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The effect of obesity in pregnancy and gestational weight gain on neonatal outcome in glucose-tolerant mothers

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Abstract

Background: Most studies showing association between mothers with obesity in pregnancy or excessive gestational weight gain (GWG) and adverse neonatal outcome were cross-sectional or retrospective. Many included patients are with gestational diabetes mellitus (GDM), which is a strong risk factor for this adverse outcome. There are no prospective studies on this topic in Malaysia. This study aimed to examine prospectively the effects of obesity in pregnancy and GWG, independent of GDM, on neonatal outcome.

Methods: Pregnant mothers in the first trimester, who presented to health clinics in Kuching, were screened. Mothers with existing diabetes mellitus or GDM were excluded using 75-g oral glucose tolerance test during the first and second trimesters. Participants with the first trimester BMI $\geq$ 23 kg/m^2 were recruited as overweight/obese group, whereas those with BMI 18.5–22.9 kg/m^2 were taken as the comparison group. At every trimester visit, mothers' weights were recorded. Babies' birth weight and occurrence of adverse neonatal outcome were documented.

Results: There were 123 mothers recruited as overweight/obese group (mean BMI 29.0 kg/m^2 $\pm$ 4.45) and 102 mothers as comparison group (mean BMI 20.4 kg/m^2 $\pm$ 1.48). The number of low birth weight was similar between groups: 9.8% in overweight/obese group, 6.9% in the comparison group ($p = 0.416$). More than half of these babies were born to mothers with inadequate GWG (58.3% in obese group vs. 57.1% in control group, $p = 0.077$). There was no significant difference in the mean birth weight (3000 g $\pm$ 454.5 vs. 3038 g $\pm$ 340.8, $p = 0.471$), preterm delivery (8.13% vs. 3.92%, $p = 0.193$), and admission rate to neonatal intensive care unit (8.13% vs. 7.85%, $p = 0.937$) between groups. There was a positive correlation between the total GWG in overweight/obese group on baby's weight ($r = 0.222$, $p = 0.013$). Inadequate GWG was not correlated with lower birth weight ($p = 0.052$).

Conclusions: Obesity in pregnancy was not associated with poor neonatal outcome in this small sample of women in Malaysia. Total GWG showed a weak correlation with baby's birth weight in overweight/obese group.

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KEYWORDS
gestational weight gain, glucose-tolerant, neonatal outcome, obesity, pregnancy

1 | INTRODUCTION

Obesity has long been perceived as a major risk factor in pregnancy, leading to serious short- and long-term consequences for both mothers and their infants.[1] Apart from adverse pregnancy outcome, it is also associated with increased risks of adverse neonatal outcome, including preterm birth and stillbirth.[2,3] While low birth weight is associated with increased risk of infant mortality,[4] macrosomia, which occurs more commonly in pregnant mothers with obesity, increases risk of obesity in the offspring at a later stage of life.[5,6] In one of the prospective analyses done in India, 46.37% of babies were macrosomic and born to mothers with prepregnancy obesity, whereas 19.47% macrosomia babies were born to mothers with normal prepregnancy weight.[7] Other studies which showed an association between mothers with obesity or having had excessive gestational weight gain and giving birth to babies with macrosomia or large for gestational age were performed as cross-sectional comparisons across births or as retrospective analyses.[8–11] Many others included mothers with comorbidities, especially gestational diabetes mellitus (GDM), which is a well-described risk factor for adverse neonatal outcomes.[12–16] A meta-analysis of studies performed in low- or middle-income countries suggested that overweight and obesity were slightly protective against low birth weight, small for gestational age and preterm babies, but no data were presented on other adverse neonatal outcomes, such as occurrence of macrosomia and stillbirth.[17]

When prepregnancy body mass index (BMI) was controlled for, increased gestational weight gain contributed to a higher probability of an infant with macrosomia.[18–20] Indeed, prepregnancy BMI and weight gain during pregnancy are two important independent factors determining pregnancy and neonatal outcomes.[21] Gestational weight gain is stratified by BMI category and largely varies among different ethnic groups.

Data comparing neonatal outcome between mothers who have obesity and mothers with normal weight is scarce in Southeast Asian countries,[22,23] especially Malaysia. Although there are several published reports from Malaysia on obesity in the general population,[24,25] no prospective studies exist on the effects of maternal obesity and neonatal outcome in the country. So far, the only data available are from a retrospective study which showed higher percentage of macrosomia babies among overweight and obese mothers and a positive association between gestational weight gain and neonatal outcome, that is, premature birth and low birth weight.[26]

Despite these associations, obesity in pregnancy and gestational weight gain have not gained as much attention of healthcare providers as diabetes mellitus in pregnancy. Providers do not consider management of obesity or weight gain in pregnancy to be equally important.[27] In this observational research, the effects of obesity in pregnancy and gestational weight gain among glucose-tolerant mothers on neonatal outcome were examined prospectively, independent of diabetes mellitus, compared with normal-weight mothers. The primary objective was to examine the effects of obesity determined in the first trimester of pregnancy on neonatal outcome, particularly macrosomia, whereas the secondary objective was to determine if gestational weight gain contributed to adverse neonatal outcome, compared with normal-weight mothers. It was hypothesized that obesity in pregnancy is associated with increased adverse neonatal outcomes and that gestational weight gain is positively correlated with neonatal outcomes.

2 | MATERIALS AND METHODS

2.1 | Subjects

From October 2017 to April 2018, mothers in their first trimester of pregnancy who attended the maternal and child health centers in Kuching area, Sarawak, were consecutively screened for suitability of this study. Only mothers in their first trimester of pregnancy who were more than 18 years of age and were agreeable to attend follow-up at the respective clinics at least once per trimester were recruited. These mothers underwent a 75-g oral glucose tolerance test (OGTT) on a specified date after recruitment while still in their first trimester. If the fasting plasma glucose was ≥7.0 mmol/L, and/or 2-h plasma glucose ≥11.1 mmol/L, the diagnosis of existing undiagnosed diabetes mellitus was made, and the mothers were excluded. Similarly, if the fasting plasma glucose was ≥5.1 mmol/L and/or 2-h plasma glucose was ≥8.5 mmol/L, the diagnosis of GDM was made, and the mothers were also excluded from the study. These mothers then received appropriate care as per clinical practice guidelines. All the other participants were recruited and underwent follow-up as per study protocol. A second 75-g OGTT was conducted between 24 and 28 weeks of gestation and participants were again excluded if GDM was diagnosed. Other exclusion criteria were participants who were known to have underlying diabetes mellitus, known to have genetic disorders affecting growth or congenital anomalies upon recruitment, mothers with multiple pregnancy, those who conceived using artificial insemination, or those known to have HIV/Hepatitis B/Hepatitis C infection.

Weight gain during the first trimester of pregnancy is negligible and hence the first-trimester BMI is known to best reflect the prepregnancy BMI.[28] Participants were divided into participant group or comparison group based on the first-trimester BMI.

As Asians generally have a higher percentage of body fat than Caucasians of the same age, sex, and BMI, with significantly increased risks for type 2 diabetes and cardiovascular disease even below the recommended WHO BMI cut-off point of 25 kg/m^2 for obesity, WHO has recommended a lower BMI cut-off of 23 kg/m^2 as overweight for

Asians, and a BMI of ≥27.5 kg/m^2 as having obesity. Based on this, participants with a BMI of ≥23 kg/m^2 were recruited as obese/overweight group and those with BMI of 18.5–22.9 kg/m^2 were recruited as the comparison group. The total gestational weight gain was calculated by the difference between third-trimester weight and first-trimester weight.

2.2 | Study protocol

Participants who fulfilled the inclusion and exclusion criteria and consented to the study were recruited. They were interviewed by the researchers in terms of their baseline demographic data. Participants' weight and height were recorded during the first visit at recruitment in their first trimester. BMI was then calculated. At every trimester visit, the mothers' weight was recorded apart from other parameters such as blood pressure and midstream urine for presence of proteinuria. The participants were followed up until the point of delivery. Birth weight and neonatal outcomes as outlined below were documented.

2.3 | Neonatal outcomes

The outcomes measured in this study included occurrence of macrosomia and low birth weight, neonatal intensive care unit (NICU) admission, stillbirth, preterm delivery, and neonatal birth weight. Macrosomia is defined as a birth weight of 4000 g or more, whereas low birth weight is a birth weight of less than 2500 g. The term macrosomia was utilized instead of large for gestational age as evaluating a baby's weight in utero is imprecise and would only serve as a potential indication of suspected macrosomia.[29,30] Stillbirth is defined as a baby born with no signs of life at or after 28 weeks' gestation. Preterm delivery is defined as birth that occurs before the start of the 37th week of pregnancy.

3 | STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 19.0 (IBM Corporation). Sample size calculation was based on the occurrence of macrosomia, which is reported to be 19.5% among normal-weight mothers and 46.4% among mothers with prepregnancy obesity. Using the formula by Kelsey et al. for case–control study,[31,32] a total sample of 100 needs to be recruited to give 80% power of study. Univariate analyses including chi-square was used to compare dichotomous outcomes between the groups, and Student's *t*-test was used to compare continuous outcomes. Multiple-logistic regression models were used to evaluate the independent variables on the outcomes, adjusting for BMI, gestational weight gain, maternal age, parity, smoking status, and gestational age. Adjusted odds ratios and 95% confidence interval were calculated. A value of $p < 0.05$ was considered significant.

4 | RESULTS

Five centers were involved in this study. A total of 500 mothers in the first trimester of pregnancy attending the clinic were consecutively screened. About 375 subjects fulfilled the inclusion and exclusion criteria and consented to the study. A total of 120 mothers developed GDM during the later trimester and were hence excluded from the study. There were 30 mothers (18 overweight/obese and 12 with normal BMI) who did not continue with the study after recruitment due to various reasons: not willing to undergo the second OGTT ($n = 24$), transferred out to other districts ($n = 4$), and spontaneous abortion in the first trimester ($n = 2$). There was no significant difference for maternal age, smoking status, blood pressure, BMI, education level, and employment status between study participants and those who did not complete the study. A total of 123 mothers were recruited as overweight/obese group (72 were obese, 51 overweight), whereas 102 mothers were of normal BMI and were recruited as the comparison group. There was no significant difference in baseline demographic data of all subjects and are displayed in Table 1.

The mean BMI of overweight/obese group at the first trimester was higher than of the comparison group (29.0 kg/m^2 ± 4.45 vs. 20.4 kg/m^2 ± 1.48, $p < 0.001$). The mean BMI of overweight mothers who were overweight during the first trimester was 25.0 kg/m^2 ± 1.29, whereas of mothers who were obese was 31.8 kg/m^2 ± 3.76. Mothers of comparison group gained significantly more weight throughout the pregnancy compared with the overweight/obese group (total GWG of 8.4 kg ± 3.8 vs. 6.5 kg ± 4.0, $p < 0.001$). Nevertheless, 56.9% of normal-weight mothers had inadequate weight gain throughout the pregnancy as per IOM recommendations, compared with 43.1% of mothers who were overweight/obese ($p < 0.001$). There was no significant difference in gestational age in between groups (overweight/obese group 267.8 days ± 11.0 vs. comparison group 268.7 days ± 7.3, $p = 0.953$). Mean first-trimester blood pressure was significantly higher in overweight/obese group compared with the comparison group (systolic 116.4 ± 10.1 vs. 108.8 ± 10.9, diastolic 74.4 ± 7.9 vs. 70.6 ± 7.4, both $p < 0.001$), although the mean blood pressure of both groups was still within the normal range.

The fetal outcomes by univariate analyses are summarized in Table 2. There were 19 babies (8.4% of total cohort) with low birth weight. About 9.8% of these babies were born to mothers who were overweight/obese, compared with 6.9% in the comparison group, although the difference was not statistically significant ($p = 0.416$). More than half of these babies were born to mothers with inadequate weight gain as per IOM recommendation (58.3% in overweight/obese group vs. 57.1% in comparison group). Nevertheless, this difference was not statistically significant ($p = 0.077$). Two babies had birth weight of >4000 g, both born to mothers from the overweight/obese group, while there were no macrosomia babies in the comparison group. There was no significant difference in other parameters between mothers who were overweight/obese versus normal-BMI mothers, in terms of mean birth weight (3000 g ± 454.5 vs. 3038 g ± 340.8, $p = 0.471$), preterm delivery (8.13% vs. 3.92%,

TABLE 1 Baseline demographic data of pregnant subjects

	Overweight/obese (n = 123)	Comparison (n = 102)	p
Age, mean (SD)	30.1 (5.0)	28.9 (4.9)	0.09
Education level, *n* (%)			0.71
No formal education	1 (0.81)	1 (0.98)	
Primary	5 (4.07)	5 (4.90)	
Secondary	73 (59.35)	67 (65.69)	
Tertiary	44 (35.77)	29 (28.43)	
Employment status, *n* (%)			0.42
Employed	66 (53.0)	61 (59.0)	
Unemployed	57 (47.0)	41 (41.0)	
Household income, median (IQR)	24,000 (30,000)	24,000 (21,900)	0.37
Smoking status, *n* (%)			1.0
Yes	1 (0.81)	1 (0.98)	
No	122 (99.2)	101 (99.0)	
Family history of type 2 diabetes, *n* (%)			0.12
Yes	27 (22.0)	14 (13.7)	
No	96 (78.1)	88 (86.3)	
Family history of hypertension, *n* (%)			0.07
Yes	52 (42.3)	31 (30.4)	
No	71 (57.7)	71(69.6)	
Family history of cardiovascular disease, *n* (%)			0.18
Yes	11 (8.9)	4 (3.9)	
No	112 (91.1)	98 (96.1)	
Body mass index, kg/m^2	29.0 (4.45)	20.4 (1.48)	<0.001
Gestational age, days	267.8 ± 11.0	268.7 ± 7.3	0.953
Gestational weight gain, kg	6.5 kg ± 4.0	8.4 kg ± 3.8	<0.001
Systolic blood pressure, mmHg	116.4 ± 10.1	108.8 ± 10.9	<0.001
Diastolic blood pressure, mmHg	74.4 ± 7.9	70.6 ± 7.4	<0.001

TABLE 2 Univariate analysis on neonatal outcome in between groups

	Overweight/obese (n = 123)	Comparison (n = 102)	P
Mean birth weight, g (SD)	3000 (454.5)	3038 (340.8)	0.471
Low birth weight, *n* (%)	12 (9.8)	7 (6.9)	0.416
Macrosomia, *n* (%)	2 (1.6)	0 (0)	NA
Preterm delivery, *n* (%)	10 (8.1)	4 (3.9)	0.193
NICU admission, *n* (%)	10 (8.1)	8 (7.9)	0.937
Stillbirth, *n* (%)	0 (0)	0 (0)	NA

Abbreviation: NICU, neonatal intensive care unit.

p = 0.193), and admission rate to neonatal ICU (8.13% vs. 7.85%, p = 0.937). The indications of neonatal ICU admission are listed in Table 3. There was no stillbirth in either group.

Further analysis showed a weak but positive correlation between total gestational weight gain in overweight/obese group on baby's weight (r = 0.222, p = 0.013), but this was not seen in the comparison

TABLE 3 Reasons for NICU admission

Reasons for NICU admission	Overweight/obese *n* (%)	Comparison *n* (%)
Premature birth	6 (4.9)	2 (2.0)
Presumed sepsis	2 (1.6)	4 (3.9)
G6PD deficiency	1 (0.8)	1 (1.0)
Moderate hypoxic ischemic encephalopathy	1 (0.8)	1 (1.0)
Total	**10 (8.1)**	**8 (7.8)**

Abbreviation: NICU, neonatal intensive care unit.

group. Inadequate gestational weight gain suggests a signal toward lower birth weight; however, it was not statistically significant ($p = 0.052$). There was no significant effect of gestational weight gain on preterm delivery ($p = 0.145$) and admission to neonatal ICU ($p = 0.446$) in overweight/obese group, as well as among the normal-BMI mothers (preterm delivery, $p = 0.679$; admission to neonatal ICU, $p = 0.390$).

5 | DISCUSSION

This study found that obesity in pregnancy was not associated with adverse neonatal outcome, including macrosomia, compared with mothers with normal BMI, despite having higher mean blood pressure. This contradicts previous data which showed that obesity in pregnancy is associated with higher birth weight compared with normal weight mothers, although a recent study demonstrated that prepregnancy obesity, in fact, might be associated with a lower probability of adverse neonatal outcome particularly preterm birth, low birth weight, and small for gestational age.[18]

The main reason for our finding was postulated to be due to inadequate weight gain seen in this cohort of mothers, especially among women with overweight/obese and were otherwise healthy. Earlier study showed increased risk of preterm delivery and neonatal ICU admission among mothers with obesity, but was only potentiated among those with excessive gestational weight gain, those who were extremely obese, as well as those with obesity-related diseases and abruptio placentae.[33–35] The mean BMI of the mothers who were obese fell into the category of class I obesity. Coupled with inadequate weight gain during pregnancy, this could have contributed to a nonsignificant difference on adverse neonatal outcomes compared with mothers of normal BMI. Nevertheless, the relatively small sample size may have left the study underpowered to identify relationships in the present sample that have been found in other investigations.

It is interesting to note that more than 50% of the mothers who were overweight/obese had gestational weight gain below the IOM recommendations, which could explain the difference seen between our data and those reported previously. Nevertheless, the findings from this study echo what was reported by Lima et al. who also found women with higher prepregnancy BMI in their cohort gaining less weight during pregnancy.[36] One of the reasons of inadequate gestational weight gain among the mothers from overweight/obese group could be due to dietary restriction by managing clinicians as seen in earlier studies.[37,38]

Second, although the proportion of low birth weight seen in the study cohort was below of that reported in literature, this study further affirms the findings that this adverse neonatal outcome is more commonly seen among mothers with inadequate weight gain in pregnancy. Gestational weight gain below the IOM recommendations is an independent risk factor for low birth weight and is proven to lead to 2–2.5 times more risk for low birth weight.[39,40] Indeed, gestational weight gain seems to play a more important role in determining baby's weight compared with prepregnancy BMI in our population, similar to what was reported recently.[36] This association, however, was seen only among mothers who were overweight/obese in pregnancy but not in the comparison group. Nevertheless, the weak correlation suggests that birth weight may be largely preset by familial factors before the perinatal period.[41] In fact, the correlation between gestational weight gain and birth weight was low among women who delivered smaller children in a Japanese cohort.[41] The higher mean blood pressure among the overweight/obese group is unlikely to have contributed to this adverse neonatal outcome as the blood pressure still fell within normal range. Weight gain in low-risk pregnancies with normal prepregnancy BMI is less likely to contribute as a risk factor for adverse perinatal outcomes.[42] This also suggests that the focus should also be on gestational weight gain, apart from their prepregnancy BMI, when managing pregnancy among women who are overweight/obese.

This study has a few clinical implications. While excessive weight gain may affect maternal health leading to development of GDM and hypertension in pregnancy and increase risk of macrosomia, inadequate gestational weight gain, on the other hand, can lead to adverse neonatal outcomes particularly low birth weight, which similarly requires more attention as it is associated with increased morbidity and mortality. Hence, clinicians need to strike a balance between preventing unfavorable maternal health versus adverse neonatal consequences. As pregnant mothers need to meet their own nutrition requirements on top of supplying adequate nutrients to the growing fetus,[43] more attention needs to be given, in an individualized manner, on dietary quality and nutrition of the mothers, to ensure adequate weight gain and fetal growth as minimum weight gain requirement among obese mothers may prevent small for gestational age.[39]

One limitation of this study is that it was conducted in a single district, with a small sample size, using convenient sampling method, hence the finding may not be generalized to the whole population of Malaysia at large. However, to the best of the researchers' knowledge, this is the first prospective study being done in Sarawak and Malaysia, which is a multiracial country, examining the association between obesity in pregnancy and gestational weight gain on adverse neonatal outcome. Another limitation is lack of information on study participants' nutritional status, lifestyle, and dietary pattern throughout the pregnancy, which may have affected gestational weight gain. However, by excluding underlying medical problems, such as antedated chronic hypertension, diabetes mellitus, and GDM among our study participants, these confounding factors which may affect our study outcomes were avoided. GDM is a well-described risk factor for macrosomia at birth, hence, by removing this confounder, the researchers were able to study the independent effect of overweight/obesity in pregnancy. Thus, the findings from this study are able to provide valuable insights into the importance of weight management throughout pregnancy, especially among mothers with obesity. Besides, the findings from this study could put further emphasis on a more comprehensive guideline on managing obesity effectively in prenatal and antenatal care in Malaysia, as well as the importance of balanced diet in ensuring adequate gestational weight gain to reduce adverse neonatal outcome. Individual advice as to nutrient intake and adequate weight gain should be given priority among pregnant mothers, especially if they have obesity or are considered high-risk pregnancies. Both maternal weight and gestational weight gain, thus, warrant equal attention and appropriate care to reduce adverse neonatal outcome.

Another strength of this study is that by including women only from the first trimester, the researchers were able to better categorize the mothers based on their prepregnancy weight. Maternal memory of prepregnancy weight was not relied upon as this could have led to bias if the weight was not accurately recalled. BMI was utilized to categorize the study participants as it is a better indicator of body composition compared with using the weight of the mothers. The researchers also looked into the possible association between weight gain during pregnancy with neonatal outcome as obesity in pregnancy may not have been the sole factor of adverse neonatal outcome. Besides, women who developed GDM in late pregnancy were excluded through a repeated OGTT during second trimester, which could have affected study outcomes.

6 | CONCLUSIONS

In conclusion, this study suggests that obesity in pregnancy alone does not seem to be associated with adverse neonatal outcome. If at all, it may suggest a signal toward this unfavorable consequence. On the other hand, inadequate gestational weight gain seemed to play a more pivotal role in increasing risks for adverse neonatal outcome, especially low birth weight, among mothers who are overweight/obese during pregnancy. However, the association between these parameters cannot be concluded at this point due to the limitations of this study. Hence, more well-designed studies with larger sample sizes are crucial to examine these possible associations. Further confirmation of these findings may lead to a better change in the care and management of obesity and weight gain in pregnancy.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Huai Heng Loh designed the conception of the study, interpreted the data, searched literature, generated figures and drafted the manuscript, Haslinda Taipin and study group acquired the data, Haslinda Taipin analyzed the data, Asri Said revised the manuscript. All authors had final approval of the final manuscript.

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