

BMJ Open Relationship between maternal hypoglycaemia and small-for-gestational-age infants according to maternal weight status: a retrospective cohort study in two hospitals

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ABSTRACT

Objective: The relationship between pre-pregnancy body mass index (BMI) and low glucose challenge test (GCT) results by maternal weight status has not been examined. This study aimed to clarify the relationship between a low GCT result and small for gestational age (SGA) by maternal weight status.

Design: A retrospective cohort study in 2 hospitals.

Setting: This study evaluated the obstetric records of women who delivered in a general community hospital and a tertiary perinatal care centre.

Participants: The number of women who delivered in both hospitals between January 2012 and December 2013 and underwent GCT between 24 and 28 weeks of gestation was 2140. Participants with gestational diabetes mellitus or diabetes during pregnancy, and GCT results of ≥ 140 mg/dL were excluded.

Finally, 1860 women were included in the study.

Primary and secondary outcome measures: The participants were divided into low-GCT (≤ 90 mg/dL) and non-low-GCT groups (91–139 mg/dL). The χ^2 tests and multivariate logistic regression analyses were conducted to investigate the association between low GCT results and SGA by maternal weight status.

Results: The incidence of SGA was 11.4% (212/1860), and 17.7% (330/1860) of the women showed low GCT results. The patients were divided into 3 groups according to their BMI (underweight, normal weight and obese). When the patients were analysed separately by their weight status after controlling for maternal age, pre-pregnancy maternal weight, maternal weight gain during pregnancy, pregnancy-induced hypertension, thyroid disease and difference in hospital, low GCT results were significantly associated with SGA (OR 2.10; 95% CI 1.14 to 3.89; $p=0.02$) in the underweight group.

Conclusions: Low GCT result was associated with SGA at birth among underweight women. Examination of maternal glucose tolerance and fetal growth is necessary in future investigations.

Strengths and limitations of this study

- To the best of our knowledge, this study is the first to clarify the relationship between low glucose challenge test (GCT) result and small for gestational age (SGA) by maternal weight status.
- We collected data from two hospitals, and the generalisability of the results may be relatively high.
- Conducting the analyses by each prenatal weight status was possible because the number of participants was relatively large.
- Data regarding history of childbirth, intake of alcohol and caffeine, antiphospholipid syndrome, maternal smoking status, kidney disease and inflammatory bowel disease were not considered in this study, although these are potential contributors for SGA.
- We hypothesised that low GCT results may have occurred as a result of high insulin sensitivity that has continued from early pregnancy, but we did not investigate the relationship between maternal weight gain and insulin sensitivity.

INTRODUCTION

Small for gestational age (SGA) is associated with increased perinatal mortality and morbidity¹ as well as future risk of developing obesity, cardiovascular disease and type 2 diabetes.² Several studies suggested that prenatal identification of SGA is an effective preventive measure to reduce the risk of adverse perinatal outcomes and stillbirth, with appropriate close monitoring and timing of birth.^{3–4} However, most SGA babies remain undetected via ultrasound until birth.⁵ Therefore, identifying the causes of SGA and defining strategies to improve early detection of SGA are important. SGA is attributed to many factors, such as aneuploidy, placental insufficiency, infection and connective tissue disease.^{2–6} Moreover, several studies suggested

that birth weight is related to insulin resistance in normal and gestational diabetic pregnancies.^{2–7} For instance, Caruso *et al*⁸ reported that women with unexplained fetal growth restriction (FGR) have higher insulin sensitivity. The Japan Society of Obstetrics and Gynecology recommended the 50 g glucose challenge test (GCT) as a screening method for gestational diabetes mellitus (GDM).⁶ Women with abnormal GCT results (serum glucose levels of >140 mg/dL) subsequently undergo a 75 g oral glucose tolerance test for a definitive diagnosis. We have recently reported that a significant association exists between low GCT results and SGA infants.⁹ We hypothesise that high maternal insulin sensitivity is responsible for SGA infants.⁹ Similarly, an association between low GCT results and SGA infants has been reported. Insulin sensitivity is typically higher in underweight people than in overweight and normal weight people.^{10–11} Moreover, Catalano *et al*⁷ stated that the development of insulin resistance in late gestation is a normal process in all human pregnancies and the development of maternal insulin resistance is associated with accretion of maternal adipose tissue in early pregnancy. In other words, although abnormal GCT results are not observed in the second trimester of pregnancy, differences in insulin sensitivity may exist at a later period of the pregnancy due to the weight status of the women before pregnancy.

To the best of our knowledge, no study until now has used both pre-pregnancy body mass index (BMI) and GCT results to develop more effective identification of fetuses at risk of SGA. In our previous study, we examined the association between low GCT results and SGA infants, but the association by maternal weight status was difficult to assess because of the small sample size.

In this retrospective multicentre cohort study, we used a relatively large sample and sufficient information regarding potential confounding factors for SGA (compared with the previous studies)^{12–15} of obstetric records to clarify the relationship between low GCT results and SGA by maternal weight status.

METHODS

Participants

We collected the obstetric records of women who delivered in a general community hospital and a tertiary perinatal care centre in Japan between January 2012 and December 2013. This retrospective cohort study included all women who underwent GCT between 24 and 28 weeks of gestation. Similar to our recent research, we excluded cases of GDM or diabetes in pregnancy because they have an increased risk of macrosomia or large-for-gestational age infants. We also excluded women with GCT results of ≥ 140 mg/dL because their glucose metabolism may have been similar to that in GDM, even in the absence of a definitive diagnosis.

Data collection

Age at admission, blood pressure, presence of thyroid disease, pre-pregnancy BMI, weight gain during pregnancy and GCT results were collected from the obstetric records. Pregnancy-induced hypertension (PIH), thyroid disease, teenage pregnancy, underweight status ($\text{BMI} < 18.5 \text{ kg/m}^2$) and poor gestational weight gain ($< 5 \text{ kg}$) were used as explanatory variables because they have been previously described as risk factors for SGA.^{6, 16–21} In the present study, PIH was defined as blood pressure values of $\geq 140/90 \text{ mm Hg}$.²² Thyroid disease was defined as hypothyroidism or hyperthyroidism. Pre-pregnancy BMI was calculated according to the WHO standards ($\text{bodyweight (kg)}/\text{height (m)}^2$). We classified the participants as underweight ($< 18.5 \text{ kg/m}^2$), normal ($18.5\text{--}25.0 \text{ kg/m}^2$) and obese ($\geq 25.0 \text{ kg/m}^2$) according to the Japan Society of Obstetrics and Gynecology Guidelines for Obstetrical Practice (2014).⁶ Maternal weight gain during pregnancy was calculated by subtracting the participant's pre-pregnancy bodyweight from her bodyweight at the last prenatal visit before delivery. The participants were classified as having poor gestational weight gain ($< 5 \text{ kg}$) or non-poor gestational weight gain ($\geq 5 \text{ kg}$).⁵ SGA was defined as infants who had a weight below the 10th centile in each gestational week.²³

Statistical analyses

The Mann-Whitney U test and χ^2 test were conducted to compare maternal and neonatal outcomes. Fisher's exact test was used when the expected frequency was < 5 . When we classified women according to their GCT results, a threshold of 90 mg/dL was chosen because previous studies suggested that women with GCT results of ≤ 90 mg/dL are at risk for SGA and adverse perinatal outcomes.^{9, 15, 24} Multivariable logistic regression analysis was then carried out by dividing the groups by maternal pre-pregnancy BMI (underweight, normal and obesity) to examine the association between low GCT results and SGA while controlling for the potential confounding factors. All analyses were performed using Ekuseru-Toukei 2012 (Social Survey Research Information), and the significance level was set at $p < 0.05$.

RESULTS

The number of births during the study period was 2850, and 2140 women underwent GCT between 24 and 28 weeks of gestation. Of these births, 1860 (65.2%) were considered eligible for inclusion in this study. The mean maternal age was 31.6 ± 5.3 years, with 852 (45.8%) nulliparity, 84 (4.5%) instrumental deliveries and 555 (33.0%) caesarean deliveries.

Table 1 lists the clinical characteristics of the enrolled women. The characteristics of the low-GCT and non-low-GCT groups were almost similar, except for the lower maternal age and caesarean delivery rate in the low-GCT group. The overall incidence of SGA was 11.4%

Table 1 Clinical characteristics according to maternal glucose challenge test results

	≤90 mg/dL n=329	91–139 mg/dL n=1531	p Value
Maternal age	30.1±5.4	31.4±5.3	<0.01
Nulliparity	163 (49.5%)	689 (45.0%)	0.14
Caesarean section	74 (22.5%)	481 (31.4%)	<0.01
Instrumental delivery	12 (3.9%)	72 (4.7%)	0.39
Male sex	160 (48.6%)	751 (49.0%)	0.84
SGA	51 (15.5%)	161 (10.5%)	<0.01

Values are presented as mean±SD or number (%).
SGA, small for gestational age.

(212/1860), and 17.7% (329/1860) of women showed low GCT results. Among the 1860 women, the prevalence of SGA was significantly higher in the low-GCT group than in the non-low-GCT group (15.5% vs 10.5%; $p=0.01$) (table 1).

According to categorisation by their BMI, 380 of 1860 (20.4%) patients were underweight, 1325 (71.3%) patients were normal and 155 (8.3%) patients were obese. Low GCT results were significantly associated with SGA ($p=0.02$; OR 2.10; 95% CI 1.14 to 3.89) in the underweight group. However, no significant associations were found between low GCT result and SGA in the normal and obesity groups in the multivariable logistic regression analysis (table 2).

DISCUSSION

In this study, low GCT result was significantly associated with SGA births only among pregestational underweight women. A general consensus exists that birth weight is directly related to insulin sensitivity,^{2 7} indicating that maternal carbohydrate metabolism plays an important role in fetal growth. According to these studies, high insulin sensitivity in underweight women during early pregnancy may influence maternal carbohydrate metabolism and maternal periconceptual nutrition. Consequently, lack of insulin resistance may hinder normal carbohydrate metabolism, resulting in low maternal serum glucose levels. Dalfrà *et al*² reported that hypoglycaemia may limit fetal glucose supply and eventually result in slow fetal growth as glucose is the main fetal nutrient, which is supplied by the mother. However, this mechanism is difficult to apply in obese women because they are generally less insulin sensitive than the normal-weight population. Low maternal insulin sensitivity before conception is strongly associated with fetal fat accretion.⁷ Thus, low GCT results may have occurred as a result of the high insulin sensitivity that has continued from early pregnancy, particularly in underweight women.

Maternal abdominal palpation and serial measurements of symphysis-fundal height are used as a traditional approach to identify high-risk cases for SGA. However, the detection rate of this approach is <30%.²⁵ Recently, the combination of fetal parameters,

biochemical indices and maternal demographics has been shown to be predictive for SGA.^{26 27} However, measuring biochemical indices for all pregnant women without additional cost is extremely difficult. Thus, this method is often restricted to high-risk pregnancies. In contrast, if 50 g GCT may also provide diagnostic information regarding SGA, this method is useful because it is widely used for GDM screening in Japan. Therefore, additional cost or patient examinations are unnecessary.

Our study has several limitations. First, data regarding a prior history of childbirth, intake of alcohol and caffeine, antiphospholipid syndrome, maternal smoking status, kidney disease and inflammatory bowel disease, which may affect insulin sensitivity, were not considered in this study, although these are potential contributors for SGA.^{6 28–30} Some women with SGA in this study may be affected by the aforementioned risk factors. Second, we hypothesised that low GCT results may have occurred as a result of high insulin sensitivity that has continued from early pregnancy. However, there are no data available regarding the insulin sensitivity of the patients in this study, and we did not investigate the relationship between maternal weight gain and insulin sensitivity. van Raaij *et al*³¹ reported that maternal weight gain can influence subsequent maternal insulin resistance; thus, examining their relationship may be necessary. Regular measurement of insulin sensitivity during pregnancy can clarify the relationship between maternal weight gain and GCT results. Third, the generalisability of our findings may be limited by the homogeneity of this cohort, which contained only Japanese women. Finally, although insulin sensitivity might be associated with SGA, using the GCT result as a proxy indicator of insulin sensitivity might be difficult. This is because the former may have low reliability and may be affected by many factors, such as age, body weight, living environment, change in life partner and situation in which the meal was consumed.⁹ According to previous studies,^{9 15 24} low GCT results are useful to predict SGA and perinatal adverse outcomes. This study suggests that low GCT results were significantly associated with SGA among pregestational underweight women. In the future, further investigation is necessary to apply low GCT results as a risk factor for SGA. For example, if insulin sensitivity could be

Table 2 ORs of maternal risk factors for the delivery of a small-for-gestational-age infant analysed separately by maternal weight status

Variables	SGA (n)	Non-SGA (n)	Crude		Adjusted	
			OR	95% CI	OR	95% CI
<i>BMI</i> <18.5 kg/m ²						
Low GCT						
No	41	256	1.0	Reference	1.0	Reference
Yes	20	63	1.98	1.08 to 3.62	2.28	1.21 to 4.28
PIH						
No	57	315	1.0	Reference	1.0	Reference
Yes	4	4	5.52	1.34 to 22.7	5.58	1.29 to 24.1
Maternal height, cm						
≥150	49	294	1.0	Reference	1.0	Reference
<150	12	25	2.88	1.36 to 6.11	3.88	1.73 to 8.72
Thyroid disease						
No	60	313	1.0	Reference	1.0	Reference
Yes	1	6	0.87	0.10 to 7.35	0.79	0.09 to 6.89
Teenage pregnant woman						
No	59	306	1.0	Reference	1.0	Reference
Yes	2	13	0.79	0.17 to 3.63	1.00	0.20 to 4.90
Tertiary perinatal care centre						
No	27	179	1.0	Reference	1.0	Reference
Yes	34	140	1.61	0.93 to 2.79	2.06	1.14 to 3.72
<i>18.5</i> ≤ <i>BMI</i> ≤ <i>25.0</i> kg/m ²						
Low GCT						
No	105	989	1.0	Reference	1.0	Reference
Yes	29	202	1.35	0.87 to 2.09	1.32	0.85 to 2.06
PIH						
No	126	1155	1.0	Reference	1.0	Reference
Yes	8	36	2.03	0.93 to 4.48	1.96	0.89 to 4.34
Maternal height, cm						
≥150	121	1088	1.0	Reference	1.0	Reference
<150	13	103	1.13	0.62 to 2.08	1.09	0.59 to 2.01
Thyroid disease						
No	131	1168	1.0	Reference	1.0	Reference
Yes	3	23	1.16	0.34 to 3.92	1.16	0.34 to 3.96
Teenage pregnant woman						
No	131	1172	1.0	Reference	1.0	Reference
Yes	3	19	1.41	0.41 to 4.84	1.40	0.40 to 4.87
Tertiary perinatal care centre						
No	69	635	1.0	Reference	1.0	Reference
Yes	65	556	1.41	0.41 to 4.83	1.07	0.75 to 1.54
<i>BMI</i> >25.0 kg/m ²						
Low GCT						
No	15	125	1.0	Reference	1.0	Reference
Yes	2	13	1.28	0.26 to 6.23	1.58	0.25 to 9.96
PIH						
No	13	127	1.0	Reference	1.0	Reference
Yes	4	11	3.55	0.99 to 12.8	4.34	1.09 to 17.3
Maternal height, cm						
≥150			1.0	Reference	1.0	Reference
<150					6.74	1.88 to 24.2
Thyroid disease						
No	16	135	1.0	Reference	1.0	Reference
Yes	1	3	2.81	0.28 to 28.7	1.51	0.12 to 19.6
Teenage pregnant woman						
No	16	137	1.0	Reference	1.0	Reference
Yes	1	1	8.5	0.51 to 143.6	14.3	0.73 to 281.7
Tertiary perinatal care centre						
No	11	90	1.0	Reference	1.0	Reference
Yes	6	48	1.02	0.36 to 2.93	1.07	0.75 to 1.54

BMI, body mass index; GCT, glucose challenge test result; PIH, pregnancy-induced hypertension; SGA, small for gestational age.

measured on the same day of GCT examination, further evidence may be obtained for the relationship between low GCT results and SGA.

Although some limitations exist, the design and number of participants were the strengths of this study. First, since we collected the data from two hospitals, the generalisability of results may be relatively high. One hospital is a general community hospital, and the other is a tertiary perinatal care centre. Second, conducting the analyses by each prenatal weight status was possible because the number of participants was relatively large. However, with regard to the subanalysis according to maternal weight status, this study is probably underpowered. Therefore, we would like to conduct a more large-scale prospective study in the future.

In conclusion, low 50 g GCT results were significantly associated with SGA among pregestational underweight women. These results suggest that women who were underweight before pregnancy with low GCT results may be considered as relatively high-risk cases. In addition, the association between insulin sensitivity and fetal growth should be examined in future studies.

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