *Front Physiol*. 2018;8:1129.
- White SL, Perkovic V, Cass A, et al. Is low birth weight an antecedent of CKD in later life? A systematic review of observational studies. *Am J Kidney Dis*. 2009;54:248–261.
- Das SK, Mannan M, Faruque A, Ahmed T, McIntyre HD, Al Mamun A. Effect of birth weight on adulthood renal function: a bias-adjusted meta-analytic approach. *Nephrology*. 2016;21:547–565.
- Nyengaard JR, Bendtsen TF. Glomerular number and size in relation to age, kidney weight, and body surface in normal man. *Anat Rec*. 1992;232:194–201.
- Zhang Z, Quinlan J, Hoy W, et al. A common RET variant is associated with reduced newborn kidney size and function. *J Am Soc Nephrol*. 2008;19:2027–2034.
- Luyckx VA, Brenner BM. The clinical importance of nephron mass. *J Am Soc Nephrol*. 2010;21:898–910.
- Kooijman MN, Bakker H, van der Heijden AJ, et al. Childhood kidney outcomes in relation to fetal blood flow and kidney size. *J Am Soc Nephrol*. 2014;25:2616.
- Kandasamy Y, Smith R, Wright I, Lumbers ER. Relationships between glomerular filtration rate and kidney volume in low-birth-weight neonates. *J Nephrol*. 2013;26:894–898.
- Kandasamy Y, Smith R, Wright I, Lumbers ER. Reduced nephron endowment in the neonates of Indigenous Australian peoples. *J Dev Orig Health Dis*. 2014;5:31–35.
- Mishra K, Datta V, Aarushi A, Kaur Narula M, Iyer RS, Nangia S. The association between weight for gestational age and kidney volume: a study in newborns in India. *Iran J Pediatr*. 2014;24:93–99.
- Miliku K, Voortman T, Bakker H, Hofman A, Franco OH, Jaddoe V. Infant breastfeeding and kidney function in school-aged children. *Am J Kidney Dis*. 2015;66:421–428.
- Ferdous F, Ma E, Raqib R, Wagatsuma Y. Birth weight influences the kidney size and function of Bangladeshi children. *J Dev Orig Health Dis*. 2017;9:386–394.
- Kooijman MN, Bakker H, Franco OH, Hofman A, Taal HR, Jaddoe V. Fetal smoke exposure and kidney outcomes in school-aged children. *Am J Kid Dis*. 2015;66:412–420.
- Hokke S, Arias N, Armitage JA, et al. Maternal glucose intolerance reduces offspring nephron endowment and increases glomerular volume in adult offspring. *Diabetes Metab Res Rev*. 2016;32:816–826.
- Hokke SN, Armitage JA, Puelles VG, et al. Altered ureteric branching morphogenesis and nephron endowment in offspring of diabetic and insulin-treated pregnancy. *PLoS ONE*. 2013;8:e58243.
- Nankervis A, Conn J. Gestational diabetes mellitus - negotiating the confusion. *Aust Fam Physician*. 2013;42:528–531.
- Konje JC, Bell SC, Morton JJ, De Chazal R, Taylor DJ. Human fetal kidney morphometry during gestation and the relationship between weight, kidney morphometry and plasma active renin concentration at birth. *Clin Sci*. 1996;91:169–175.
- Hinchliffe SA, Sargent PH, Howard CV, Chan YF, van Velzen D. Human intrauterine renal growth expressed in absolute number of glomeruli assessed by the disector method and Cavalieri principle. *Lab Invest*. 1991;64:777–784.
- Nelson RG, Morgenstern H, Bennett PH. Intrauterine diabetes exposure and the risk of renal disease in diabetic Pima Indians. *Diabetes*. 1998;47:1489–1493.
- Pavkov ME, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Nelson RG. Effect of intrauterine diabetes exposure on the incidence of end-stage renal disease in young adults with Type 2 diabetes. *Diab Care*. 2010;33:2396–2398.
- Khalil CA, Travert F, Fetita S, et al. Fetal exposure to maternal Type 1 diabetes is associated with renal dysfunction at adult age. *Diabetes*. 2010;59:2631–2636.
- Lee YQ, Collins CE, Gordon A, Rae KM, Pringle KG. The relationship between maternal obesity and diabetes during pregnancy on offspring kidney structure and function in humans: a systematic review. *J Dev Orig Health Dis*. 2018;10(4):406–419.

38. Verburg BO, Geelhoed J, Steegers E, et al. Fetal kidney volume and its association with growth and blood flow in fetal life: the Generation R Study. *Kidney Int.* 2007;72:754-761.
39. Neves HM, Sgarbosa F, Calderon I, et al. Does hyperglycemia in pregnancy change fetal kidney growth? A longitudinal prospective study. *Revista Brasileira de Ginecologia e Obstetrícia.* 2013;35:442-446.
40. Cappuccini B, Torlone E, Ferri C, et al. Renal echo-3D and microalbuminuria in children of diabetic mothers: a preliminary study. *J Dev Orig Health Dis.* 2013;4:285-289.
41. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361:1339-1348.
42. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med.* 2005;352:2477-2486.
43. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. *Ann Intern Med.* 2013;159:123-129.
44. Billionnet C, Mitancher D, Weill A, et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. *Diabetologia.* 2017;60:636-644.
45. Farrar D, Simmonds M, Bryant M, et al. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. *BMJ.* 2016;354:i4694.
46. Martin F. The diagnosis of gestational diabetes. *Med J Aust.* 1991;155:112.
47. Stewart ZA, Wallace EM, Allan CA. Patterns of weight gain in pregnant women with and without gestational diabetes mellitus: an observational study. *Aust N Z J Obstet Gynaecol.* 2012;52:433-439.
48. Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements - a prospective study. *Am J Obstet Gynecol.* 1985;151:333-337.
49. *Stata Statistical Software. Release 15 [computer program].* College Station, TX: StataCorp LLC; 2017.
50. Nankervis A, McIntyre H, Moses R, et al. *ADIPS Consensus Guidelines for the testing and Diagnosis of Hyperglycaemia in Pregnancy in Australia and New Zealand (modified November 2014).* Australasian Diabetes in Pregnancy Society; 2014.
51. Abell SK, Boyle JA, Earnest A, et al. Impact of different glycaemic treatment targets on pregnancy outcomes in gestational diabetes. *Diabetic Med.* 2018;36:177-183.
52. Teh WT, Teede HJ, Paul E, Harrison CL, Wallace EM, Allan C. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. *Aust N Z J Obstet Gynaecol.* 2011;51:26-30.
53. Templeton M, Pieris-Caldwell I. *Gestational diabetes mellitus in Australia, 2005-06.* Canberra, Australia: AIHW; 2008.
54. McDonald R, Karahalios A, Le T, Said J. A retrospective analysis of the relationship between ethnicity, body mass index, and the diagnosis of gestational diabetes in women attending an Australian antenatal clinic. *Int J Endocrinol.* 2015;2015:297420.
55. Reddy M, Wallace EM, Mockler JC, et al. Maternal Asian ethnicity and obstetric intrapartum intervention: a retrospective cohort study. *BMC Pregnancy Childbirth.* 2017;17:3.
56. Wong VW. Gestational diabetes mellitus in five ethnic groups: a comparison of their clinical characteristics. *Diabetic Med.* 2012;29:366-371.
57. Bos AF, Aalders AL, van Doormaal JJ, Martijn A, Okken A. Kidney size in infants of tightly controlled insulin-dependent diabetic mothers. *J Clin Ultrasound.* 1994;22:443-446.

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