

HAROLDO MILLET NEVES^{1,4}

FÁBIO SGARBOSA²

IRACEMA MATTOS PARANHOS CALDERON^{3,4}

LUANA SCHNEIDER VIANNA⁴

ANA CAROLINA MONTEIRO SANTINI⁴

LINO SIEIRO NETTO⁵

ADRIANO DIAS^{4,6}

Does hyperglycemia in pregnancy change fetal kidney growth? A longitudinal prospective study

*A hiperglicemia na gravidez altera o crescimento renal fetal?
Um estudo prospectivo longitudinal*

Original Article

Keywords

Diabetes
Fetus/metabolism
Hyperglycemia/metabolism
Pregnancy complications
Women health

Palavras-chave

Diabetes
Feto/metabolismo
Hiperglicemia/metabolismo
Complicações na gravidez
Saúde da mulher

Abstract

PURPOSE: To measure fetal renal volume in normoglycemic and hyperglycemic pregnancies. **METHODS:** A longitudinal prospective study was conducted and included 92 hyperglycemic and 339 normoglycemic pregnant women attended at the prenatal service of a hospital from Rio de Janeiro State. Ultrasound examinations were performed to estimate gestational age at baseline and the kidney volume was estimated using the prolate ellipsoid volume equation. **RESULTS:** Fetal kidney volume growth between normoglycemic and hyperglycemic pregnancies are significantly different. The fetal kidney volume growth in pregnancy is positively correlated with gestational age explained by these predictor equations, by group: normal renal volume = $\exp(6.186+0.09 \times \text{gestational week})$; hyperglycemic renal volume = $\exp(6.978+0.071 \times \text{gestational week})$ and an excessive growth pattern for hyperglycemic pregnancies may be established according to gestational age. **CONCLUSION:** This is important for early detection of abnormalities in pregnancy, particularly in diabetic mothers.

Resumo

OBJETIVO: O estudo foi desenvolvido para medir o volume renal fetal em gestações normoglicêmicas e hiperglicêmicas. **MÉTODOS:** Estudo prospectivo longitudinal, incluindo 92 gestantes hiperglicêmicas e 339 normoglicêmicas que procuraram o serviço pré-natal de um hospital no estado do Rio de Janeiro. A ultrassonografia foi realizada para estimar idade gestacional e volume renal foi estimado utilizando a equação de volume elipsoide. **RESULTADOS:** O crescimento fetal e os volumes renais entre gestações normoglicêmicas e hiperglicêmicas são estatisticamente distintos. O aumento do volume renal fetal na gravidez é correlacionada com a idade gestacional, de acordo com as seguintes equações preditores, por grupo: volume renal normal = $\exp(6,186+0,09 \times \text{semana de gestação})$; e volume renal hiperglicêmico = $\exp(6,978+0,071 \times \text{semana de gestação})$. **CONCLUSÃO:** Estes dados são importantes para detecção precoce de anormalidades na gravidez, principalmente em mães diabéticas.

Correspondence

Adriano Dias
Faculdade de Medicina de Botucatu,
Universidade Estadual Paulista "Júlio de Mesquita Filho"
Avenida Prof. Montenegro, Distrito de Rubião Junior, s/n
CEP: 18618-970
Botucatu (SP), Brazil

Received on

06/08/2013

Accepted with modifications

04/10/2013

Study carried out at Ambulatório de pré-natal do Hospital Geral de Nova Iguaçu – Nova Iguaçu (RJ), Brazil.

¹Serviço de Ultrassonografia do Hospital Geral de Nova Iguaçu – Nova Iguaçu (RJ), Brazil.

²Faculdade de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP – Botucatu (SP), Brazil.

³Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP – Botucatu (SP), Brazil.

⁴Programa de Pós-graduação em Ginecologia, Obstetrícia e Mastologia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP – Botucatu (SP), Brazil.

⁵Hospital Geral de Nova Iguaçu – Nova Iguaçu (RJ), Brazil.

⁶Departamento de Saúde Pública, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP – Botucatu (SP), Brazil.

Conflict of interests: none.

Introduction

Human fetal growth is characterized by sequential patterns of tissue and organ growth, differentiation, and maturation that are determined by maternal provision of substrate, placental transfer of these substrates, and fetal growth potential ruled by the genome^{1,2}. Subsequently, fetal growth can be influenced by environmental, nutritional, and hormonal factors².

There is strong evidence that insulin, which is secreted by pancreatic beta cells during the second half of pregnancy, and analogous factors (insulin-like growth factors I and II) play a role in regulating uterine and placental growth as well as fetal weight³⁻⁵ as they are potent stimulators of cellular division and differentiation³.

Hyperglycemia causes the decreased insulin sensitivity and the relative inability to increase insulin secretion in response to increased blood glucose. Glucose crosses the placenta by facilitated diffusion, and the fetus maintains 70–80% of the maternal concentration. This results in a carbohydrate surplus to the fetus, which, in turn, increases insulin secretion. Hyperinsulinemia causes direct fetal growth stimulation, and increased cellular glucose utilization, increased fat deposition, and increased protein production. This leads to overgrowth and the birth of an infant with macrosomia. In the third trimester of pregnancy, fetal growth is primarily a function of increased cell size. In general, fat deposition in human fetuses occurs from the second trimester, and is insulin-dependent^{6,7}.

Fetal organ enlargement is surrounded by controversy, and studies on the influence of maternal hyperglycemia on fetal kidney volume are scarce. Furthermore, in a study of the mechanisms involved in the pathogenesis of diabetic embryopathy, high glucose levels were found to induce defects in the genitourinary system⁸. Thus, within this framework, the purpose of this study was to investigate whether maternal glycemia influences fetal kidney growth by measuring fetal kidney volume in normoglycemic and hyperglycemic pregnancies.

Methods

This longitudinal prospective study included only singleton pregnant women, 92 hyperglycemic and 339 normoglycemic, sequentially enrolled from the prenatal outpatient in Rio de Janeiro State, Southeastern Brazil. The minimum sample size was estimated to be nine measurements per gestational week for each group, based on an expected mean difference in renal growth of at least 30% between groups (estimated at 38th week of pregnancy, considering 5 and 20% for type I and II errors, respectively)⁹.

Following the completion of a medical history questionnaire, women reporting alcohol abuse, hypertension, smoking, and systemic infections, collagenosis, or heart disease were not included in the study. Cases of fetal renal anomalies as evidenced by abnormal fetal kidney measurements, were also excluded, and referred to specialized care in fetal medicine.

Hyperglycemia was screened by oral glucose tolerance test with 75 g of dextrosol between 24 and 32 weeks of gestation. Women with one abnormal 75 g oral glucose tolerance test value were considered hyperglycemic¹⁰.

Gestational age was estimated by ultrasound scanning at 11–14 weeks of pregnancy. Between 22nd and 38th weeks, ultrasound examinations were carried out to measure the longitudinal, anteroposterior, and transverse diameters of fetal kidneys. Renal length was measured from the upper to the lower pole, and the anteroposterior diameter was obtained from the kidney longitudinal section. The cross-sectional view was obtained at the level of the renal pelvis or in the position where the renal section was the largest observed measurement. Fetal respiratory movements were used to define the gap between the kidneys and adjacent parenchyma (such as intestinal loops and adrenal glands). Kidney volume (mm³) was estimated using the prolate ellipsoid volume equation¹¹: $\text{volume} = \text{length} \times \text{width} \times \text{height} \times 0.5233$.

All ultrasound examinations were performed by a specialized single observer using General Electric Logic 400[®] equipment (Milwaukee, EUA, USA) with a high-resolution convex probe (3.5 MHz).

Routine ultrasound examinations are repeated every two weeks. However, given that not all women attended all scheduled visits, gestational week was treated as an independent variable, and weekly measurements were randomly distributed. As a result, the number of measurements per subject was heterogeneous.

All women with hyperglycemia were initially treated with diet and physical activities. When glycemic mean (GM) indicated inadequate glycemic control, human insulin (regular or NPH) was also used. GM was estimated based on the arithmetic mean of six glucose values measured every two hours from 8 a.m to 6 p.m once a week. All glucose determinations were obtained by the glucose oxidase method¹², and a GM of 66.7 mmol/L (120 mg/dL) was considered adequate.

Statistical tests were performed using IBM/SPSS Statistics Software, v. 19.0. A generalized linear model was adjusted considering repeated measures in time assuming a gamma distributed random error with a log link function (generalized estimating equations)¹³. The p-value for the significance of between-group difference in fetal renal volume was determined by the Wald test. Median and

quartile renal growth curves were smoothed by second grade polynomial adjustment¹⁴.

The study was approved by the Ethics Committee of Nova Iguaçu General Hospital under number 004/20060 on 14 September, 2006 and written informed consent was obtained from all subjects. The research was carried out according to the Declaration of Helsinki, reviewed in 2008.

Results

For the generalized linear model the predictor variable was gestational age, and the response variable was fetal kidney volume, which resulted in statistically significant generalized estimating equations, and showed that the gestational week/fetal renal volume relation could predict renal growth in normoglycemic (renal volume = $\exp(6.186 + 0.09 \times \text{gestational week})$) and hyperglycemic groups (renal volume = $\exp(6.978 + 0.071 \times \text{gestational week})$) (Figure 1).

Wald test revealed that fetal renal volume evolution on both sides was significantly different between groups ($p < 0.001$ and $p = 0.007$, for the right and left sides, respectively).

Polydramnios was found in 1.7 and 0.2% in the hyperglycemic and normoglycemic groups, respectively, and the overall proportion of adequate maternal glycemic control was 79.7% considering a GM of 120 mg/dL as the cutoff point.

Table 1 shows the median fetal kidney volume by gestational week, expressed as median, 1st, and 3rd quartiles in both normoglycemic and hyperglycemic groups.

Figures 2 and 3 show the curves of both 50 and 75th percentile kidney volumes in the normoglycemic group, and the 50th percentile kidney volume in the hyperglycemic group (for left and right sides). The 50th percentile kidney volume curves for the hyperglycemic group was almost always larger than the 75th percentile kidney volume curves for the normoglycemic group.

The fetal kidney abnormalities detected in the hyperglycemic group that caused the exclusion of measurements from the analysis were: one case of bilateral renal agenesis, one case of unilateral renal hypoplasia, and two cases of mild hydronephrosis.

Discussion

In this study, measurements were to be taken starting at 22 weeks of gestation because kidney visualization prior to that age was very poor in our sample of women. Moreover, in obese pregnant, the sound beam was attenuated by the adipose tissue preventing the precise definition of the fetal kidney shape. Others studies on

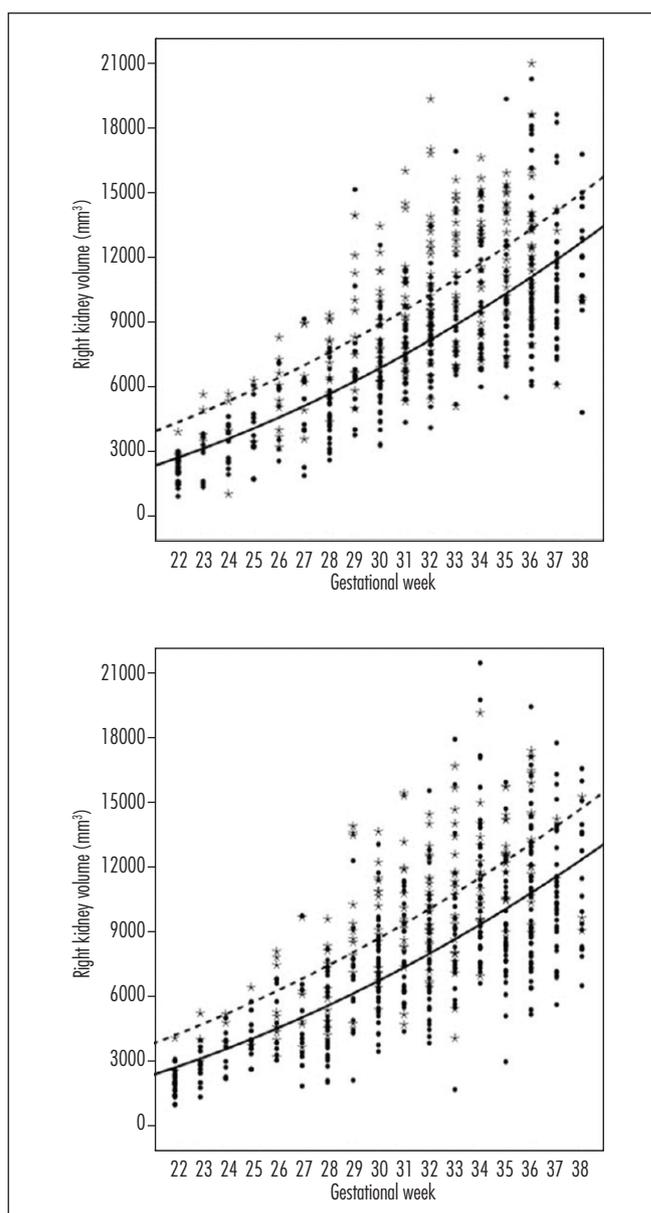


Figure 1. Relationship between fetal kidney volume and gestational week in normoglycemic and hyperglycemic pregnancies.

fetal kidney started the measurements at 20 weeks¹⁵, 24 weeks¹⁶, 20 weeks¹¹, 20 weeks¹⁷, and 18 weeks¹⁸, apparently corroborating the assertion that early pregnancy age hampers measurements.

The serial biometric examination of the fetal kidney performed between 22 and 38 weeks of gestation allowed assessing the progression of kidney volume using the ellipse equation¹¹. Median fetal kidney volume in hyperglycemic pregnancies was significantly larger than the 75th percentile kidney volume in normoglycemic pregnancies during nearly the entire follow-up period, even though normal GM values were achieved in 80% of the cases. This suggests that fetal kidney volume is

Table 1. Fetal kidney volumes* expressed as 3rd quartiles, between the 22nd and 38th weeks of gestation according to laterality, in mm³

Gestation week	Slide	Normoglycemic		Hyperglycemic	
		n	75 th	n	75 th
22	R	24	2525.26	2	4946.16
	L	25	2354.98	2	6591.09
24	R	12	4059.49	4	5540.97
	L	10	4066.36	3	5172.90
26	R	10	6239.67	9	6892.85
	L	10	6652.40	9	7625.62
28	R	28	5729.34	12	8775.57
	L	27	6395.67	11	8107.48
30	R	40	8065.93	17	10846.39
	L	39	8191.27	17	11100.88
32	R	40	9375.20	26	13185.24
	L	39	9571.93	25	11428.64
34	R	35	12744.58	18	13870.17
	L	33	13401.00	18	13070.53
36	R	51	13655.21	18	14419.91
	L	47	12902.95	16	16184.07
38	R	16	14010.59	2	11082.26
	L	17	13767.16	3	15213.74

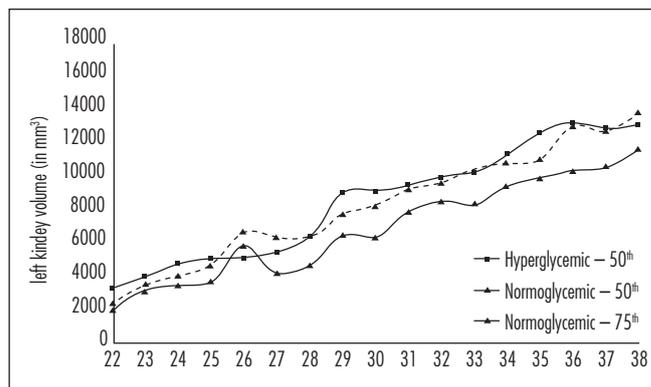
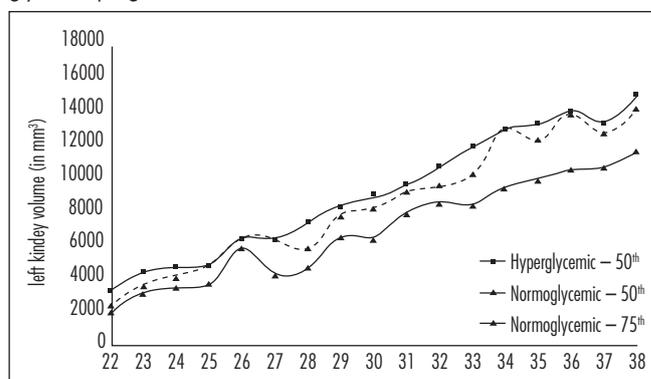
*For normoglycemic group: renal volume = $\exp(6.186 + 0.09 \times \text{gestational week})$; for hyperglycemic group: renal volume = $\exp(6.978 + 0.071 \times \text{gestational week})$.

also affected by maternal hyperglycemia, including the kidneys in the list of target organs for fetal organomegaly.

As previously reported, insulin is a regulator of cell growth¹⁹. Maternal hyperglycemia leads to fetal hyperinsulinemia, providing a stimulating environment for fetal organomegaly. Other mechanisms related to cell growth involve some fibroblast growth factors (FGFs) and insulin-like growth factors²⁰ that have been reported to positively correlate with fetal size in the second and third trimesters of pregnancy. FGF concentrations have been demonstrated to be high in diabetic pregnancies, which are commonly associated with changes in fetal tissue FGF-receptors impairing nephrogenesis in fetuses exposed to high glucose concentrations²¹.

Growth acceleration in fetuses large-for-gestational age exposed to maternal hyperglycemia becomes evident in the second trimester, around 18–24 weeks of pregnancy^{20,22,23}.

Given that, in cases of macrosomia, the fetal organs exposed to maternal diabetogenic environment tend to grow larger than in normoglycemic pregnancies, gestational age estimation based only on biometry (biparietal diameter, femoral length, and abdominal circumference) may be

**Figure 2.** Median of left fetal kidney volumes (in mm³) in hyperglycemic pregnancies versus 75th percentile median kidney volumes in normoglycemic pregnancies.**Figure 3.** Median of right fetal kidney volumes (in mm³) in hyperglycemic pregnancies versus 75th percentile median kidney volumes in normoglycemic pregnancies.

impaired. The good correlation between gestational age and kidney volume found in both study groups suggests that kidney volume can be an auxiliary measurement in determining gestational age. In addition, the laterality of the organ does not interfere with renal volume estimation^{17,24}. It is noteworthy, however, that the literature concerning laterality is scarce.

The results of this study show that, in agreement with the literature, maternal hyperglycemia is associated with fetal kidney volume growth modification, that is, hyperglycemia in utero increases fetal kidney volume. These findings are useful because they allow, in cases of gestational hyperglycemia, the construction of a kidney volume growth curve that shows a significant association with gestational age.

Contributions to authors

All authors have participated in the manuscript's design and drafting. All authors have participated in the study's review of the data shown and they have read and approved of the final manuscript version.

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