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Association between maternal factors and fetal macrosomia in full-term singleton births

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Abstract

Background: Macrosomia, defined as a birth weight of ≥4000 g, is associated with a high risk of birth injury. Fetal growth is highly correlated with maternal conditions, and several maternal factors are associated with neonatal birth size. The current study aimed to assess maternal factors related to fetal macrosomia in a Taiwanese population.

Methods: The medical records of pregnant mothers and their newborns were retrospectively reviewed. All singleton pregnancies delivered at and after 37 weeks of gestation were included in the analysis. Maternal and neonatal conditions were evaluated according to different birth weights.

Results: A total of 4262 infants were enrolled in our study. The mean birth weight was 3156 ± 383 g, including 77 (1.8%) cases with birth weight ≥4000 g, and 154 (3.6%) infants with birth weight <2500 g. The mean maternal body weight before delivery was 67.6 ± 10.0 kg. The mean 6-month gestational weight gain (6mGWG) was 12.3 ± 4.2 kg, and the mean maternal body mass index (BMI) was 26.2 ± 3.6 kg/m^2. The maternal weight, height, and 6mGWG, gestational age, and placental weight were significantly positively correlated with neonatal birth weight. The odds ratios of macrosomia were 3.1 in neonates born to mothers with a 6mGWG of ≥15 kg, 6.3 in those born to mothers with gestational diabetes mellitus, and 4.1 in those born to mothers with a BMI of ≥30 kg/m^2. Newborn macrosomia was associated with adverse events in pregnant mothers and newborn infants.

Conclusion: Gestational diabetes mellitus, 6mGWG, and maternal BMI are significantly correlated with neonatal macrosomia in full-term singleton births. Further, neonatal macrosomia is an important cause of maternal and neonatal morbidity. Hence, pregnant women should undergo maternal counseling for weight management before and during pregnancy, and the appropriate delivery method should be identified to prevent perinatal adverse events.

Keywords: Birth weight; Large for gestational age; Macrosomia; Maternal factors; Neonate

1. INTRODUCTION

Fetal growth is significantly correlated with maternal conditions. Fetal or neonatal macrosomia is defined as a neonatal birth weight of ≥4000 g. This condition is associated with various adverse effects, which include a high risk of hemorrhage during delivery and uterine rupture in mothers and birth injury, hypoglycemia, and later-life metabolic syndrome in newborns.[1–5] Maternal body size, such as height, weight, and body mass index (BMI), gestational weight gain (GWG), and gestational diabetes mellitus (GDM) are associated with a higher neonatal birth weight and length. Further, based on previous studies in the literature, the other risk factors include maternal underlying diseases (eg, insulin-dependent diabetes mellitus, chronic hypertension), pre-pregnancy obesity, genetics, multiparity, male sex, advanced maternal age, and prolonged labor.[6–9]

In recent years, the incidence rate of fetal macrosomia has been increasing globally[10–13] despite recommendations on the ideal maternal GWG during pregnancy and preventive measures against maternal obesity.[14,15] To the best of our knowledge, studies have only explored the prevalence of fetal macrosomia in Taiwan, but no study has evaluated the association between maternal risk factors and perinatal and postnatal outcomes in large for gestational age (GA) newborns in this nation.[9] The current study aimed to evaluate maternal factors correlated with fetal macrosomia in a Taiwanese population.

2. METHODS

2.1. Patients

We retrospectively reviewed the medical records of pregnant mothers and their newborns who were born at Taipei Veterans

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General Hospital from January 2013 to June 2016. All singleton pregnancies delivered at a GA of ≥37 weeks were included in the analysis. However, patients without data on maternal 6-month GWG (6mGWG) were excluded.

2.2. Data collection

We collected the data of both pregnant mothers and their newborns. Information on maternal weight, height, and BMI, 6mGWG, underlying diseases, and pregnancy-related complications was obtained. Further, data on the birth weight, birth length (BL), GA, Apgar scores, and delivery-related details (such as fetal distress during delivery, delivery method, placental weight, and presence of meconium-stained amniotic fluid) of newborns were acquired.

2.3. Definition of study parameters

Pregnancy-induced hypertension (PIH), preeclampsia, and GDM were diagnosed according to international standards. PIH was defined as a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. In addition, the criteria for PIH include an increase of ≥30 mmHg in maternal systolic blood pressure or ≥15 mmHg in diastolic blood pressure during the third trimester of pregnancy. Preeclampsia is defined as PIH with proteinuria after 20 weeks of gestation. In Taiwan, as a part of prenatal examinations, all pregnant women routinely undergo the oral glucose tolerance test (OGTT), an assessment of blood glucose levels at 0, 1, and 2 hours after loading with 75 g of oral glucose. GDM was defined as an abnormal OGTT result (fasting blood glucose level of ≥92 and <126 mg/dL, 1-hour OGTT blood glucose level of ≥180 mg/dL, or 2-hour OGTT glucose level of ≥153 and <200 mg/dL). We defined 6mGWG as maternal BW change between delivery and 6 months prior to delivery. Meconium stain was defined as meconium passage before delivery. Further, difficult delivery was defined as the use of any assistive devices, such as forceps and vacuum, during delivery or failed vaginal delivery resulting in cesarean section (C-section). Macrosomia was defined as a birth weight of ≥4000 g, low birth weight (LBW) as a birth weight of <2500 g, and normal birth weight (NBW) as a birth weight of <4000 g and ≥2500 g based on international standards.

2.4. Statistical evaluation

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 22, IBM Corporation, Armonk, NY, USA). Data were expressed as mean ± SD and median as range or percentage as appropriate. The chi-square test or the Fisher exact test was used to assess differences in categorical variables between two groups. Analysis of variance was used to compare means among greater than three groups. Two-tailed p values of <0.05 were considered statistically significant in all analyses. Univariate and multivariate logistic regression analyses were used to calculate the odds ratios (ORs) of factors associated with fetal macrosomia.

2.5. Ethics approval

This study was approved by the institutional review board of Taipei Veterans General Hospital (VGHIRB 2016-12-006CC).

3. RESULTS

3.1. Characteristics of patients

During the study period, 4262 singleton full-term infants were delivered. Among them, 77 (1.8%) and 154 (3.6%) had a birth weight of ≥4000 and <2500 g, respectively. The mean birth weight of all infants was 3156 ± 383 g (range: 1606–4910 g) (Table 1). The mean maternal weight was 67.6 ± 10.0 kg (range: 36-122 kg), and the mean maternal height was 160 ± 5 cm (range: 142-178 cm). The mean 6mGWG was 12.3 ± 4.2 kg (range: -4 to 45 kg), and the mean BMI was 26.2 ± 3.6 kg/m^2. The mean placental weight was 690 ± 145 g (range: 250-1300 g).

3.2. Positive correlation between neonatal birth weight and maternal factors

Using the Pearson correlation coefficient, the association between neonatal birth weight and maternal anthropometric measurements and other factors was evaluated. Results showed that neonatal birth weight was positively correlated with maternal weight, height, and BMI, 6mGWG, GA, and placental weight ($p < 0.05$). Nevertheless, there was no significant correlation between neonatal birth weight and maternal age ($p = 0.08$).

3.3. Maternal factors among neonates in different weight groups

We further compared maternal factors among the macrosomia, NBW, and LBW groups (Table 2). The maternal factors of the macrosomia group significantly differed from those of the NBW group. The mothers of the macrosomia group had higher height, weight, BMI, 6mGWG, GA, placental weight, and volume of blood loss than the mothers of the NBW and LBW groups. Moreover, a significant difference was observed in all maternal factors, except for volume of blood loss, between the NBW and LBW groups. However, the maternal age did not significantly differ among the three groups.

In terms of maternal underlying diseases, only preeclampsia/PIH and maternal diabetes were associated with neonatal birth weight. The incidence of preeclampsia/PIH was significantly lower in the NBW group than in the macrosomia and LBW groups. The macrosomia group had a higher incidence of maternal diabetes than the NBW and LBW groups. Nevertheless, the results did not significantly differ.

3.4. Receiver operating characteristic curve

Fig. 1 shows the receiver operating characteristic curve between the characteristics of mothers and infants with macrosomia. Placental weight had the greatest area under the curve, followed by maternal weight and BMI. The upper quartile of maternal data was set as the cutoff value for detecting fetal macrosomia. A placental weight of 780 g had a sensitivity of 76% and specificity of 74%. A maternal weight of 73 kg had a sensitivity of 76% and specificity of 63%. A maternal BMI cutoff value of 28.2 kg/m^2 had a sensitivity of 75% and specificity of 58%. A maternal BMI cutoff value of ≥30 kg/m^2, which is the definition of obesity according to the World Health Organization, had a sensitivity of 87% and specificity of 48% in detecting macrosomia. Thus, this value was used in further univariate and multivariate analyses.

3.5. Univariate and multivariate analyses of maternal factors

We further investigated maternal parameters via univariate and multivariate analyses (Table 3). Based on univariate analyses, a maternal height of ≥164 cm, maternal weight of ≥73 kg,

Table 1

Frequency of macrosomia according to neonatal birth weight

Birth weight (g)	Number (n)	Percentage (%)
≥4000	77	1.8
2500-3999	4031	94.6
<2500	154	3.6

Table 2

Characteristics of maternal conditions based on different neonatal birth weight

Maternal characteristics	Macrosomia	NBW	LBW	*p*
Maternal age (y)	33 ± 4	33 ± 4	34 ± 4	0.990
Maternal height (cm)	163 ± 5[a,b]	160 ± 5[b]	159 ± 5	<0.001
Maternal weight (kg)	80 ± 14[a,b]	68 ± 10[b]	64 ± 10	<0.001
Maternal BMI	30 ± 5[a,b]	26 ± 4[b]	25 ± 4	<0.001
Maternal diabetes, n (%)	14 (18.2)[a,b]	133 (3.3)	9 (5.8)	<0.001
PIH/preeclampsia, n (%)	4 (5.2)[a]	75 (1.9)[b]	16 (10.4)	<0.001
6mGWG (kg)	15 ± 5[a,b]	12 ± 4[b]	11 ± 4	<0.001
GA (wk)	39.1 ± 0.9[a,b]	38.8 ± 1.0[b]	37.9 ± 0.9	<0.001
Placenta weight (g)	870 ± 144[a,b]	692 ± 140[b]	548 ± 130	<0.001
Blood loss (mL)	511 ± 378[a,b]	329 ± 336	317 ± 306	<0.001
Uterine problems, n (%)	5 (6.5)	445 (11.0)	15 (9.7)	0.400
Maternal infection, n (%)	26 (33.8)	1202 (29.8)	57 (37.0)	0.129
SLE, n (%)	0 (0)	18 (0.4)[b]	4 (2.6)	0.001
Thyroid disease, n (%)	6 (7.8)	151 (3.7)	6 (3.9)	0.186
Malignancy, n (%)	0 (0)	57 (1.4)	3 (1.9)	0.491
Other maternal disease, n (%)	26 (33.8)	1052 (26.1)	37 (24.0)	0.262

Data are shown as mean ± SD.

6mGWG = 6-month gestational weight gain; BMI = body mass index; GA = gestational age; LBW = low birth weight; NBW = normal birth weight; PIH = pregnancy-induced hypertension; SLE = systemic lupus erythematosus.

[a]$p < 0.05$ vs NBW.

[b]$p < 0.05$ vs LBW.

maternal BMI of ≥30 kg/m^2, GDM, 6mGWG of ≥15 kg, GA of ≥39 weeks, and placental weight of ≥780 g were significantly associated with neonatal macrosomia. Nevertheless, PIH/preeclampsia was not correlated with macrosomia.

In the multivariate analysis, maternal height and BMI, GDM, 6mGWG, and placental weight were significantly correlated with neonatal macrosomia. However, there was no significant correlation between maternal weight (95% CI = 0.37-1.80) and GA (95% CI = 0.92-2.80).

3.6. Neonatal outcomes, comparison among groups of different weights

We found the rate of hypoglycemia was 33.3% for initial blood sugar ranged from 40 to 59 mg/dL and 15.4% for initial blood sugar <40 in macrosomia neonates. Approximately 11.5% and 10.3% of neonates with macrosomia presented with respiratory distress and ecchymosis, respectively, after birth. The other adverse effects of macrosomia included cephalohematoma (3.9%), polycythemia (2.6%), clavicular fracture (1.3%), severe birth asphyxia (1.3%), and intrauterine fetal mortality (1.3%).

Compared with the NBW and LBW groups, the macrosomia group had higher C-section rates, volume of maternal blood loss, and placental weight. Further, the macrosomia group had higher incidence rates of fetal distress and lower 5-min Apgar scores than the NBW and LBW groups. Moreover, there was a higher incidence of hypoglycemia and ecchymosis in the macrosomia group than in the LBW and NBW groups. A significant correlation was observed between macrosomia and perinatal adverse effects (Table 4). In the subgroup analysis, there was no significant correlation between neonatal birth or maternal weight, BMI, and 6mGWG and C-section.

4. DISCUSSION

Our study showed that the prevalence rate of macrosomia at our tertiary medical center in Taiwan was 1.8%. Our results were comparable with those of a study conducted by Hung et al.[9] They showed that 169 of 10 973 neonates presented with macrosomia, with a prevalence rate of approximately 1.54% in Taiwan. The prevalence of macrosomia in Taiwan was lower than that in other countries. Further, the prevalence rates of macrosomia were 9.15%, 8.63%, 7.3%-7.56%, and 3.22% in Hawaii, Belgium, China, and Korea, respectively.[3,16–19] In Japan, the prevalence rate was lower at 0.76%.[20] The prevalence rate of the macrosomia was similar to the obesity rates of different country, corresponding to the previous study of the relationship of pre-pregnancy maternal weight to the macrosomia.[3,9,21]

The current research found a positive correlation between maternal BMI and 6mGWG and neonatal birth weight. This result was in accordance with that of a previous Taiwanese study conducted by Hung et al.[9,22] In addition, positive correlations between maternal BMI, 6mGWG and neonatal birth weight were observed in previous studies performed in China, Japan, Iran, the United Kingdom, Belgium, and other developing countries.[9,13,18–20,23,24] Women with a high BMI, particularly those with obesity, are at higher risk of giving birth to large babies.[23,25–27]

Most studies focused on GWG rather than maternal BMI. Moreover, based on the 2009 Institute of Medicine (IOM) guidelines, the gain of gestational weight (GWG) must not exceed 12.5-18, 11.5-16, 7-11.5, and 5-9 kg in underweight, normal weight, overweight, and obese women, respectively.[14] Based on our result, a 6mGWG of >15 kg was associated with macrosomia. Nomura et al[28,29] investigated the GWG recommended by the IOM and Japanese guidelines according to race. Considering that Asian women have a lower pre-gestational weight and BMI, their GWG should not be as high as that recommended by the IOM. Further, the optimal GWG among Japanese women may be slightly below the value suggested by the IOM. However, this phenomenon disappeared while regional BMI categories was applied, and the IOM guidelines could be applicable to Asian women.[30] A previous Taiwanese study had a similar result. That is, pregnant women with an abnormal GWG according to the IOM guidelines were at high risk of maternal and neonatal adverse outcomes. In our study, a 6mGWG of >15 kg, which is similar to the value recommended by the IOM regardless of pre-gestational weight, was considered a risk factor of macrosomia and other neonatal adverse effects.[9]

Glucose metabolism and hyperinsulinism affect fetal growth. Maternal GDM, a common pregnancy-related metabolic

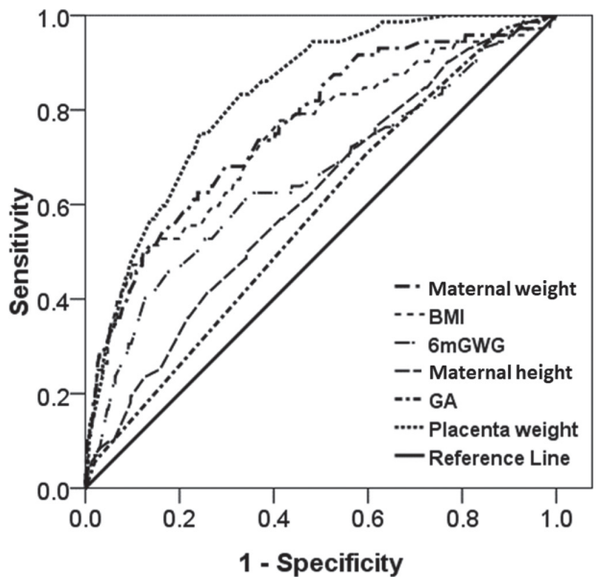

Fig 1. The receiver operating characteristic curve between the different characteristics of mothers and neonates with macrosomia. 6mGWG = 6-month gestational weight gain; BMI = body mass index; GA = gestational age.

disease, is also associated with a higher fetal growth. In maternal hyperglycemia cases, maternal glucose, but not insulin, could cross the placenta. Fetal hyperglycemia stimulates fetal hyperinsulinemia and increases insulin-like growth factor levels. This phenomenon further results in increased fetal growth. Hence, neonates become large for GA.[31] In our study, neonates born to mothers with GDM had a higher incidence of macrosomia than those born to mothers without GDM (18.2% vs 3.3%). This finding is similar to that of other previous studies.[17,19,24,32]

Mothers who give birth to neonates with macrosomia are at high risk of adverse events such as C-section and increased volume of blood loss.[5,22,24,33] In the study of Boulet et al,[34] the C-section rate in the United States was 27.3%. Based on another research conducted by Ng et al[25] in Australia, the adjusted OR of C-section or the use of instrumental procedures was 1.98 (95% CI = 1.10-3.55). In a Taiwanese study, the C-section rates were 54.4% in neonates with macrosomia and 18.2% in those with NBW.[35] In our study, the C-section rates were 48.1% in neonates with macrosomia and 23.9% in neonates with NBW (OR = 2.9510, 95% CI = 1.88-4.64). The incidence rate and the OR of macrosomia were higher compared to the studies of western country and similar to the studies in Taiwan. Said et al[4] found that in addition to high C-section rates, the other adverse maternal complications of macrosomia were postpartum hemorrhage, second-degree perineal lacerations, and prolonged labor.

Inappropriate birth weight for GA is correlated with adverse perinatal events in full-term neonates. In our study, the incidence rates of hypoglycemia and perinatal trauma were high in neonates with macrosomia. That is, 50% had an initial blood glucose level of <60 mg/dL. Further, 15.4% had an initial blood glucose level of <40 mg/dL, which required emergent management, such as early feeding and intravenous glucose supplementation. Several studies have reported that the incidence of hypoglycemia is high in neonates with macrosomia.[36–38] Said et al[4] showed that hypoglycemia was common in infants born via C-section. Further, it might be caused by delayed feeding initiation and intravenous therapy after birth. In Taiwan, although infants with macrosomia can be admitted to the ward for further surveillance and management, close monitoring for hypoglycemia is still important.

Following neonatal hypoglycemia, respiratory distress is the second most common complication of macrosomia, accounting for 11.5% of all cases. Generally, neonates with this condition are closely monitored in an incubator, and some may require noninvasive respiratory support or intubation. Similarly, Das et al[39] reported a high prevalence rate of respiratory distress. That is, 11.9% of neonates with macrosomia had respiratory distress after birth. Moreover, the incidence rate of respiratory distress was high among neonates with a birth weight of >4500 g. In addition to birth weight, C-section and intrauterine hyperglycemia may affect lung maturity and respiratory function after birth.[40] Thus, neonates with a birth weight of >4000 g should be cautiously observed for signs of respiratory distress such as tachypnea, nasal flaring, and subcostal and suprasternal retractions.

The current study had several limitations. First, our data were collected from patients admitted at a single tertiary center in northern Taiwan. The institution is a referral center for high-risk pregnancies. However, it also follows-up normal pregnancies. Hence, the sample size was not large enough. Further, compared with mothers at local hospitals and clinics, which account for a large proportion of healthy term infants, the mothers at our institution have advanced age and are, thus, at high risk of a difficult pregnancy, which can then affect newborns. Thus, the current research might not have identified the actual macrosomia ratio or maternal risk in northern Taiwan. However, it emphasized the association between maternal factors and fetal macrosomia. Further, the different level of medical institutions or sample size had minimal effects on the primary study results.

Second, we collected the data form admission of this delivery period of our hospital. Nevertheless, information on neonatal condition including birth weight and injury and any labor

Table 3

Univariate and multivariate analysis of maternal factors related to neonatal macrosomia

		Univariate analysis		Multivariate analysis	
Maternal factors	**n**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Anthropometric measurements					
Maternal height ≥164 cm	1125	2.12 (1.35-3.35)	0.001	2.08 (1.21-3.57)	0.008
Maternal weight ≥73 kg	1128	5.3 (3.33-8.57)	<0.001	0.82 (0.37-1.80)	0.616
Maternal BMI ≥30	573	6.29 (3.99-9.93)	<0.001	5.34 (2.51-11.39)	<0.001
Pregnancy parameters					
Maternal diabetes	156	6.33 (3.46-11.56)	<0.001	6.77 (3.56-13.67)	<0.001
PIH/preeclampsia	95	2.47 (0.88-6.89)	0.085		
6mGWG ≥15 kg	1092	3.05 (1.94-4.80)	<0.001	2.49 (1.47-4.22)	0.001
GA ≥39 wk	2561	1.79 (1.08-2.96)	0.024	0.92-2.80	0.095
Placenta weight ≥780 g	942	9.43 (5.43-16.40)	<0.001	7.42 (4.20-13.09)	<0.001

6mGWG = 6-month gestational weight gain; BMI = body mass index; GA = gestational age; OR = odds ratio; PIH = pregnancy-induced hypertension.

Table 4

Characteristics of neonatal conditions of different birth weight

Neonatal characteristics	Macrosomia (n = 77)	NBW (n = 4031)	LBW (n = 154)	*p*
Birth weight (kg)	4185 ± 202[a,b]	3169 ± 324[b]	2311 ± 188	<0.001
Body height (cm)	52 ± 2[a,b]	49 ± 2[b]	45 ± 2	<0.001
1-min Apgar, median (IQR)	8 (1)	8 (1)	8 (1)	0.09
5-min Apgar, median (IQR)	9 (0)	9 (0)	9 (0)	0.866
Apgar <6 at 5 min	3 (3.9)[a]	35 (0.9)[b]	4 (2.6)	0.003
Fetal distress, n (%)	16 (20.8)[a]	355 (8.8)[b]	30 (19.5)	<0.001
Cesarean section, n (%)	37 (48.1)[a,b]	962 (23.9)	45 (29.2)	<0.001
Difficult delivery, n (%)	24 (31.2)	943 (23.4)	27 (17.5)	0.062
Meconium stain, n (%)	11 (14.3)	360 (9.0)	15 (9.7)	0.262

Data are shown as mean ± SD.

IQR = interquartile range; LBW = low birth weight; NBW = normal birth weight.

[a]$p < 0.05$ vs NBW.

[b]$p < 0.05$ vs LBW.

difficulties in previous gestation was not acquired. Moreover, the association between previous pregnancy and macrosomia in the current pregnancy was not evaluated in this study.

Third, there was no data on blood glucose levels among healthy NBW term neonates. Hence, only the incidence rates of hypoglycemic episodes between the macrosomia and sick LBW term babies were compared. The actual difference of hypoglycemia and other adverse effects between neonates with macrosomia and healthy NBW neonates was unknown. However, in the current study, neonates with macrosomia had a higher incidence rate of morbidity than sick NBW term babies. This finding might also be significant in healthy NBW groups.

In conclusion, maternal factors such as GDM, 6mGWG, and BMI are significantly correlated with fetal macrosomia in full-term singleton births. Fetal macrosomia causes maternal and neonatal morbidity. The maternal complications include a high risk of hemorrhage during delivery and uterine rupture. The neonatal complications include birth trauma and hypoglycemia. Therefore, pregnant mothers should undergo maternal counseling for weight management during pregnancy. In addition, they must be screened based on the identified risk factors of fetal macrosomia and treated as high-risk delivery with appropriate delivery planning and after care.

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