

Association between neonatal birthweight and risk of maternal glucose intolerance after gestational diabetes mellitus

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Keywords

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ABSTRACT

Aims/Introduction: To evaluate whether the neonatal birthweight (NBW) is associated with early postpartum glucose intolerance in women with gestational diabetes mellitus.

Materials and Methods: A total of 1,113 women diagnosed with gestational diabetes mellitus who completed an oral glucose tolerance test at 6–9 weeks postpartum between 1 April 2014 and 8 January 2020 were included in this observational prospective cohort study. They were grouped by neonatal birthweight quartiles, and the odds ratios of postpartum glucose intolerance for different levels of neonatal birthweight were assessed.

Results: A lower NBW quartile was associated with an increased maternal risk of postpartum glucose intolerance after gestational diabetes mellitus. The adjusted odds ratios for maternal glucose intolerance were 1.69 (95% confidence interval 1.13–2.51) in the lowest NBW quartile (NBW 1,980–2,930 g) when compared with the highest NBW quartile (NBW 3,410–4,610 g). The association between lower NBW and maternal glucose intolerance was significantly stronger in women who delivered a girl. Additionally, NBW $\geq 3,100$ g appears to be associated with a lower risk of maternal glucose intolerance postpartum.

Conclusions: Our findings suggest that low NBW is a previously unrecognized risk factor for maternal glucose intolerance after gestational diabetes in early postpartum in South China.

INTRODUCTION

Gestational diabetes mellitus (GDM) identifies women who have a defect in β -cell function, such that they are unable to secrete sufficient insulin to fully compensate for the insulin resistance of pregnancy¹. Our previous study showed that the risk of developing type 2 diabetes in women with previous GDM increased linearly by 9.6‰ for every additional 1 year of follow up, and almost one-fifth of women with GDM would develop type 2 diabetes when the follow-up duration extended to 10 years². Even in the early postpartum period, women with a diagnosis of GDM are up to 50% likely to develop glucose intolerance³. Furthermore, half of the women with persistent glucose intolerance in the early postpartum period would develop type 2 diabetes within 5 years after the delivery⁴. Therefore, several guidelines have emphasized the importance and necessity of a postpartum glucose tolerance test for women

with previous GDM to screen for type 2 diabetes^{5,6}. However, the low rates of screening tests postpartum hint that we need to make more effort to increase the compliance of the caregivers and patients⁷. Distinguishing risk factors early and consequently targeting women at high risk for postpartum glucose intolerance might increase the compliance of postpartum screening, and initiate early diagnosis and intervention that can prevent or delay the onset of type 2 diabetes.

Neonatal birthweight (NBW) is an indicator apparently familiar to obstetricians and women who have given birth. Two common complications of maternal hyperglycemia involving birthweight include fetal growth restriction and fetal macrosomia, which seem contradictory, but reasonable. Fetal macrosomia could be the consequence of undetected maternal hyperglycemia⁸, and the mechanism is based on the Pedersen hypothesis that maternal hyperglycemia led to fetal hyperglycemia, which evoked an exaggerated fetal response to insulin⁹.

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Given the central role of β -cell dysfunction in determining a woman's risk of GDM and postpartum impaired glucose tolerance, we hypothesized that neonatal birth weight reflecting partial beta cell dysfunction could hold implications for the maternal aberrant glucose tolerance risk after delivery. Although previous studies have addressed the importance of prenatal ultrasound estimation of fetal birthweight for the prediction of oral glucose tolerance test results during pregnancy^{10,11}, there are no reports on the prediction value of NBW for maternal glucose intolerance after delivery so far. Thus, we carried out an observational prospective cohort study of women with GDM to investigate the association between NBW and the risk of maternal impaired glucose tolerance in the postpartum period, in the hope of discovering a new risk factor that has never been suspected previously.

METHODS

Study design

This study was carried out as part of an ongoing cohort study of pregnant women who received antenatal care at one of the largest regional university hospitals in South China (The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China). This study was reviewed and approved by the institutional review board of The First Affiliated Hospital of Sun Yat-sen University (reference number: [2014]No. 93). All participants provided written informed consent, and the ethics committee approved this consent. Women without prediabetes or diabetes in early pregnancy received a 75-g oral glucose tolerance test (OGTT) between 24 and 28 weeks of gestation. The diagnosis of GDM was based on the International Association of Diabetes and Pregnancy Study Groups criteria¹². All women with GDM were referred to the GDM outpatient clinic consisting of dietitians and obstetricians who would offer dietary and exercise advice to help achieve glycemic targets.

Glycemic targets for women with GDM were based on the American Diabetes Association recommendation¹³. Obstetricians reviewed blood glucose self-monitoring records at each visit. When more than half of the glucose values at any given time point were still elevated within 2 weeks after lifestyle interventions, including exercise and dietary instruction, subcutaneous insulin therapy was initiated. Women with GDM who delivered a live singleton at full-term between 1 April 2014 and 8 January 2020 were recruited in this study. Participants were invited for a visit 6–9 weeks postpartum to undergo a 75-g OGTT. Women were eligible for the present analysis unless they met one or more of the following exclusion criteria: pregestational diabetes mellitus, including pre-existing type 1 or type 2 diabetes mellitus and overt diabetes first diagnosed during pregnancy; multiple pregnancy; preterm labor; or missing data on postpartum OGTT. Ultimately, a total of 1,113 participants were included.

Study assessment

Baseline characteristics and the obstetric history were collected at the first antenatal care visit. Gestational age was determined based on the last menstrual period (LMP) or ultrasound

biometric measurements in our cohort study. If menstrual cycle characteristics and the date of onset of the last menstrual bleed could be clearly established, LMP was used to initially assess gestational age. When the gestational age by LMP was not consistent with the ultrasound biometric measurements in the first trimester, crown–rump length was used to determine gestational age. When the gestational age by LMP was not consistent with ultrasound biometric measurement in the second trimester and crown–rump length in first trimester was not available, a combination of multiple biometric parameters (biparietal diameter, head circumference, abdominal circumference and femur length) was used to determine gestational age. Prepregnancy body mass index (BMI) was calculated as the prepregnancy weight (self-reported by participants) in kilograms divided by height in meters squared (kg/m^2). Gestational weight gain (GWG) was calculated as the difference in weight between predelivery and prepregnancy.

Hemoglobin A1c (HbA1c) values were regularly measured before delivery (often 1 day before programmed delivery and in the day of emergency delivery) in our cohort study. As American Diabetes Association has recommended¹⁴, HbA1c target of <6% is optimal during pregnancy if it can be achieved without significant hypoglycemia, and HbA1c can be used as a secondary measure of glycemic control in pregnancy, as it represents an integrated measure of glucose, after self-monitoring of blood glucose. Thus, HbA1c values in the third trimester before delivery that were not <6% were recognized to be poor glycemic control.

Pregestational diabetes mellitus included established diabetes before pregnancy and overt diabetes first diagnosed during pregnancy. Established diabetes could be diagnosed easily by a past history provided by patients. The strategy of screening for overt diabetes first diagnosed during pregnancy was as follows. In early pregnancy, cut-offs for tests used to detect overt diabetes in the non-pregnant population are recommended (fasting plasma glucose ≥ 7.0 mmol/L, random plasma glucose ≥ 11.1 mmol/L or HbA1c $\geq 6.5\%$). Women who were not previously diagnosed with diabetes would carry out a 75-g OGTT, with plasma glucose measurement when the patient was fasting, and at 1 and 2 h, at 24–28 weeks of gestation. The diagnosis of GDM was made when any serum glucose value was met or exceeded the thresholds during OGTT: fasting blood glucose 5.1 mmol/L; 1-h glucose 10.0 mmol/L; and 2-h glucose 8.5 mmol/L. However, fasting plasma glucose ≥ 7.0 mmol/L or 2-h value ≥ 11.1 mmol/L during OGTT was considered as pregestational diabetes mellitus¹⁵. According to the World Health Organization 1999 criteria¹⁶, type 2 diabetes was defined as fasting glucose ≥ 7.0 mmol/L, and/or 2-h glucose ≥ 11.1 mmol/L. Prediabetes was defined as either impaired fasting glucose (fasting glucose ≥ 6.1 mmol/L and <7.0 mmol/L) or impaired glucose tolerance (IGT; 2-h glucose ≥ 7.8 mmol/L and <11.1 mmol/L). Postpartum glucose intolerance consisted of type 2 diabetes and prediabetes. Fasting glucose <6.1 mmol/L and 2-h blood glucose <7.8 mmol/L were identified as normal.

Statistical analysis

Women were grouped based on the NBW quartiles, which were calculated according to the distribution of NBW. Continuous variables are presented as the mean and standard deviation (SD), and categorical variables as frequencies with percentages. Tests for differences in means were assessed using the Mann–Whitney *U*-test or the Kruskal–Wallis test for continuous variables, using the χ^2 -test (or Fisher's exact test in the case of small cell frequencies) for independence for categorical variables. Logistic regression models were used for data analysis with postpartum glucose disturbance as a binary response variable and categories of NBW as explanatory variables. For continuous variable analysis, odds ratios (ORs) for risk of postpartum glucose intolerance were calculated for a 1-SD decrease (383 g) in NBW.

Additional comparisons of postpartum glucose disturbance among quartiles of NBW were carried out using multivariable logistic regression analysis adjusted for the following confounders: model I, unadjusted model; model II, adjusted for maternal age, prepregnancy BMI, gestational age at delivery, neonatal sex and GWG; model III, model II plus adjusted for HbA1c $\geq 6.0\%$ before delivery, hypertensive diseases and insulin treatment during pregnancy. Unadjusted and adjusted ORs were shown with the 95% confidence intervals (CIs).

An adjusted model using a restricted cubic spline with five knots was constructed to show the association between the risk of maternal glucose intolerance and continuous covariate of NBW, using a reference value of 3,000 g.

Subgroup analysis of the study participants stratified by the demographics and underlying risk factors for postpartum glucose intolerance was also examined.

We used Stata, version 15.0 (StataCorp, College Station, TX, USA) for all analyses. A two-tailed *P*-value < 0.05 for main effects and interactions was considered statistically significant.

RESULTS

Baseline characteristics

In total, 1,113 women were included for the final analysis. The overall rate of postpartum OGTT screening in the study population was 38% (1,113/2,930).

The OGTT was carried out at 7.6 ± 1.8 weeks after delivery. Of all women with an OGTT postpartum, the incidence rates of glucose intolerance postpartum, impaired fasting glucose, IGT, prediabetes and type 2 diabetes were 34.6, 1.3, 30.9, 31.8 and 3.2%, respectively.

Table 1 shows the characteristics of participants by NBW quartiles: quartile 1 (Q1; 1,980–2,930 g), quartile 2 (Q2; 2,930–3,160 g), quartile 3 (Q3; 3,160–3,410 g) and quartile 4 (Q4; 3,410–4,610 g). Prepregnancy BMI, gestational age at delivery and GWG increased markedly with ascending quartiles of NBW (all $P < 0.01$). Meanwhile, the proportion of multiparity and male neonates increased significantly with ascending

quartiles of NBW (all $P < 0.01$). Although the prevalence of postpartum glucose intolerance slightly decreased with ascending quartiles of NBW ($P = 0.11$), the incidence of postpartum glucose intolerance in Q1 (38.5%) was significantly higher than that in Q4 (29.1%; $P = 0.02$).

Association with postpartum glucose intolerance

Table 2 shows the unadjusted and adjusted ORs of postpartum glucose intolerance. In multivariable logistic regression models with the highest NBW quartile (Q4) as the reference group, the risks of postpartum aberrant glucose tolerance were increased in Q1, with an unadjusted OR of 1.52 (95% CI 1.07–2.17), 1.50 (95% CI 1.04–2.15) and 1.49 (95% CI 1.03–2.15) for postpartum glucose intolerance, prediabetes and IGT, respectively. The differences persisted after adjustment for maternal age, prepregnancy BMI, gestational age at delivery, neonatal sex, GWG, HbA1c $\geq 6.0\%$ before delivery, hypertensive diseases and insulin treatment during pregnancy. Other than in Q1, the risks of postpartum aberrant glucose tolerance were also increased in Q2, with an adjusted OR of 1.53 (95% CI 1.05–2.23), 1.54 (95% CI 1.05–2.25) and 1.59 (95% CI 1.08–2.33) for postpartum glucose intolerance, prediabetes and IGT, respectively. However, the risk of type 2 diabetes did not differ among all quartiles of NBW in all models.

Next, results for analyses of NBW as a continuous variable, with all models, are shown in Table 3. The ORs for an decrease in NBW by 1 SD (383 g) were highest for postpartum glucose intolerance 1.14 (95% CI 1.01–1.29). Similarly, increased risks were found for postpartum glucose intolerance and prediabetes after adjusting confounding factors, for which the ORs for each 1 SD decrease in NBW were 1.19 (95% CI 1.03–1.37) and 1.18 (95% CI 1.02–1.36), respectively. However, the risk of IGT and type 2 diabetes did not increase significantly with 1 SD decrease in NBW in all models.

In the adjusted restricted cubic spline models, after adjustment for maternal age, prepregnancy BMI, gestational age at delivery, neonatal gender, GWG, HbA1c $\geq 6.0\%$ before delivery, hypertensive diseases and insulin treatment during pregnancy, we found a NBW $\geq 3,100$ g appeared to be associated with a lower risk with higher NBW (Figure 1).

Stratified analysis

Figure 2 shows subgroup analyses stratified by demographics and potential risk factors for postpartum glucose intolerance. As shown, one interaction effect between subgroup and NBW was identified: lowest NBW (Q1) was associated with a greater risk of postpartum glucose intolerance in women with female neonates (adjusted OR 2.0, 95% CI 1.10–3.60) than with male neonates (adjusted OR 1.21, 95% CI 0.69–2.10, $P < 0.01$ for interaction). No significant interaction effects were identified for maternal age, prepregnancy BMI, multiparity and mode of delivery. However, lower NBW was significantly predictive of postpartum glucose intolerance in those who delivered vaginally.

Table 1 | Baseline characteristics of study population stratified into groups based on neonatal birthweight quartiles

	Total n = 1,113	NBW quartiles				P-value
		Q1 (1,980–2,930 g) n = 278	Q2 (2,930–3,160 g) n = 278	Q3 (3,160–3,410 g) n = 279	Q4 (3,410–4,610 g) n = 278	
Maternal age (years)	33.4 ± 4.5	33.3 ± 4.5	33.4 ± 4.5	33.1 ± 4.2	33.8 ± 4.6	0.38
Multiparity	497 (44.7)	112 (40.3)	117 (42.1)	124 (44.4)	144 (51.8)	<0.01
Previous GDM	82 (16.5)	18 (16.1)	23 (19.7)	19 (15.3)	22 (15.3)	0.77
Prepregnancy BMI (kg/m ²)	21.8 ± 3.1	21.2 ± 2.7	21.2 ± 2.8	22.0 ± 3.0	22.9 ± 3.3	<0.01
Predelivery BMI (kg/m ²)	26.2 ± 3.1	25.3 ± 2.9	25.7 ± 2.8	26.4 ± 2.9	27.6 ± 3.4	<0.01
Gestational weight gain (kg)	11.2 ± 4.2	10.2 ± 4.2	11.3 ± 3.9	11.2 ± 4.2	12.2 ± 4.2	<0.01
Cesarean delivery	605 (54.4)	143 (51.4)	136 (48.9)	150 (53.7)	176 (63.3)	<0.01
Hypertensive diseases	51 (4.6)	16 (5.8)	13 (4.7)	16 (5.7)	6 (2.2)	0.14
Gestational age at delivery (weeks)	38.9 ± 0.9	38.5 ± 0.9	38.9 ± 0.8	39.0 ± 0.8	39.2 ± 0.7	<0.01
Neonatal sex (male)	600 (53.9)	119 (42.8)	144 (51.8)	162 (58.1)	175 (62.9)	<0.01
OGTT during pregnancy (mmol/L)						
Fasting plasma glycaemia	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.6 ± 0.5	4.7 ± 0.5	<0.01
Glycaemia 1 h	9.8 ± 1.3	9.7 ± 1.5	9.9 ± 1.3	9.8 ± 1.3	9.9 ± 1.2	0.25
Glycaemia 2 h	8.8 ± 1.2	8.9 ± 1.3	8.8 ± 1.1	8.9 ± 1.1	8.7 ± 1.2	0.28
Insulin treatment (%)	13 (1.2)	3 (1.1)	2 (0.72)	2 (0.72)	6 (2.2)	0.34
Insulin dose per day (units)	18.2 ± 10.4	21.0 ± 13.5	21.0 ± 12.7	10.0 ± 2.8	18.5 ± 10.9	0.12
HbA1c value before delivery (%)	5.4 ± 0.4	5.4 ± 0.4	5.4 ± 0.3	5.4 ± 0.4	5.4 ± 0.5	0.88
Frequency of HbA1c ≥6.0% before delivery	60 (5.4)	15 (5.4)	10 (3.6)	14 (5.0)	21 (7.6)	0.22
Postpartum OGTT (mmol/L)						
Fasting plasma glycaemia	4.8 ± 0.5	4.8 ± 0.5	4.8 ± 0.5	4.8 ± 0.5	4.8 ± 0.5	0.40
Glycaemia 2 h	7.2 ± 1.8	7.2 ± 1.8	7.3 ± 1.7	7.1 ± 1.8	7.1 ± 1.7	0.41
IFG	15 (1.3)	8 (2.9)	3 (1.1)	0 (0)	4 (1.4)	0.03
IGT	344 (30.9)	94 (33.8)	93 (33.8)	86 (30.8)	71 (25.5)	0.13
Prediabetes	354 (31.8)	99 (35.6)	94 (33.8)	86 (30.8)	75 (27.0)	0.14
Type 2 diabetes	36 (3.2)	9 (3.2)	9 (3.2)	9 (3.2)	9 (3.2)	1.0
Postpartum glucose intolerance	385 (34.6)	107 (38.5)	102 (36.7)	95 (34.1)	81 (29.1)	0.11

Data are expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are expressed as number (percentage). P-values are presented for comparison among four quartiles group. BMI, body mass index; HbA1c, hemoglobin A1c; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

Table 2 | Odds ratios for the association between neonatal birthweight quartiles and postpartum impaired glucose tolerance

	NBW	n (%)	Model I OR (95% CI)	P	Model II OR (95%CI)	P	Model III OR (95%CI)	P
Postpartum glucose intolerance	Q1	107 (27.8)	1.52 (1.07–2.17)	0.02	1.65 (1.11–2.45)	0.02	1.69 (1.13–2.51)	<0.01
	Q2	102 (26.5)	1.41 (0.99–2.01)	0.06	1.49 (1.03–2.18)	0.03	1.53 (1.05–2.23)	0.02
	Q3	95 (24.7)	1.26 (0.88–1.80)	0.21	1.31 (0.91–1.89)	0.15	1.34 (0.92–1.94)	0.12
	Q4	81 (21.0)	Reference		Reference		Reference	
Prediabetes	Q1	99 (28.0)	1.50 (1.04–2.15)	0.03	1.71 (1.14–2.56)	<0.01	1.73 (1.16–2.60)	<0.01
	Q2	94 (26.6)	1.38 (0.96–1.99)	0.08	1.51 (1.03–2.22)	0.03	1.54 (1.05–2.25)	0.03
	Q3	86 (24.3)	1.21 (0.84–1.74)	0.32	1.28 (0.88–1.86)	0.20	1.30 (0.89–1.90)	0.17
	Q4	75 (21.2)	Reference		Reference		Reference	
IGT	Q1	94 (27.3)	1.49 (1.03–2.15)	0.03	1.67 (1.11–2.51)	0.01	1.67 (1.11–2.50)	0.01
	Q2	93 (27.0)	1.47 (1.02–2.12)	0.04	1.59 (1.08–2.33)	0.02	1.59 (1.08–2.33)	0.02
	Q3	86 (25.0)	1.30 (0.90–1.88)	0.17	1.36 (0.93–1.99)	0.11	1.36 (0.93–1.99)	0.11
	Q4	71 (20.6)	Reference		Reference		Reference	
Type 2 diabetes	Q1	9 (25.0)	1.00 (0.39–2.56)	1.00	0.73 (0.25–2.10)	0.56	0.82 (0.28–2.45)	0.71
	Q2	9 (25.0)	1.00 (0.39–2.56)	1.00	0.84 (0.31–2.24)	0.72	0.97 (0.35–2.64)	0.99
	Q3	9 (25.0)	1.00 (0.39–2.55)	0.99	0.91 (0.35–2.37)	0.84	1.07 (0.40–2.87)	0.86
	Q4	9 (25.0)	Reference		Reference		Reference	

Model I: not adjusted. Model II: adjusted for maternal age, prepregnancy body mass index, gestational age, neonatal sex and gestational weight gain. Model III: adjusted for variables in model II plus hypertensive diseases, insulin treatment during pregnancy and hemoglobin $\geq 6.0\%$ before delivery.

Table 3 | Adjusted odds ratios for association between neonatal birthweight as a continuous variable and postpartum impaired glucose tolerance

	Postpartum glucose intolerance		Prediabetes		IGT		Type 2 diabetes	
	OR	P	OR	P	OR	P	OR	P
Model I	1.14 (1.01–1.29)	0.04	1.12 (0.99–1.27)	0.08	1.11 (0.98–1.26)	0.11	1.16 (0.83–1.63)	0.39
Model II	1.18 (1.02–1.36)	0.03	1.17 (1.01–1.35)	0.04	1.15 (0.99–1.33)	0.06	1.07 (0.73–1.57)	0.74
Model III	1.19 (1.03–1.37)	0.02	1.18 (1.02–1.36)	0.03	1.15 (0.99–1.33)	0.06	1.14 (0.77–1.69)	0.52

Model I: adjusted odds ratios for postpartum impaired glucose tolerance with a decrease in neonatal birthweight level of 1 standard deviation (383 mg). Model II: model I plus maternal age, prepregnancy body mass index, gestational age, gestational weight gain and neonatal sex. Model III: model II plus hemoglobin A1c $\geq 6\%$ before delivery, hypertensive diseases and insulin treatment during pregnancy.

DISCUSSION

In the present cohort study, we showed there were significantly inverse, graded associations between NBW and the risk of maternal postpartum glucose intolerance after GDM, which were also well in line with an increase in postpartum glucose intolerance risk of approximately 14% per 1-SD decrease in NBW. These associations remained significant, and were slightly enhanced even after adjustment for known postpartum impaired glucose risk factors and factors associated with NBW, such as gestational age at delivery, neonatal sex, maternal glycemic control, maternal prepregnancy BMI¹⁷ and gestational weight gain¹⁸. Additionally, NBW $\geq 3,100$ g appears to be associated with a lower risk of maternal glucose intolerance postpartum. Furthermore, the risk of postpartum glucose intolerance associated with low NBW is stronger in women carrying a female fetus.

Several risk factors of postpartum glucose intolerance and type 2 diabetes in women with GDM have been identified to

date, including higher prepregnancy BMI, previous polycystic ovarian syndrome¹⁹, family history of type 2 diabetes, non-white ethnicity, advanced maternal age, higher glycemic values at GDM screening²⁰, insulin treatment during pregnancy²¹, hypertensive disorders during pregnancy²² and so on²³. However, there are few available reports on the association between NBW and early postpartum impaired glucose. The present study is the first to our knowledge to provide evidence that lower NBW is a risk factor for early postpartum glucose disturbance after GDM.

We are aware that just two studies^{24,25} by other investigators showed there was no significant association between NBW and early postpartum impaired glucose, which was inconsistent with the present results. This could be attributed to the insufficient sample size (one was 381 and the other was 138), different ethnicity (Korea and New Zealand) and no adjustment for potential factors associated with NBW. Previous studies have presented a significantly positive association between GWG and

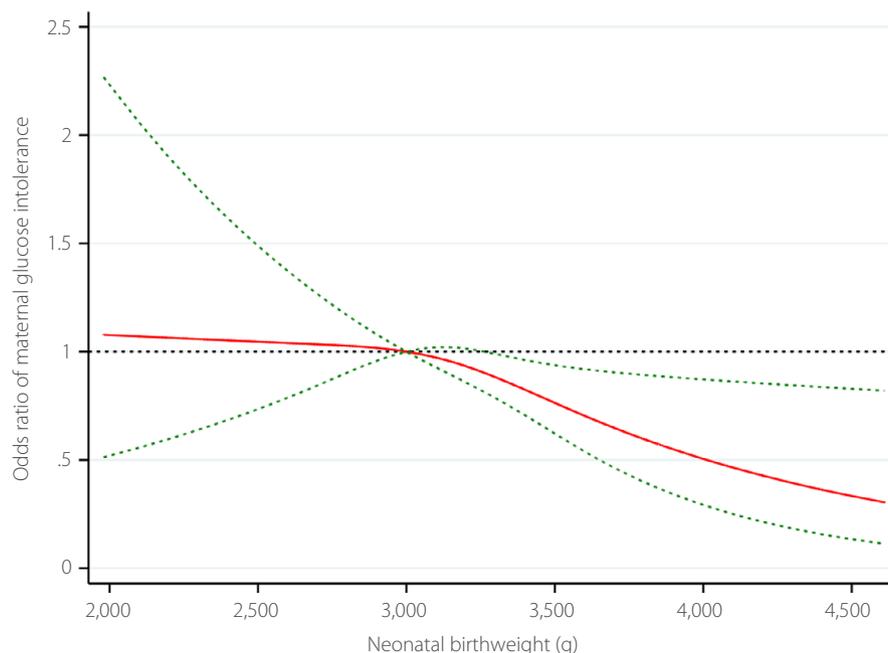


Figure 1 | Association of neonatal birthweight (NBW) and maternal glucose intolerance in an adjusted cubic spline model. The adjusted cubic spline model shows the relationship between NBW and the risk of maternal glucose intolerance, when a NBW of 3,000g is taken as the reference. A NBW $\geq 3,100$ g appears to be associated with a decreased risk with higher NBW. The dashed green curves represent the upper and lower 95% confidence limits, respectively. The horizontal black line represents the odds ratio of 1.

high NBW¹⁸, and the weight was significantly lower for newborns whose mother was underweight compared with newborns whose mother was obese¹⁷. Coincidentally, our finding that prepregnancy BMI and GWG increased markedly with ascending quartiles of NBW corroborates again that prepregnancy BMI and GWG were important confounders that should be taken into account during the analysis.

Additionally, several studies have reported the association of NBW and the risk for type 2 diabetes after GDM^{24,26–29}. These results were accordance with our partial result that the risk for merely type 2 diabetes was not associated with NBW. However, in the present study, NBWs were slightly lower in newborns of women with type 2 diabetes than those without type 2 diabetes ($3,116 \pm 383$ g vs $3,172 \pm 382$ g), which was similar to the findings of Schaefer-Graf *et al.*²⁸. Owing to the limited number of type 2 diabetes patients in the present research (just 36), further studies including larger samples and various ethnicities are warranted to verify the findings of the present study.

Furthermore, the main result of our study seems to contradict the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study³⁰, which indicated that maternal hyperglycemia less severe than that in diabetes mellitus was associated with increased birthweight. However, the HAPO study only established the association between the results of a one-time diagnostic test and birthweight. Second, the HAPO study did not adjust potential confounders, such as gestational weight gain of the participants and glycemic control during pregnancy, which

could affect fetal growth. Finally, the follow-up study of HAPO evaluated the long-term outcomes between women with GDM and those without it, but it did not compare the characteristics of different glucose tolerance status after delivery among women with GDM³¹. Therefore, there is not enough evidence to conclude that the present study is contrary to the HAPO study.

The underlying mechanism of the link between lower NBW and postpartum glucose intolerance in women with GDM in the present study remains unclear. We speculated that it might be attributed to insulin, the key potential fetal growth driver. In the landmark study of Pedersen⁹, it was pointed out that owing to the transplacental glucose transport, maternal hyperglycemia leads to elevated fetal glucose levels, in turn stimulating fetal insulin release. However, it could only explain partial mechanisms, as birthweight is not clearly related to indexes of maternal glycemic control in GDM³². Increasing evidence underlies the role of maternal concentrations of insulin in NBW³³. Often, fetal overgrowth occurs when maternal insulin levels are elevated in GDM³⁴, whereas maternal insulin levels are lower in women with a growth-restricted fetus than in women with a normal growth fetus³⁵.

Powe *et al.*³⁶ used the distributions of insulin sensitivity and secretion in women with normal glucose tolerance to classify GDM into three subtypes: predominant insulin secretion defect, predominant insulin sensitivity defect and both defects. Compared with women with normal glucose tolerance, women with

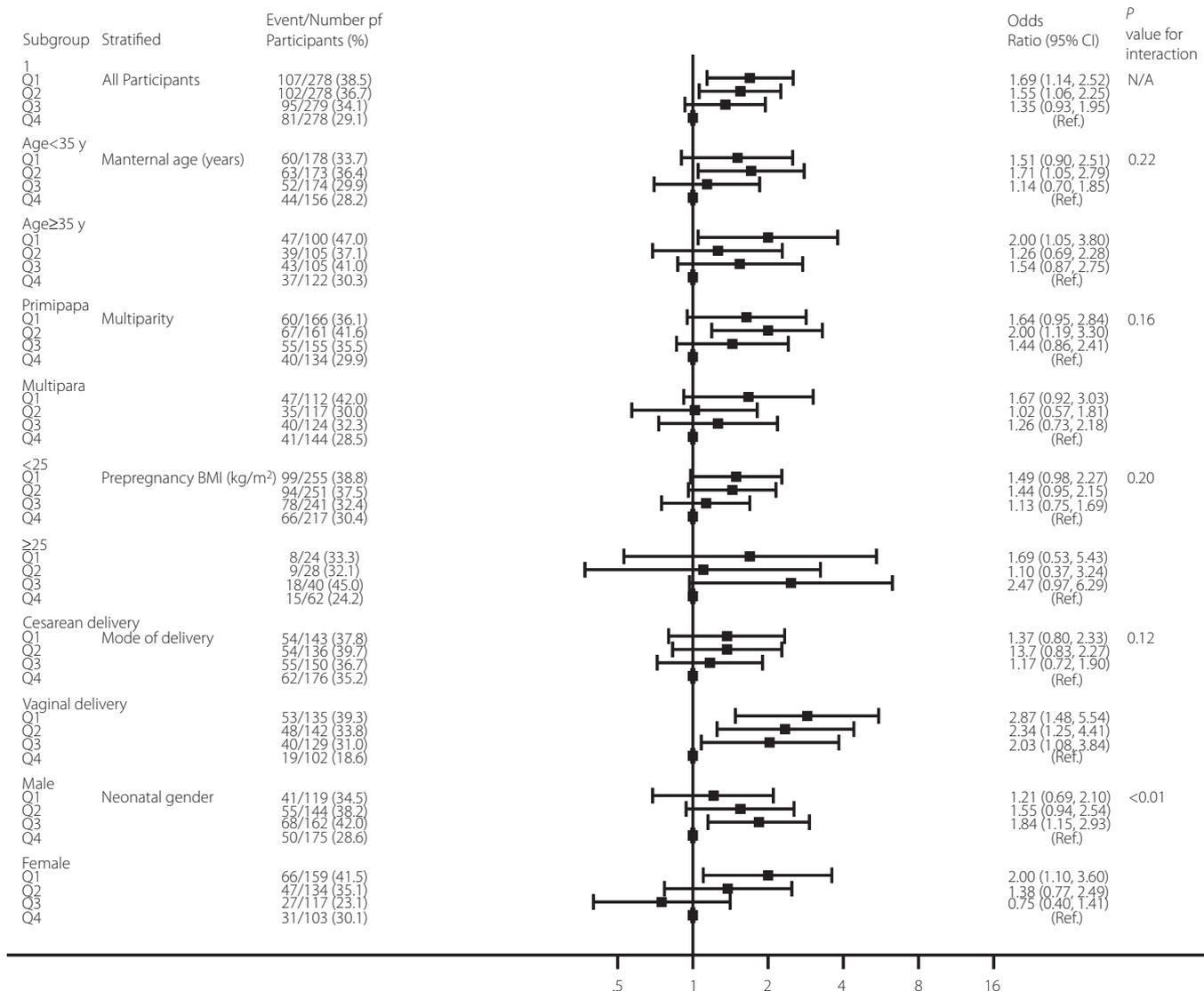


Figure 2 | Association between neonatal birthweight and maternal glucose intolerance in subgroups. Models adjusted for maternal age, prepregnancy body mass index (BMI), gestational age at delivery, neonatal sex, gestational weight gain, hemoglobin A1c ≥6.0% before delivery, hypertensive diseases and insulin treatment during pregnancy (subgroup used in stratification is not included in the model). CI, confidence interval; N/A, not available; Q1, quartile 1; Q2, quartile 2; Q3, quartile 3; Q4, quartile 4.

GDM with predominant insulin sensitivity defects had larger infants, whereas birthweights of infants of women GDM with predominant insulin secretion defects were similar to those of women with normal glucose tolerance. However, we could not know whether women with GDM with predominant insulin secretion defects were more vulnerable to postpartum impaired glucose tolerance, owing to a lack of postpartum information of that study. Fortunately, several studies elaborated on the association between maternal insulin secretion and postpartum glucose intolerance in women with GDM.

Metzger *et al.*³⁷ pointed out that impaired insulin secretion at diagnosis of GDM predicted postpartum diabetes. Katayama

*et al.*³⁸ also found that postpartum glucose intolerance was associated with a sustained decrease of insulin secretion during pregnancy and postpartum, whereas insulin resistance made a rapid improvement after delivery in all GDM participants regardless of whether the postpartum glucose tolerance status was normal or not. In line with the aforementioned research, our previous findings³⁹ disclosed insulin secretion dysfunction, rather than insulin resistance, was the primary contributor to the early abnormal glucose tolerance postpartum in women with GDM. Thus, we postulate that GDM women with defective insulin secretion who are more likely to delivery lower birthweight newborns are at higher risk for postpartum glucose

intolerance. However, further studies are warranted to elucidate the specific mechanisms.

Notably, the risk of postpartum glucose intolerance associated with lower NBW was stronger in women who carried female fetuses. One explanation is that women with GDM while carrying a female fetus have a higher risk of early progression to abnormal glucose regulation than those who gave birth to a male infant⁴⁰.

The important clinical implication of the present data is to provide evidence for a new risk factor for postpartum glucose intolerance that might be otherwise missed in routine care. Previous findings hint that GDM was significantly associated with higher birthweight, compared with women with normal glucose tolerance in pregnancy, which might mislead us to believe that only higher birthweight should be paid attention to. Indeed, the predictive value of low birthweight on maternal impaired glucose tolerance has never been identified before. Fortunately, the present study identified NBW as a risk factor for maternal postpartum impaired glucose tolerance, which can help care providers to be on the alert, thereby reducing the occurrence of postpartum impaired glucose tolerance through active lifestyle intervention at an early stage.

The main strength of the present study was the large cohort with well-ascertained variables about demographic, medical and obstetric history. In addition, we present data on the predictive value of NBW to detect glucose intolerance. However, several limitations merit discussion. First, all participants of the present study were from only one research center. Second, despite the large size of the cohort, few participants manifested type 2 diabetes in the postpartum period, which made the analysis underpowered to detect a difference in the risk for type 2 diabetes. Third, although we controlled for a number of key covariates associated with postpartum impaired glucose, we acknowledge that residual confounding remains a possibility.

In conclusion, an inverse, graded association between NBW and the risk of postpartum glucose intolerance in women with GDM was confirmed, which provided an opportunity to target women at high risk for glucose disturbance easily in early postpartum. Further studies are required to validate these findings in a more generalized population, and to explore the potential mechanisms.

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DISCLOSURE

The authors declare no conflict of interest.

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