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ORIGINAL ARTICLE

Adverse Pregnancy Outcomes Are Associated With Lower Cut-offs for Maternal Hyperglycemia in Malaysian Women: A Retrospective Cohort Study

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ABSTRACT

Introduction: This cohort aimed to determine glycemia distribution of pregnant women and maternal glycemia categories and its correlation with adverse pregnancy outcomes among Malaysian women. **Methods:** A retrospective cohort study of normal glycemia pregnant women. Binary logistic regression was used to examine the associations between maternal glycemia categories and adverse outcomes. **Results:** Women with elevated fasting plasma glucose (FPG) were at lower risk of having SGA infants ($aOR_{FPG\ 4}$= 0.64, 95% CI= 0.47 – 0.85; $aOR_{FPG\ 6}$= 0.68, 95% CI= 0.43–0.98; aORFPG 7= 0.64, 95% CI= 0.42–0.96) than those women in category 1. Women in the higher 2-hour plasma glucose (2hPG) category had a nearly two-fold risk of having LBW and LGA infants. Hyperglycemia less severe than gestational diabetes mellitus (GDM) was associated with LGA (aOR= 1.22, 95% CI= 1.07 – 1.88) and caesarean delivery (aOR= 1.80, 95% CI= 1.20 – 2.69), in the meanwhile GDM was associated with caesarean delivery (aOR= 1.33, 95% CI= 1.02 –1.79). **Conclusion:** Cut-off points for FPG and 2hPG that relate to adverse pregnancy outcomes started at 4.9 – 5.0 mmol/l and 7.5 – 7.7 mmol/l. These cut-off points were lower than the current recommended criteria of Clinical Practice Guideline (CPG) of Malaysia for GDM diagnosis. Large-scale studies are required to identify the optimal GDM cut-off.

Keywords: Pregnancy outcomes, Maternal glycemia, Gestational diabetes mellitus, Hyperglycemia

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as diabetes that first diagnosed in the second trimester, with no overt diabetes before or in early gestation (1). Worldwide, GDM is a common metabolic disorder during pregnancy, whereby about 21.3 million of live births were affected by hyperglycemia and approximately 86.4% of the cases attributed to GDM (2). Among Asian countries, Malaysia reported a much higher prevalence of GDM (13.5%) (3) compared to other Asian populations (2 – 7%) (4,5). Considering the magnitude of the problem and the multitude effects of GDM for both mother and child, the assessment of the association between maternal glucose level and birth outcomes may reveal a locally significant threshold for the GDM diagnosis.

There has been a debate on the most appropriate maternal glycemia threshold for GDM diagnosis. In 2008, the multicenter Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study provided compelling evidence that maternal glycemia below those GDM diagnostic criteria had positive linear association with adverse pregnancy outcomes (6). The HAPO findings led to the revision of the GDM diagnostic criteria. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) subsequently recommended a new GDM glucose level threshold, with a cut-off of either or both FPG ≥ 5.1 mmol/l or 8.5 mmol/l after 2-hour (7). In 2013, the World Health Organization (WHO) adopted the IADPSG guideline and revised the GDM cut-off threshold (8). This adoption has led to controversy, as the revised threshold resulted in an increased prevalence of GDM. Furthermore, there has

been a lack of evidence on the effectiveness of this criterion in improving adverse outcomes of pregnancy (9).

Previously, the practiced diagnostic guidelines for GDM in Malaysia were based on the frequently used WHO cut-off thresholds, with both/either a FPG ≥ 5.6 mmol/l and/or a 2hPG ≥ 7.8 mmol/l in an oral glucose tolerance test (OGTT) test (10), which differ from the IDAPSG criteria. In 2017, the Ministry of Health of Malaysia reviewed the CPG and further proposed a lower GDM diagnostic criterion to having one or more abnormal values of FPG ≥ 5.1 mmol/l and 2hPG ≥ 7.8 mmol/l in OGTT test (11). Both guidelines were derived by consensus of the task force members using findings from the literature.

Several maternal characteristics, such as maternal age (12,13), parity (12) and height (14,15), as well as environmental factors, such as dietary intake (16,17), physical activity (18,19), and smoking (13,20), are associated with GDM risk. Chu et al. (2010) found that the GDM prevalence was lower among non-Hispanic blacks (3.5%), Hispanics (3.6%) or non-Hispanic whites (3.8%) compared to Asian/Pacific American (6.3%). In Asia, Japanese women (3.7%) had the lowest GDM prevalence and Indian (8.6%) had the highest GDM prevalence (21,22).

The general application of the worldwide cut-off value for diagnosing GDM for the Malaysian population may, therefore, be questioned. The correct interpretation of maternal glycemia values requires knowledge of the influencing factors and the application of appropriate cut-offs associated with greater risks of adverse outcomes. Thus, this study aimed to identify the maternal glycemia distribution in pregnant women in Malaysia and to examine the maternal glycemia cut-off level that is associated with adverse pregnancy outcomes. This finding can serve as a basis for future investigation on the cut-off level of maternal glycemia in relation to GDM diagnosis.

MATERIALS AND METHODS

Respondents

A retrospective cohort study of 1967 normal glycemia pregnant woman attending antenatal care at Senawang Maternal Child Health (MCH) clinic and Ampangan MCH clinic between January 2010 and December 2012. The exclusion criteria for this study were: i) diabetes in pregnancy (DIP) at < 14th weeks of gestation, ii) multiple gestation, iii) incomplete pregnancy data and birth records. A statistical formula for a retrospective cohort study was used to calculate sample size (23), with a risk ratio (RR) of 5.5 of having macrosomic infants in women presenting with abnormal glucose level during pregnancy (24). Therefore, a minimum of 572 pregnant women were needed to achieve 80% statistical power at 5% significance in order to detect a significant RR of 5.5.

This study was approved by the Medical Research Ethics Committee (MREC), Ministry of Health Malaysia (KKM/NIHSEC/08/0804/P12-613) and the Medical Research Ethics Committee (MREC), Universiti Putra Malaysia (UPM/FPSK/100-9/2-MJKEtika). Permission was also granted by the Head of Seremban District Health Office. Informed consent was not required due to the study design of a retrospective study and all participants in this study were anonymized.

Sources of data

Data source was antenatal clinic cards of pregnant women who attending MCH clinics for antenatal check-up. Data were extracted by trained enumerators. The antenatal clinic cards consisted of the demographic characteristics, obstetric history, antenatal care information, and birth information (e.g., gender, gestational age, length, head circumference, and birth weight).

Maternal glycemia during pregnancy

According to the Perinatal Care Manual (Third edition) Guidelines, selective screening is use whereby only pregnant women with GDM risk attending the first prenatal care at MCH clinics must undergo a standard 2-hour 75-g OGTT as early as possible and those with normal OGTT results in the early pregnancy have to repeat the OGTT test between 28-32 weeks of gestation (10). In this study, universal screening was done whereby all the pregnant women attending the first prenatal care had to undergo OGTT test as early as possible (< 14th weeks) and those with normal first OGTT test were requested to repeat the OGTT test between 28-32 weeks. The average gestational week for the 2nd OGTT test in this sample was 28.4 ± 1.5 weeks with majority (91%) did the test at week 28 and above. FPG and 2hPG between the 28-32 weeks were divided equally into six categories using sextile as cut-off points. The 6th category of FPG and 2hPG were further divided into two categories, maternal hyperglycemia and GDM based on the Clinical Practical Guidelines (CPG) Malaysia cut-off for GDM, which were FPG ≥ 5.1 mmol/l or/and 2hPG ≥ 7.8 mmol/l (25). Thus, a total of 7 categories for FPG and 2hPG were derived (Table I).

Table I: Maternal glycemia categories

Categories	Plasma glucose level (mmol/l)	
	Fasting	2-hour
1	< 4.0	< 4.9
2	4.0 to 4.1	4.9 to 5.5
3	4.2 to 4.3	5.6 to 5.9
4	4.4 to 4.5	6.0 to 6.5
5	4.6 to 4.8	6.6 to 7.4
6	4.9 to 5.0	7.5 to 7.7
7	≥ 5.1	≥ 7.8

Pregnancy outcomes

The pregnancy outcomes evaluated were pre-term delivery, low birth weight (LBW), high birth weight (HBW), small-for-gestational-age (SGA), large-for-gestational age (LGA), and cesarean delivery. Pre-term delivery was defined as delivery before 37 weeks of gestation (26). LBW was defined as birth weight less than 2,500 g (27), while HBW was defined as a birth weight more than 4,000g (28). The fetal growth charts for Malaysian female and male infants were used as a reference for infant's birthweight percentile by gestational age. Infants with birth weight greater than the 90th percentile for gestational age were considered as LGA, while those with birth weight below the 10th percentile for gestational age were considered as SGA (27).

Statistical analysis

All analyses were preformed using IBM SPSS version 22. Binary logistic regression was performed to determine the associations between maternal glycemia and the risk of adverse outcomes. Maternal characteristics (BMI at first prenatal visit, age, parity and total gestational weight gain (GWG)) found to be significant with maternal glycemia were included in the multiple logistic regression as covariates. As the study found significant associations between FPG and 2hPG with GDM risk starting at 4.9 to 5.0 mmol/l for FPG and 7.5 to 7.7 mmol/l for 2hPG, these categories were then labeled as hyperglycemia less severe than GDM as the FPG and 2hPG values did not meet the GDM diagnosis criteria. Analysis was further performed to examine the associations between maternal glycemia (normal, hyperglycemia less severe than GDM, and GDM) and the risk of adverse outcomes of pregnancy.

RESULTS

Demographic characteristics of women and their newborns

Table II shows the demographic characteristics of 1976 pregnant women. About 1,647 were Malay (83.7%), 92 were Chinese (4.7%), 228 were Indian, and 9 were other races (11.6%). The mean gravidity and parity of women were 2.65 ± 1.52 and 1.42 ± 1.31, respectively. Forty-three percent of women were either overweight (28.6%) or obese (14.7%). Approximately two-thirds (67.1%) had inappropriate GWG; 48.2% presented with insufficient GWG, while 18.9% had excessive GWG. There were 1003 male infants (51.0%) and 964 female infants (49.0%). About 7.8% of infants were born preterm (< 37 weeks). The mean length, head circumference and weight at birth were 49.12 ± 2.54 cm, 32.90 ± 1.97 cm and 3.03 ± 0.46 kg, respectively. About 10.0% of infants were categorized as LBW infants. One-third of infants were SGA (33.7%), while a small percentage of infants (7.7%) were LGA.

Table II: Demographic characteristics of women and their newborns (N= 1,967)

Characteristics	n	*M SD*
Year of registration		
2010	651 (33.0)	
2011	896 (45.6)	
2012	420 (21.4)	
Age at registration (years)		28.98 ± 4.57
≤ 20	61 (3.1)	
21 – 30	1275 (64.8)	
31 – 40	606 (30.8)	
> 40	25 (1.3)	
Ethnicity		
Malay	1647 (83.7)	
Chinese	92 (4.7)	
Indian and others	228 (11.6)	
Gravidity		2.65 ± 1.52
1	505 (25.7)	
2	478 (24.3)	
3	565 (28.7)	
≥4	419 (21.3)	
Parity		1.42 ± 1.31
0	566 (28.7)	
1	525 (26.7)	
2	568 (28.9)	
≥ 3	308 (15.7)	
BMI at first booking (kg/m^2)		24.79 ± 5.71
Underweight (< 18.5)	209 (10.6)	
Normal (18.5–24.99)	906 (46.1)	
Overweight (25.00–29.99)	562 (28.6)	
Obese (≥ 30.00)	290 (14.7)	
Total gestational weight gain (GWG)[¶]		10.09 ± 4.45
Insufficient	949 (48.2)	
Normal	647 (32.9)	
Excessive	371 (18.9)	
Pregnancy outcomes		
Gestational age at delivery (weeks)		38.53 ±1.63
Preterm (< 37 weeks)	153 (7.8)	
Full-term (≥ 37 weeks)	1814 (92.2)	
Mode of delivery		
Vaginal delivery	1531 (77.8)	
Cesarean delivery	381 (19.4)	
Assisted vaginal delivery		
Forceps	10 (0.5)	
Vacuum	45 (2.3)	
Infant's gender	1003 (51.0)	
Male	964 (49.0)	
Female		
Infant's length (cm)		49.12 ± 2.54
Infant's head circumference (cm)		32.90 ± 1.97
Infant's birth weight (kg)		3.03 ± 0.46
< 2.5 (Low birth weight)	196 (10.0)	
2.5 – 2.9	647 (32.8)	
3.0 – 4.0	1095 (55.7)	
> 4.0 (High birth weight)	29 (1.5)	
Birth weight percentile[‡]		
SGA (< 10)	663 (33.7)	
AGA (10 – 50)	913 (46.4)	
AGA (51 – 90)	239 (12.2)	
LGA (> 90)	152 (7.7)	

[‡]Birth weight percentile was defined as infant's birth weight for gestational age. [¶] Total gestational weight gain (GWG) was defined as the difference between the measured weight at booking and the last clinically recorded weight before delivery (36th – 40th weeks of gestation) and further categorized according to IOM (2009) recommendation.

Maternal glycemia

The mean FPG and 2hPG for early pregnancy (< 14th weeks of gestation) were 4.39 ± 0.52 mmol/l and 5.65 ± 1.10 mmol/l (Table III). Meanwhile, the FPG and 2hPG at second trimester (28–32nd weeks of gestation) were slightly higher with means of 4.37 ± 0.51 mmol/l and

Table III: Maternal glycemia levels of pregnant women

Biochemical measurements		
Glucose level (mmol/l)		
OGTT at < 14th weeks of gestation		
Fasting plasma glucose		4.39 ± 0.52
2-hours plasma glucose		5.65 ± 1.10
OGTT at 28th weeks of gestation		
Fasting plasma glucose		4.37 ± 0.51
1 – ≤ 3.9	326 (16.6)	
2 – 4.0 – 4.1	350 (17.8)	
3 – 4.2 – 4.3	353 (17.9)	
4 – 4.4 – 4.5	358 (18.2)	
5 – 4.6 – 4.8	320 (16.3)	
6 – 4.9 – 5.0	112 (5.7)	
7 – ≥ 5.1 (GDM according to 2017 CPG criteria)	148 (7.5)	
2-hours plasma glucose		6.09 ± 1.41
1 – ≤ 4.8	346 (17.6)	
2 – 4.9 – 5.5	366 (18.6)	
3 – 5.6 – 5.9	272 (13.8)	
4 – 6.0 – 6.5	359 (18.3)	
5 – 6.6 – 7.4	319 (16.2)	
6 – 7.5 – 7.7	74 (3.8)	
7 – ≥ 7.8 (GDM according to 2017 CPG criteria)	231 (11.7)	
GDM according to previous MOH criteria	256 (13.0)	
1 criterion (FPG ≥ 5.6)	25 (9.8)	
1 criterion (2hPG ≥ 7.8)	207 (80.9)	
2 criteria (FPG ≥ 5.6 & 2hPG ≥ 7.8)	24 (9.3)	
GDM according to 2017 CPG criteria	316 (16.1)	
1 criterion (FPG ≥ 5.1)	85 (26.9)	
1 criterion (2hPG ≥ 7.8)	168 (53.2)	
2 criteria (FPG ≥ 5.1 & 2hPG ≥ 7.8)	63 (19.9)	

6.09 ± 1.41 mmol/l, respectively. For OGTT at 28th weeks, 5.7% and 3.8% of women in the FPG category 6 and 2hPG category 6. The GDM prevalence based on the previous MOH criteria and CPG criteria were 13.0% and 16.1%, respectively. Among women with GDM, most of the women (53.2 – 80.9%) diagnosed GDM by having one criterion (2hPG ≥ 7.8 mmol/l).

Associations between maternal glycemia and adverse outcomes

Table IV shows the associations between maternal plasma glucose levels and adverse pregnancy outcomes. FPG and SGA showed a significant association. Women in FPG category 4, category 6 and category 7 had lower risks for SGA infants ($aOR_{FPG\ 4}$= 0.64, 95% CI= 0.47 – 0.85; $aOR_{FPG\ 6}$= 0.68, 95% CI= 0.43 – 0.98; $aOR_{FPG\ 7}$= 0.64, 95% CI= 0.42 – 0.96) compared to women in FPG category 1, respectively. For 2hPG, there were significant associations between 2hPG with LBW and LGA. Women in the 2hPG category 7 had higher risks for LBW (aOR= 1.91, 95% CI= 1.13 – 3.22) and

Table IV: Adjusted odds ratios for association between maternal plasma glucose levels as categorical variables and pregnancy outcomes (N=1, 967)

Pregnancy Outcomes	Plasma glucose level			
	FPG		2-h PG	
	Adjusted OR [95% CI]	p-value	Adjusted OR [95% CI]	p-value
Preterm delivery (< 37 weeks)				
Level 1	1.00		1.00	
Level 2	0.32 [0.14 – 1.77]	0.01	1.57 [0.90 – 2.74]	0.11
Level 3	0.64 [0.37 – 1.10]	0.11	0.89 [0.45 – 1.76]	0.74
Level 4	1.11 [0.70 – 1.78]	0.65	1.10 [0.60 – 2.02]	0.75
Level 5	0.67 [0.39 – 1.16]	0.15	1.29 [0.71 – 2.35]	0.41
Level 6	0.97 [0.60 – 2.32]	0.64	1.62 [0.18 – 2.13]	0.20
Level 7	0.91 [0.47 – 1.76]	0.78	2.10 [0.99 – 3.79]	0.06
Low birth weight (< 2.5kg)				
Level 1	1.00		1.00	0.16
Level 2	0.72 [0.41 – 1.23]	0.23	1.42 [0.87 – 2.31]	0.92
Level 3	0.62 [0.39 – 1.02]	0.05	1.03 [0.58 – 1.81]	0.78
Level 4	0.69 [0.44 – 1.08]	0.10	0.93 [0.54 – 1.59]	0.84
Level 5	0.55 [0.34 – 1.10]	0.06	0.95 [0.54 – 1.64]	0.53
Level 6	0.66 [0.33 – 1.33]	0.24	1.30 [0.57 – 2.97]	**0.02***
Level 7	0.70 [0.38 – 1.30]	0.26	**1.91 [1.13 – 3.22]**	
High birth weight (> 4.0kg)				
Level 1	1.00		1.00	0.12
Level 2	-	-	6.01 [0.63 – 57.72]	0.10
Level 3	0.85 [0.26 – 2.79]	0.79	6.81 [0.68 – 68.38]	0.08
Level 4	1.49 [0.51 – 4.32]	0.46	7.04 [0.78 – 63.46]	0.05
Level 5	0.62 [0.15 – 2.48]	0.50	10.52 [0.16 – 95.11]	0.06
Level 6	2.60 [0.80 – 8.46]	0.11	12.29 [0.95 – 120.77]	0.08
Level 7	1.65 [0.50 – 5.48]	0.41	6.81 [0.81 – 57.56]	
SGA				
Level 1	1.00		1.00	0.26
Level 2	0.74 [0.52 – 1.06]	0.10	1.20 [0.88 – 1.63]	0.96
Level 3	0.83 [0.63 – 1.11]	0.21	1.01 [0.72 – 1.41]	0.72
Level 4	**0.64 [0.47 – 0.85]**	**0.01***	0.94 [0.69 – 1.20]	0.71
Level 5	0.77 [0.57 – 1.04]	0.08	0.94 [0.68 – 1.30]	0.46
Level 6	**0.68 [0.43 – 0.98]**	**0.04***	0.81 [0.47 – 1.42]	0.77
Level 7	**0.64 [0.42 – 0.96]**	**0.03***	0.95 [0.66 – 1.36]	
LGA				
Level 1	1.00		1.00	
Level 2	1.23 [0.66 – 2.29]	0.51	0.98 [0.81 – 2.62]	0.20
Level 3	1.23 [0.66 – 2.27]	0.51	0.66 [0.31 – 1.41]	0.29
Level 4	1.39 [0.76 – 2.54]	0.29	1.14 [0.62 – 2.11]	0.67
Level 5	1.76 [0.98 – 3.18]	0.06	1.58 [0.87 – 2.86]	0.13
Level 6	1.03 [0.46 – 2.30]	0.95	**2.12 [1.12 – 4.87]**	**0.04***
Level 7	1.12 [0.55 – 2.27]	0.76	**2.13 [1.03 – 3.52]**	**0.03***
Cesarean delivery				
Level 1	1.00		1.00	
Level 2	1.03 [0.69 – 1.55]	0.88	0.85 [0.57 – 1.29]	0.45
Level 3	0.83 [0.55 – 1.25]	0.37	0.71 [0.45 – 1.12]	0.15
Level 4	0.89 [0.59 – 1.34]	0.58	1.01 [0.73 – 1.59]	0.72
Level 5	1.16 [0.77 – 1.74]	0.47	1.38 [0.93 – 2.04]	0.11
Level 6	1.46 [0.89 – 2.40]	0.13	1.51 [0.81 – 2.81]	0.19
Level 7	1.22 [0.78 – 1.91]	0.39	1.28 [0.84 – 1.96]	0.25

Adjusted for maternal age, BMI at first booking, gestational age at OGTT, parity and total GWG

Glucose categories are defined as follows:

Fasting plasma glucose level: 1 – < 3.9 mmol/l; 2 – 4.0 to 4.1 mmol/l; 3 – 4.2 to 4.3 mmol/l; 4 – 4.4 to 4.5 mmol/l; 5 – 4.6 to 4.8 mmol/l; 6 – 4.9 to 5.0 mmol/l; 7 – ≥ 5.1 mmol/l

2-hr plasma glucose level: 1 – < 4.8 mmol/l; 2 – 4.9 to 5.5 mmol/l; 3 – 5.6 to 5.9 mmol/l; 4 – 6.0 to 6.5 mmol/l; 5 – 6.6 to 7.4 mmol/l; 6 – 7.5 to 7.7 mmol/l; 7 – ≥ 7.8 mmol/l

*p<0.05

LGA (aOR= 2.13, 95% CI= 1.03 – 3.52) compared to women in 2hPG category 1. Additionally, women in 2hPG category 6 were significantly at greater risk of LGA (aOR= 2.12, 95% CI= 1.12 – 4.87). No significant association was observed for preterm delivery, HBW and cesarean delivery with FPG and 2hPG.

Hyperglycemia less severe than GDM was defined as either FPG 4.9 to 5.0 mmol/l or/and 2hPG 7.5 to 7.7 mmol/l. About 7.3% and 16.1% of the women had hyperglycemia less severe than GDM and GDM, respectively. Hyperglycemia less severe than GDM was significantly associated with cesarean delivery (aOR= 1.80, 95% CI= 1.20 – 2.69) and LGA (aOR= 1.22, 95%

CI= 1.07 – 1.88). GDM women was only significantly associated with cesarean delivery (aOR= 1.33, 95% CI= 1.02 –1.79) (Table V).

Table V: Associations between maternal glycemia and pregnancy outcomes (N=1,967)

Pregnancy outcomes	Maternal glycemia[†]			
	Hyperglycemia less severe than GDM (n= 144)		GDM according to CPG criteria[§] (n= 316)	
	OR [95% CI]	p-value	OR [95% CI]	p-value
Preterm (< 37 weeks)	0.97 [0.49 – 1.89]	0.92	1.61 [0.98 – 2.41]	0.06
Low birth weight (< 2.5kg)	0.80 [0.43 – 1.53]	0.51	1.62 [0.92 – 2.36]	0.07
High birth weight (> 4.0kg)	1.46 [0.50 – 4.25]	0.49	1.10 [0.49 – 2.48]	0.82
SGA	0.80 [0.55 – 1.17]	0.25	0.90 [0.69 – 1.17]	0.42
LGA	**1.22 [1.07 – 1.88]**	**0.02***	1.01 [0.53 – 1.93]	0.98
Cesarean delivery	**1.80 [1.20 – 2.69]**	**0.001****	**1.33 [1.02 – 1.79]**	**0.04***

Note. [†]Normal glycemia as a reference (n= 1507).
Hyperglycemia, less severe than GDM was defined as either or both FPG 4.9 – 5.0 mmol/l or 2hPG 7.5 – 7.7 mmol/l.
[§] GDM was defined as either or both FPG ≥ 5.1 mmol/l or 2hPH ≥ 7.8 mmol/l.
Adjusted maternal age, BMI at first booking, parity and gestational age at OGTT, and total GWG
*p<0.05, **p<0.001

DISCUSSION

In this study, both FPG and 2hPG cut-off levels to detect adverse pregnancy outcomes were at 4.9 – 5.0 mmol/l (category 6 of FPG) and 7.5 – 7.7 mmol/l (category 6 of 2hPG), which were categorized as hyperglycemia less severe than GDM. It is also noted that the Malaysia CPG criteria for GDM diagnosis were not able to predict all adverse pregnancy outcomes, such as in this study subjects. The results of the present study were consistent with the HAPO hypothesis (26,29) that pregnant women with hyperglycemia that is less severe than the current GDM diagnostic cut-offs were significantly associated with adverse pregnancy outcomes, such as LGA, and cesarean delivery. However, two previous landmark randomized trials failed to demonstrate that the pregnancy adverse outcomes were markedly improved by a lower diagnostic threshold for GDM (30,31). A nationwide study with greater sample size is required to confirm these study findings before such criteria are generalized to all pregnant women in Malaysia. If the results are replicated in such study, then it is imperative that maternal hyperglycemia cut-off values be re-examined with the treatment costs and benefits.

This study found that the OR for LGA increased across maternal glycemia categories with the OR of 2.12 in the 2hPG category 6, and followed by the 2hPG category 7, with the OR of 2.13. This finding was consistent with the HAPO study in that the OR for LGA increased with increasing maternal glycemia categories, with the OR of 5.01 for the highest category of the FPG (29,32). This pattern was similar to another pregnancy outcome (cesarean delivery) in that the odds ratio (OR) increased across maternal glycemia categories; however, this association was not significant. This study only focused on term birth, birth weight, fetal size and cesarean delivery for the determination of the diagnostic glycemia threshold. Future studies should also include other pregnancy outcomes that are related to diabetic fetopathies, such as percentage body fat, cord blood serum C peptide and neonatal hypoglycemia. These pregnancy outcomes are not only related to the pathophysiology of GDM, but also with future adult metabolic abnormalities in adult life.

The LBW prevalence in this study (10%) was relatively lower than the prevalence reported by studies conducted in Kuala Lumpur (11.1%) and Negeri Sembilan (12.6 – 14.0%) (33,34), but higher than those of studies conducted in Kelantan (3.7 – 8.7%) (35,36). The differences in the LBW prevalence between the studies could be due to the differences in methodology applied, such as study design and inclusion criteria. This study also found that women in the highest category of 2hPG (category 7) had higher risk for LBW infants. Although no significant association between 2hPG with preterm delivery was observed, a similar trend was found in which women with higher 2hPG had increased risk of preterm delivery. This could be possible due to a large proportion of the LBW infants (42.5%) were born preterm. Interaction effects between covariates (age, parity, total GWG, BMI at first prenatal visit, and gestational age at delivery) with 2hPG on LBW were further examined. Significant associations between higher 2hPG and a higher risk for LBW were only observed in inadequate GWG women (aOR= 1.79, 95% CI= 1.08 – 3.39) and those delivered at full-term (aOR= 2.02, 95% CI= 1.10 – 3.73). Although insufficient GWG is a risk factor for LBW (37,38), whether having hyperglycemia further increases the LBW risk in women with below recommended GWG is unknown. It is also possible that regardless of maternal glycemia level, inadequate GWG is an important determinant of LBW. The association between hyperglycemia and risk of LBW among full-term infants could be due to pregnancy complications, intrauterine growth restriction, and birth defects (39). However, further investigation is warranted to explore the association between hyperglycemia and LBW, as well as the role of GWG in the association between hyperglycemia and LBW.

There were 33.7% of infants born SGA in this sample, whereby were lower than in India (36.5%) (40) and Pakistan (36.0%) (41), but much higher than in Vietnam (15.7%) (42), Korea (11.4%) (43), and China (10.4%) (44). However, the comparison between studies should be done with caution because of methodology differences. The methods for determining gestational age differed between studies might affect the gestational length estimates. This study found that women in the FPG category 6 and category 7 were at significantly lower risk for having SGA infants and this finding was in line with previous studies (29,44). Glucose is an important nutrient for fetal growth (45). Maternal hyperglycemia or GDM leads to fetal hyperglycemia and increased growth, which results in a lower risk of SGA (29).

This study has several limitations. This cohort might not be representative of all pregnant women in Malaysia as it only enrolled pregnant women from clinics in the Seremban District. In addition, most of the women in this study were Malays (83.7%). This study used retrospective health clinic data whereby information such as previous obstetric history (e.g. GDM and pre-eclampsia) and family history of diabetes as well as critical neonatal outcomes (e.g. hypoglycemia, hyperinsulinemia, stillbirth, neonatal intensive care admission, and respiratory distress) were not extracted, although these are important risk factors and health consequences of GDM. The findings on the association between LBW and maternal glycemia should be interpreted with caution as no stratification was performed by ethnic groups and maternal characteristics. Although poor control of glycemic during pregnancy was associated with adverse pregnancy outcomes, such as SGA, LBW, and preterm delivery (46,47), the glycemic control of women during pregnancy in this sample was unknown. This study did not distinguish between elective or non-elective cesarean delivery. Fukatsu et al. (2016) reported that the non-elective cesarean delivery rate was higher among GDM women (35.6%) compared to normal glycemic women (22.1%) (48). Another limitation was the use of last menstruation period (LMP) dates to estimate gestational age (GA). Estimation of GA using last menstrual cycle date may be associated with SGA prevalence misclassification compared to ultrasound-based estimates (49,50).

CONCLUSION

In conclusion, 7.3% and 16.1% of women had hyperglycemia less severe than GDM and GDM, respectively. While FPG was significantly associated with SGA, 2hPG was significantly associated with LBW and LGA. Women with hyperglycemia less severe than GDM had significantly higher risk of LGA and caesarean delivery, whereas women with GDM was significantly associated with caesarean delivery. Future studies are warranted to identify the optimal cut-off level of maternal glycemia for detecting adverse pregnancy outcomes. Additionally, large-scale and well-design trials are needed to examine the cost-effectiveness of therapeutic strategies for management of hyperglycemia less severe than GDM that could improve pregnancy outcomes.

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