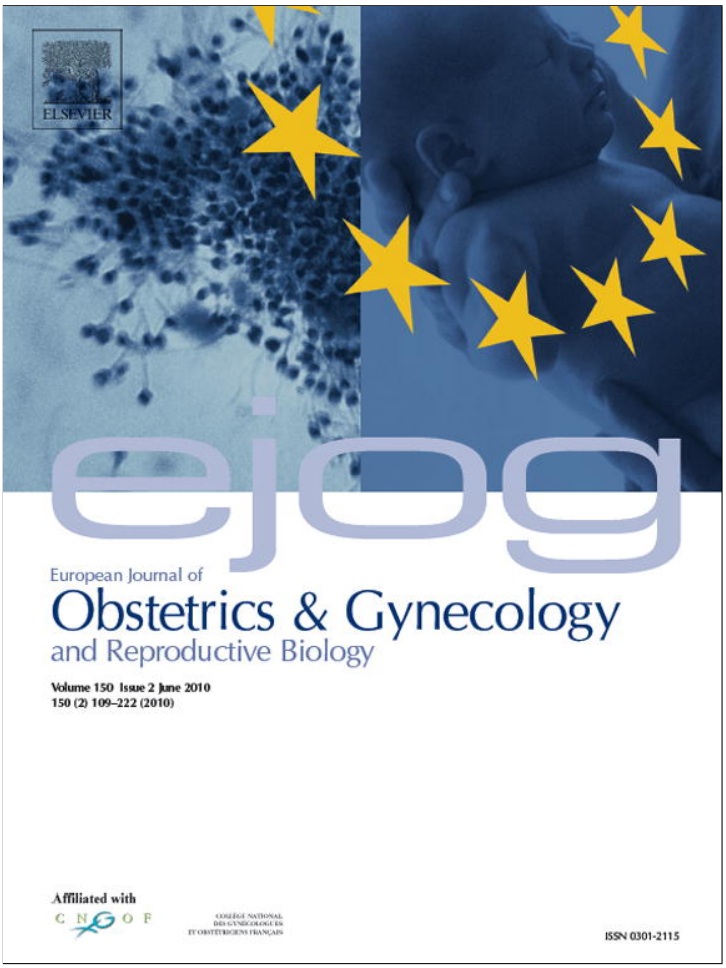

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Physiology and clinical value of glycosuria after a glucose challenge during pregnancy

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ABSTRACT

Objective: Urine testing for glucose is commonly performed during pregnancy but little is known about the regulation and clinical value of glycosuria because studies are hampered by its low prevalence and intermittent nature. The aim of this study was to compare the urine and plasma response 60 min after a 50 g oral glucose challenge in the setting of gestational diabetes mellitus (GDM) screening.
Study design: Of 338 consecutively enrolled gravidas, 325 completed the study. Glycosuria was measured semi-quantitatively (0, 1, 2 or 3+) and venous plasma glucose was measured.
Results: Post-challenge glycosuria occurred in 26.2% of gravidas. Women with 2 or 3+ glycosuria showed higher plasma glucose ($p < 0.001$), lower height ($p = 0.004$) and lower body weight throughout pregnancy ($p = 0.014$); however, glycosuria was not related to age, parity, body mass index (BMI), highest blood pressure or newborn size at birth. The sensitivity for a GDM diagnosis was 8.2%. Comparison of pure "urine" responders (i.e., any glycosuria but glucose <130 mg/dl, $n = 50$) with "plasma" responders (no glycosuria but plasma glucose ≥140 mg/dl, $n = 29$) showed that urine responders were younger and had a lower body weight and BMI than plasma responders.
Conclusion: Glycosuria after an oral glucose challenge depends on the plasma glucose excursion, and is more pronounced in gravidas with lower height and body weight, who presumably have a smaller plasma distribution volume. Post-load glycosuria is a poor predictor of GDM, pre-eclampsia and newborn size at birth, and therefore has limited clinical benefit.

1. Introduction

Glycosuria testing at each prenatal visit continues to be practiced in many European countries despite consensus that glycosuria is not a valid screening test for gestational diabetes mellitus (GDM). The American Diabetes Association recommends the glucose challenge test (GCT) at 24–28 weeks gestational age (GA) for the screening of GDM, and lists glycosuria as a pre-screening clinical characteristic that may prompt glucose evaluation at the first prenatal visit [1]. Yet surprisingly little is known about this extremely common measurement. Older physiological studies show that glycosuria occurs more frequently during pregnancy because of reduced tubular reabsorption of filtered glucose [2]. Studies on glycosuria are hampered by its variable but generally low prevalence and its typically intermittent nature. In a US cohort of >2500 gravidas, the prevalence of glycosuria rose from 1.7% in the first two trimesters to 8.6% in the third trimester [3]. Glycosuria was present in only 3.6% of 1001 gravidas in Germany at 33 ± 3 weeks GA [4].

In order to clarify the physiological and clinical relevance of glycosuria, we decided to study glycosuria 60 min after the GCT (which consists of a 50 g glucose load), immediately before blood sampling. We anticipated that this would increase the glycosuria prevalence. In addition, the plasma and urine response to a glucose load might be compared.

2. Materials and methods

2.1. Patients

The departmental ante-partum care trajectory recommends that a GCT should be carried out between 24 and 28 weeks GA in all pregnancies; in practice, this occurs either at our own clinic or at the office of the family physician/private midwife involved in the ante-partum care. For this study, we included all consecutive women receiving a GCT at our clinic between April 1st and September 30th, 2008. GCTs were performed regardless of time of day or previous meals, and consisted of a 50 g oral glucose load with no adding of lemon extract, as this might influence the measurement [5]. The gravidas were asked not to eat, drink, smoke or chew gum for the next hour, and to remain within the clinic boundaries. The patients were asked to provide their routine urine

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sample at the time of the blood sample (60 min after glucose load) rather than at the time of their weight check. Clinic midwives were informed about the purpose of the study and they checked for glycosuria (®Combur3-Test, Roche Diagnostics, Vilvoorde, Belgium) as they routinely do. The urine stick indicates no glycosuria, 1+ glycosuria (corresponding to 50 mg/dl or 2.8 mmol/l), 2+ (100 mg/dl or 5.5 mmol/l) or 3+ (300 mg/dl or 17 mmol/l). A venous blood sample was subsequently drawn and sent to the laboratory. Plasma glucose was measured by a colorimetric–enzymatic method (hexokinase-glucose-6-phosphate-dehydrogenase, Roche application code 668) on a Hitachi/Roche-Modular P analyzer. An abnormal GCT was defined as a plasma venous glucose concentration of ≥140 mg/dl (7.8 mmol/l). A subsequent 100 g oral glucose tolerance test (OGTT) with ≥2 abnormal plasma glucose values according to the Carpenter–Coustan criteria (fasting, 95 mg/dl; 1 h, 180 mg/dl; 2 h, 155 mg/dl; and 3 h, 140 mg/dl) was defined as GDM; nutritional counselling by a dietician or/and insulin were then instituted. All clinical data pertaining to the mother and baby were retrieved from the patients' notes and electronic records. Pre-pregnancy weight was obtained at the first visit, based on the patients' recall. Weight gain was calculated between pre-pregnancy weight and weight recorded at GCT, and weight gain between the recording at the GCT and the final visit; the total weight gain was the sum.

2.2. Data analysis

We used the NCSS software, version 2004 (Kaysville, UT, USA). Birth weight of twins was averaged. The birth weight standard deviation (SD)-score was computed as (actual–mean) birth weight/birth weight SD for a particular GA, with mean and SD-values obtained from more than 429,000 births [6]. Small-for-GA (≤10th percentile), appropriate-for-GA (11–90th percentile) and large-for-GA (>90th percentile) babies were identified using the same database. For glycosuria, the results were stratified into three groups: no glycosuria, 1+ glycosuria, and 2–3+ glycosuria; for the plasma glucose level, the group with a value of ≥140 mg/dl was compared with the <140 mg/dl group. Continuous variables were compared using two-sample *t*-tests taking account of normality and variance (two groups) or one-way ANOVA (three groups); if the ANOVA-test showed a p value <0.05, Bonferroni's *post hoc* multiple-comparison test was used to compare individual groups. The χ^2-test was used for comparisons of categorical variables. Multiple regression analysis was done using Huber's method (robust regression). Data are presented as means (standard error of mean, SEM).

3. Results

From 338 consecutive women enrolled in the study, 13 women were excluded from analysis because they did not have a complete follow-up and delivered elsewhere. Thirteen of the 325 included pregnancies were twin pregnancies (4%). The maternal age was 30.6 (0.3) years (range 18–49). One hundred and fifty-four (47.4%) were nulliparous, 110 (33.9%) were primiparous, and 61 (18.8%) were ≥para 2. The GCT was carried out at 26.0 (0.9) weeks GA (range 23.0–32.8); 54 (16.6%) of the tests were abnormal. Forty-six of these women (85%) underwent an OGTT, which was abnormal in 10 cases, translating into a 3% (10/317) incidence of GDM (Fig. 1). All GDM women received medical nutrition therapy, and two patients were treated with insulin as well.

Of the total group, 26.2% had a positive glycosuria testing. Table 1 shows that positive glycosuria was not related to age or parity, but that positive glycosuria was related to both shorter stature and lower body weight before pregnancy and throughout pregnancy; yet there was no relationship with the BMI. Women with positive glycosuria tended to have a lower total gestational weight gain, but no difference in the pre- or post-GCT weight gain could be identified. The amount of glycosuria was also strongly related to the GCT result; 50% of patients with 2 or 3+ glycosuria

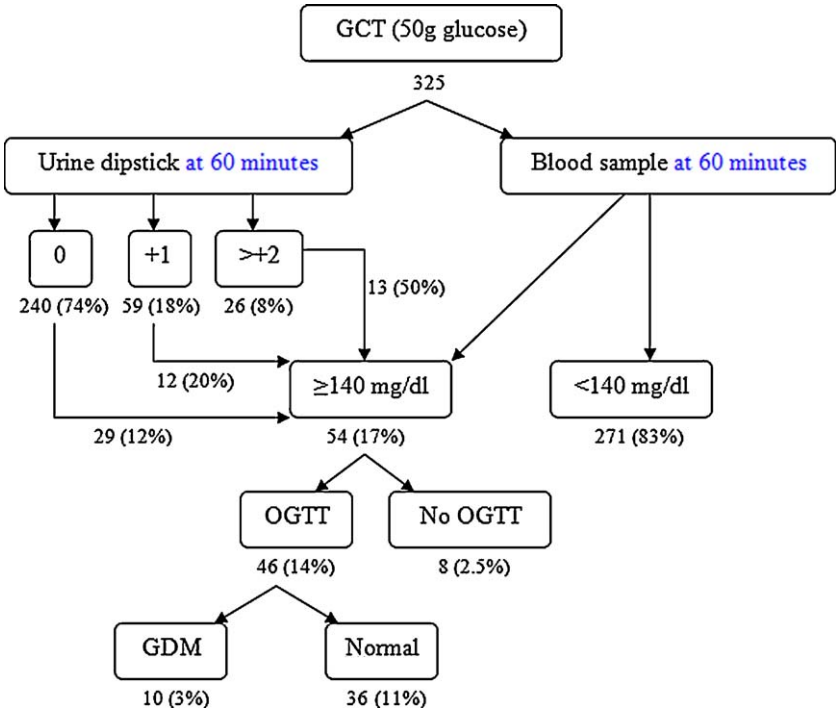

Fig. 1. Flow diagram of the study. Urine: 0 = no glycosuria, 1+ = glycosuria to 50 mg/dl or 2.8 mmol/l, >2+ = >100 mg/dl or >5.5 mmol/l. GCT: abnormal when plasma venous glucose concentration ≥140 mg/dl (7.8 mmol/l). OGTT (100 g glucose): abnormal when ≥2 abnormal plasma glucose values according to the Carpenter–Coustan criteria (fasting, 95 mg/dl; 1 h, 180 mg/dl; 2 h, 155 mg/dl; and 3 h, 140 mg/dl). GDM, gestational diabetes mellitus.

Table 1
Pregnancy characteristics according to the degree of maternal glycosuria at the GCT.

	0 (n = 240)	1+ (n = 59)	2 or 3+ (n = 26)	ANOVA p	χ^2-test p
Maternal age (year)	30.5 (0.3)	31.4 (0.7)	29.7 (0.9)	0.27	
Nulliparity (n, %)	108 (45%)	30 (51%)	16 (62%)	0.23	
Height (cm)	167 (0.4)	165 (0.8)	163 (1.4)*	0.014	
Pre-pregnancy body weight (kg)	65.9 (0.8)	62.5 (1.2)	58.6 (1.5)*	0.004	
Pre-pregnancy BMI (kg/m^2)	23.7 (0.3)	23.1 (0.5)	22.0 (0.7)	0.14	
Body weight at GCT (kg)	74.1 (0.9)	71.7 (1.5)	66.7 (1.8)*	0.011	
Body weight at final visit (kg)	80.1 (0.8)	77.2 (1.6)	71.9 (2.0)*	**0.005**	
Total weight gain (kg)	14.1 (0.4)	13.2 (1.4)	10.5 (3.1)	0.089	
Weight gain before GCT (kg)	6.9 (0.8)	5.4 (2.1)	3.0 (3.9)	0.31	
Weight gain after GCT (kg)	7.2 (0.7)	7.8 (1.7)	7.5 (2.8)	0.93	
Highest systolic blood pressure (mm Hg)	127 (1)	128 (2)	126 (3)	0.75	
Highest diastolic blood pressure (mm Hg)	79 (0.6)	80 (1)	78 (2)	0.73	
Pre-eclampsia (n, %)	8 (3.3)	2 (3.4)	2 (7.7)		0.53
GA at GCT (week)	26.0 (0.1)	25.7 (0.2)	26.5 (0.3)	0.08	
Plasma glucose at GCT (mg/dl)	113 (2)	120 (4)	137 (6)**	<0.001	
Plasma glucose ≥140 mg/dl (n, %)	29 (12)	12 (20)	13 (50)		<0.001
Treated GDM (diet or/and insulin, %)	3 (1.3)	5 (8)	2 (8)		0.006
GA at delivery (week)	39.1 (0.1)	39.2 (0.2)	38.5 (0.4)	0.16	
Twin pregnancy (n, %)	9 (3.8)	2 (3.4)	2 (7.7)	0.60	
Birth weight (g)	3356 (33)	3310 (61)	3072 (99)*	0.025	
Birth weight SD-score	+0.21 (0.07)	+0.10 (0.13)	−0.09 (0.13)	0.33	
Length (cm)	50.3 (0.2)	49.8 (0.3)	50.1 (0.4)	0.49	
Head circumference (cm)	34.6 (0.1)	34.5 (0.2)	34.3 (0.3)	0.56	
SGA/AGA/LGA (%)[a]	7/76/16	9/79/12	4/96/0		0.21

[a]SGA, small-for-GA; AGA, appropriate-for-GA; and LGA, large-for-GA (analysis in singletons only).
* A significant difference from 0 glycosuria group according to Bonferroni's multiple-comparison test.
** A significant difference from 0 to 1+ glycosuria groups according to Bonferroni's multiple-comparison test.

had a positive GCT. Positive glycosuria was not related to blood pressure or the development of pre-eclampsia. Finally, positive glycosuria was related to a lower birth weight, but not SD-score, length or head circumference.

By contrast, Table 2 shows that gravidas with a positive GCT were older and had a higher BMI, largely owing to a shorter stature. Total weight gain tended to be lower in gravidas with a positive GCT, owing to a reduced post-GCT weight gain. There was no difference in highest recorded systolic ($p = 0.90$) or diastolic ($p = 0.98$) blood pressure, or pre-eclampsia incidence ($p = 0.11$) (data not shown). There was no difference in birth weight (Table 2), length ($p = 0.13$) or head circumference ($p = 0.23$) (data not shown).

Table 3 compares "plasma" responders to the GCT—i.e., a plasma glucose value of ≥140 mg/dl but no glycosuria—with "urine" responders to the GCT—i.e., any degree of glycosuria but a completely normal plasma glucose level (<130 mg/dl, which is the strictest cut-off value for the GCT [1]). Plasma responders were older and had a higher body weight and BMI through pregnancy than urine responders, but the stature of plasma and urine responders was not different. There was no difference in total weight gain, or weight gain before ($p = 0.72$) or after ($p = 0.22$) the GCT. The highest recorded systolic ($p = 0.85$) and diastolic ($p = 0.37$) blood pressure was comparable, as was the incidence of pre-eclampsia ($p = 0.26$). The birth data were comparable as well (Table 3).

Table 2
Pregnancy characteristics according to the GCT result (plasma glucose measurement).

	<140 mg/dl (n = 271)	≥140 mg/dl (n = 54)	Two-sample t-test p	χ^2-test p
GA at GCT (week)	26.0 (0.1)	25.9 (0.2)	0.57	
Maternal age (year)	30.2 (0.3)	32.6 (0.8)	<0.001	
Height (cm)	166.3 (0.4)	164.4 (1.0)	0.059	
Pre-pregnancy body weight (kg)	64.4 (0.7)	66.2 (1.6)	0.21	
Pre-pregnancy BMI (kg/m^2)	23.2 (0.3)	24.4 (0.5)	0.02	
Body weight at GCT (kg)	72.9 (0.8)	74.4 (1.7)	0.30	
Total weight gain (kg)	13.8 (0.5)	12.9 (0.7)	0.06	
Weight gain before GCT (kg)	6.2 (0.8)	6.9 (1.7)	0.71	
Weight gain after GCT (kg)	7.6 (0.7)	6.0 (1.6)	0.004	
GA at delivery (week)	39.1 (0.1)	39.0 (0.3)	0.67	
Twin pregnancy (n, %)	10 (3.7%)	3 (5.6%)		0.52
Birth weight (g)	3345 (30)	3224 (77)	0.11	
Birth weight SD-score	+0.19 (0.06)	+0.32 (0.14)	0.18	
SGA/AGA/LGA (%)[a]	7/77/16	8/84/8		0.35

[a]SGA, small-for-GA; AGA, appropriate-for-GA; and LGA, large-for-GA (analysis in singletons only).

Table 3
Comparison between "plasma" and "urine" responders to a GCT.

	Plasma glucose ≥140 mg/dl but no glycosuria (n = 29)	Plasma glucose <130 mg/dl but glycosuria 1, 2 or 3+ (n = 50)	Two-sample t-test p	χ^2-test p
GA at GCT (week)	25.8 (0.3)	25.9 (0.2)	0.93	
Plasma glucose at GCT (mg/dl)	156 (3)	104 (2)	<0.001	
Maternal age (year)	33.9 (1.0)	30.9 (0.7)	0.036	
Height (cm)	166.1 (1.3)	165.3 (0.9)	0.89	
Pre-pregnancy body weight (kg)	70.8 (2.2)	61.1 (1.3)	<0.001	
Pre-pregnancy BMI (kg/m^2)	25.8 (0.7)	22.5 (0.5)	<0.001	
Body weight at GCT (kg)	79.1 (2.3)	70.0 (1.6)	0.002	
Body weight at final visit (kg)	83.9 (2.5)	76.0 (1.8)	0.006	
Total weight gain (kg)	13.2 (1.0)	11.6 (2.2)	0.50	
GA at delivery (week)	39.0 (0.4)	39.1 (0.2)	0.89	
Twin pregnancy (n, %)	2 (6.9)	2 (4)		0.57
Birth weight (g)	3257 (105)	3255 (63)	0.99	
Birth weight SD-score	+0.05 (0.21)	+0.02 (0.13)	0.55	
SGA/AGA/LGA (%)[a]	11/78/11	8/83/8		0.84

[a]SGA, small-for-GA; AGA, appropriate-for-GA; LGA, large-for-GA (analysis in singletons only).

Since we found a relationship between glycosuria and birth weight (Table 1), this issue was further explored in a multiple regression analysis, with birth weight as the dependent variable and the following independent variables: maternal age, parity (nulliparous or parous), pre-pregnancy body weight, height, total weight gain, highest recorded diastolic blood pressure, GCT result, glycosuria (0, 1+ or ≥2+), and smoking (yes or no); and GA at delivery and newborn sex. This analysis was performed in 295 singleton pregnancies with complete data. In the regression model (F-ratio = 21.0, R^2 = 0.471, p <0.001), birth weight was related to later GA (F-ratio = 133.7, partial R^2 = 0.322, $p < 0.001$), taller stature (F-ratio = 18.7, partial R^2 = 0.062, $p < 0.001$), male sex (F-ratio = 17.1, partial R^2 = 0.057, $p < 0.001$), no smoking (F-ratio = 14.2, partial R^2 = 0.048, $p < 0.001$), more robust weight gain (F-ratio = 11.3, partial R^2 = 0.038, $p < 0.001$), and higher parity (F-ratio = 7.2, partial R^2 = 0.025, p = 0.008); however, age (p = 0.22), pre-pregnancy body weight (p = 0.18), diastolic blood pressure (p = 0.43), post-challenge plasma glucose (p = 0.31) and post-challenge glycosuria (p = 0.66) did not contribute to the model.

4. Comment

The novel finding of the current study is that glycosuria after a 50 g glucose load in the setting of GDM screening is related to (1) higher plasma glucose excursion, and (2) lower body size (both height and weight) (Table 1). A comparison of urine and plasma responders to the glucose load reveals that urine responders have a lower body weight and are younger than plasma responders, while height is comparable in both groups (Table 3).

Body weight is correlated with both pre-pregnancy plasma volume and plasma volume expansion during pregnancy [7]. Thus, gravidas with lower body weight are expected to have a lower plasma distribution volume. The relationship between body weight and glomerular function is unclear because studies use BMI rather than body weight and correct glomerular filtration rate for height or body surface [8,9]. Nonetheless, the filtration fraction (i.e., glomerular filtration rate/effective renal plasma flow) is lower in healthy people with low BMI [8], suggesting that the glycosuria in gravidas with low body weight is not the result of a more effective filtration process.

Body weight is known to affect the kinetics of hormones and drugs taken orally. For example, serum estradiol is higher in estrogen-treated postmenopausal women with lower body weight [10]. Also, hormone steady-state levels are reached later in obese women starting an oral contraceptive [11].

Short stature is a more important risk factor for GDM than is high pre-pregnancy body weight [12–15]. Lower height is also a risk factor for impaired glucose tolerance in non-pregnant adults [16]. Short stature is associated with insulin resistance [13,16] but the underlying pathophysiological pathways remain to be elucidated [15].

In this study, the plasma glucose response but not the degree of glycosuria is related to the subject's BMI. BMI is an index of adiposity, and as such probably a better marker for GDM than is body weight [12,14]; indices of abdominal adiposity (waist circumference, waist-to-hip ratio) may be even more precise markers [17]. However, glycosuria is related to the gravida's body frame and size, but not her adiposity.

A higher age is another major risk factor for GDM, and together with increased adiposity explains the rising prevalence of glucose intolerance during pregnancy [18,19]. As expected, glycosuria is not associated with age.

Thus, although glycosuria depends on the plasma glucose excursion and is more prominent in shorter gravidas, glycosuria fails to capture the clinical risk profile of GDM. In the current study, post-load glycosuria has a sensitivity of only 8.2% to diagnose GDM, with only 29% (25/85) of women with glycosuria having an abnormal GCT. This is comparable to the results of Buhling et al. [4] who reported a sensitivity of 10.8% for pre-load glycosuria.

Since glycosuria equates energy loss, glycosuria might be a determinant of gestational weight gain. Indeed, weight gain occurs in diabetic subjects upon intensifying their glycemic control [20]; the disappearance of glycosuria is thought to contribute to this weight gain [21]. In addition, women with GDM were reported to have a lower gestational weight gain [22]. Here, we confirm that women with a positive GCT experience a lower weight gain in the third trimester. This may be explained in part to the institution of nutrition therapy (in 10/54 subjects), but since the other women did not receive such therapy, other factors must be involved. We demonstrate a trend for a lower total weight gain in women with 2+ or 3+ glycosuria, but apparently no lower weight gain in the third trimester when glycosuria is quantitatively more important. Gribble et al. [3] reported that incidental glycosuria in the third trimester is unrelated to gestational weight gain. In sum, the available data are not definitive and further studies are needed in larger samples.

We document no relationship of post-load glycosuria with the highest recorded systolic or diastolic blood pressure, or the incidence of pre-eclampsia. Buhling et al. [4] reported a higher diastolic but not systolic blood pressure in glycosuria-positive

women. The discrepancy might be explained by the fact that the latter study examined pre-load glycosuria at about 34 weeks GA, which may reflect insulin resistance to a greater degree than post-load glycosuria at 24–28 weeks GA. The association between insulin resistance and hypertension during pregnancy is well established [23].

Birth weight is slightly lower in pregnancies with 2+ or 3+ glycosuria, but without differences in other size measurements. In addition, neither the urine nor the plasma post-load response is a significant predictor of birth weight in a multiple regression. The plasma result might seem surprising in view of the linear relationship between the maternal fasting or post-load plasma glucose level and the risk of a large-for-GA baby, as shown definitively in the HAPO study [24]. However, the HAPO subject sample was very large (>25,000), while our findings in a much smaller sample would indicate that other factors are more important. Indeed, we replicate a similar finding from a previous study at our centre [25] and findings from other studies [26,27]. Even in women with GDM, maternal obesity is a more important risk factor for macrosomia than is the severity of hyperglycemia [28].

This study has limitations and strengths. While ethnic background was not recorded, our clinic serves a diverse population comparable to other series [18]. Pre-pregnancy weight was self-reported at the first antenatal visit. Systematic reviews have concluded that women tend to underreport their weight [29,30]; however, we also recorded weight at the GCT and at the final visit. Glycosuria testing was performed by clinic nurses, but urine glucose testing is a routine practice at our clinic. Finally, the follow-up of an abnormal GCT (oral glucose tolerance test, GDM management) was the responsibility of the treating obstetrician. The strength of the current study is that it is the first study to compare the plasma and urine response to an oral glucose load at the same time.

In conclusion, glycosuria after a glucose challenge test during pregnancy depends on the plasma glucose excursion and is more pronounced in women with smaller body size (height and weight). Glycosuria is not related to age, parity or BMI (adiposity). In addition, glycosuria is a poor predictor of pregnancy outcome including GDM, pre-eclampsia and newborn size at birth.

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