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THE INFLUENCE OF MATERNAL GESTATIONAL DIABETES MELLITUS STATUS AND FOETAL SEX ON INFANT OUTCOMES: A REGISTRY AUDIT

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ABSTRACT (250 words)

Background: Gestational diabetes mellitus (GDM) is associated with infant morbidities and mortality. Male foetal sex is another risk factor for adverse pregnancy outcome. This study aimed to describe the proportion of infant outcomes with maternal GDM status, and to determine whether both maternal GDM status and foetal sex had influence on macrosomia and preterm birth.

Materials and Methods: This was a review and audit of Birth Registry for year 2015. Total of 1077 infants born to GDM mothers and non-GDM mothers were selected via simple random sampling with a ratio of 1:2. Multiple logistic regression models were built to determine the association of maternal GDM status, foetal sex with macrosomia, and preterm birth.

Result: A higher proportion of macrosomia, preterm birth and stillbirth were found among infants born to GDM mothers. Male foetal sex (AOR 2.41, 95% CI: 1.23, 4.74, p=0.010) and GDM status (AOR 4.09, 95% CI: 2.20, 7.58, p<0.001) were significantly associated with macrosomia, but not with preterm birth.

Conclusion: Focused antenatal services should be offered to GDM mothers carrying male foetuses since male foetal sex and GDM status were predictors for macrosomia.

Keywords: foetal sex, GDM, macrosomia, preterm birth

1.0 Introduction

Prevalence of gestational diabetes mellitus (GDM) is rising globally due to increase obesity rate and delayed family formation among women (NICE, 2015). Malaysia has a higher prevalence of GDM, at 7.6% in 2012 (Ravichandran Jeganathan & Shamala Devi Karalasingam, 2015), as compared to other developed country such as Canada (2.5%) (Xiong, Saunders, Wang, & Demianczuk, 2001). The incidence of GDM in Kelantan was 9.1% in 2012, which was the fourth highest in Malaysia (Ravichandran Jeganathan & Shamala Devi Karalasingam, 2015).

GDM is related to various adverse perinatal outcomes (Khan, Ali, & Khan, 2013), which could lead to immediate morbidity and also affect latter adult health. Infant born to diabetic mothers, regardless of types of diabetes, are at higher risk of developing metabolic syndrome and obesity (Luo et al., 2010; Nayak et al., 2013). Women posed higher risk for GDM when there is family history of diabetes mellitus (Nayak et al., 2013), advanced maternal age, prior history of neonatal death and major foetal anomaly (Xiong et al., 2001), as well as carrying male foetuses (Khalil & Alzahra, 2013; Retnakaran & Shah, 2015). Male foetal sex is also an independent risk factor for many adverse pregnancy outcomes, such as preterm birth (Di Renzo, Rosati, Sarti, Cruciani, & Cutuli, 2007), macrosomia, birth trauma and caesarean delivery (Abedzadeh-Kalahroudi, Talebian, Jahangiri, Mesdaghinia, & Mohammadzadeh, 2015).

However, whether both GDM and foetal sex have an association with infant outcomes is still unclear. This study first aimed to determine the proportion of infant outcomes with maternal GDM status, and secondly to determine the association of maternal GDM status and foetal sex on macrosomia and preterm birth.

2.0 Materials and Methods

This was a registry audit study. The Birth Registry of Hospital *Universiti Sains Malaysia* (Hospital USM) was reviewed for year 2015. HUSM is a tertiary centre situated in *Kubang Kerian, Kelantan*, north-east of peninsular Malaysia. It is also one of the regional centres for high risk pregnancies. All births were stratified into infants born to GDM mothers and non-GDM mothers. Then, infants born to GDM mothers and non-GDM mothers were further selected by simple random sampling, with a ratio of 1:2, to ensure adequate GDM cases for better comparison of infant outcomes with non-GDM cases. This disproportionate stratified random sampling was conducted to obtain a total of 1077 sample units, based on a pre-calculated sample size. Type I error was set at 0.05, and the power of this study was set at 90%. This study included all infants born in Hospital USM throughout the year 2015. The total birth recorded in Hospital USM for 2015 was 8530.

The exclusion criteria were those infants born to mothers with pre-existing diabetes and/ or hypertension, multiple pregnancies, infants born before arrival to the labour ward and non-Malaysian cases. The operational definition of macrosomia is "*baby with birth weight of 4000g or more*" (Mansor, Arumugam, & Omar, 2010; Tian et al., 2015). Preterm birth is defined as "*birth less than 37 weeks of gestation*" (Royal College of Obstetricians and Gynaecologists, 2011). Stillbirth is defined as " *a baby delivered with no signs of life known*

to have died after 24 completed weeks of pregnancy" (Royal College of Obstetricians and Gynaecologists, 2010).

Incomplete or missing data in the registry were retrieved from patient's folder in the Patient Record Unit, Hospital USM. Data was entered, inspected, cleaned and analysed by using SPSS version 22. All variables were categorized according to the literatures. Although all infant outcomes were recorded, only macrosomia and preterm birth were selected for further modelling. Other outcomes such as stillbirths could not be modelled due to the small sample size. Simple logistic regression was performed to determine the possible factors associated with macrosomia and preterm birth. The factors explored were maternal age, maternal parity, maternal GDM status, maternal status of pregnancy-induced hypertensive disorders (PIH), maternal history of miscarriage and foetal sex. Mothers' ethnicity could not be analysed in the simple logistic regression or further due to the lack of variance in the ethnicity variable where majority of the sample was Malays. Kelantan was a Malay majority state (Department of Statistics Malaysia, 2015).

Multiple logistic regression was then conducted to evaluate independent factors associated with macrosomia and preterm birth as two separate models. Maternal GDM status and foetal sex were retained in the models regardless of level of significance found in the simple logistic regression analysis, whereas the other factors would be considered if $p < 0.25$ in simple logistic regression analysis. Final model with adjusted odds ratio and 95% confidence interval were used to measure the strength of association between infant outcomes and factors associated. The permission to use the related data was obtained from Hospital USM Administration Office and Labour Room managerial staffs after obtaining approval from Human Research Ethical Committee of *Universiti Sains Malaysia*.

3.0 Result

3.1 Characteristics of sample units

A total of 1077 sample units were obtained in this study, with 718 infants born to non-GDM mothers and 359 infants born to GDM mothers. The *Malays* was the dominant ethnic group, which was n=1056 (98.1%). There was a total of 591 male infants and 486 female infants in the sample. More male infants were born to GDM mothers, with the male to female ratio of four to three; whereas among non-GDM mothers the infants' sex ratio was closer to one. However, Pearson Chi-Square test showed no significant association between maternal GDM status and foetal sex ($p = 0.299$). Majority (33.3%) of the mothers were in the 25-29 years old category, with parity of two to four (54.8%). Most of the mothers had no previous history of miscarriage (79.9%). Infants born to mothers with PIH were recorded at 6.5% (refer Table 1). There was a male infant predominance for macrosomia, preterm birth, stillbirth and other outcomes. There were 12 cases of stillbirth and two cases of shoulder dystocia. Other infant outcomes recorded in this study included one case of cord prolapse, two cases of foetal anomaly, six cases of intrauterine growth restriction and 18 cases with oligohydramnios. Three cases with intrauterine growth restriction was also born preterm. The sample characteristics were shown in Table 1.

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Table 1: Distribution of sample characteristics and infant outcomes (n= 1077)

Variables	Overall		Macrosomia		Preterm Birth		Stillbirth		Shoulder Dystocia		Others[c]	
	Mean (SD)[a] / Median (IQR)[b]	n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)
GDM Status												
No		718 (66.7)	702 (68.2)	16 (34.0)	682 (66.9)	36 (62.1)	711 (66.8)	7 (58.3)	717 (66.7)	1 (50.0)	695 (66.2)	23 (85.2)
Yes		359 (33.3)	328 (31.8)	31 (66.0)	337 (33.1)	22 (37.9)	354 (33.2)	5 (41.7)	358 (33.3)	1 (50.0)	355 (33.8)	4 (14.8)
Fetal Sex												
Female		486 (45.1)	474 (46.0)	12 (25.5)	463 (45.4)	23 (39.7)	484 (45.4)	2 (16.7)	485 (45.1)	1 (50.0)	473 (45.0)	13 (48.1)
Male		591 (54.9)	556 (54.0)	35 (74.5)	556 (54.6)	35 (60.3)	581 (54.6)	10(83.3)	590 (54.9)	1 (50.0)	577 (55.0)	14 (51.9)
Maternal age	30.6 (5.5)[a]											
≤24 years old		132 (12.3)	126 (12.2)	6 (12.8)	124 (12.2)	8 (13.8)	132 (12.4)		0131 (12.2)	1 (50.0)	131 (12.5)	1 (3.7)
25-29 years old		359 (33.3)	343 (33.3)	16 (34.0)	339 (33.3)	20 (34.5)	356 (33.4)	3 (25.0)	359 (33.4)	0	343 (32.7)	16 (59.3)
30-34 years old		329 (30.5)	319 (31.0)	10 (21.3)	317 (31.1)	12 (20.7)	326 (30.6)	3 (25.0)	328 (30.5)	1 (50.0)	324 (30.9)	5 (18.5)
≥35 years old		257 (23.9)	242 (23.5)	15 (31.9)	239 (23.4)	18 (31.0)	251 (23.6)	6 (50.0)	257 (23.9)	0	252 (24.0)	5 (18.5)
Parity	2.0 (2.0)[b]											
1		346 (32.1)	338 (32.8)	8 (17.0)	325 (31.9)	21 (36.2)	342 (32.1)	4 (33.3)	346 (32.2)	0	336 (32.0)	10 (37.0)
2-4		590 (54.8)	560 (54.4)	30 (63.8)	564 (55.3)	26 (44.8)	586 (55.0)	4 (33.3)	588 (54.7)	2 (100.0)	576 (54.9)	14 (51.9)
≥5		141 (13.1)	132 (12.8)	9 (19.2)	130 (12.8)	11 (19.0)	137 (12.9)	4 (33.3)	141 (13.1)	0	138 (13.1)	3 (11.1)
History of miscarriage												
0		860 (79.9)	825 (80.1)	35 (74.5)	815 (80.0)	45 (77.6)	851 (79.9)	9 (75.1)	859 (79.9)	1 (50.0)	840 (80.0)	20 (74.1)
1		163 (15.1)	153 (14.8)	10 (21.3)	153 (15.0)	10 (17.2)	162 (15.2)	1 (8.3)	162 (15.1)	1 (50.0)	157 (15.0)	6 (22.2)
2		38 (3.5)	37 (3.6)	1 (2.1)	36 (3.5)	2 (3.5)	37 (3.5)	1 (8.3)	38 (3.5)	0	37 (3.5)	1 (3.7)
≥3		16 (1.5)	15 (1.5)	1 (2.1)	15 (1.5)	1 (1.7)	15 (1.4)	1 (8.3)	16 (1.5)	0	16 (1.5)	0
Status of PIH												
No		1006 (93.4)	962 (93.4)	44 (93.6)	961 (94.3)	45 (77.6)	996 (93.5)	10 (83.3)	1005 (93.5)	1 (50.0)	979 (93.2)	27(100.0)
Yes		71 (6.6)	68 (6.6)	3 (6.4)	58 (5.7)	13 (22.4)	69 (6.5)	2 (16.7)	70 (6.5)	1 (50.0)	71 (6.8)	0

[c] include cord prolapse, fetal anomaly, intrauterine growth restriction, oligohydramnios

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3.2 Proportion of infant outcomes according to GDM status

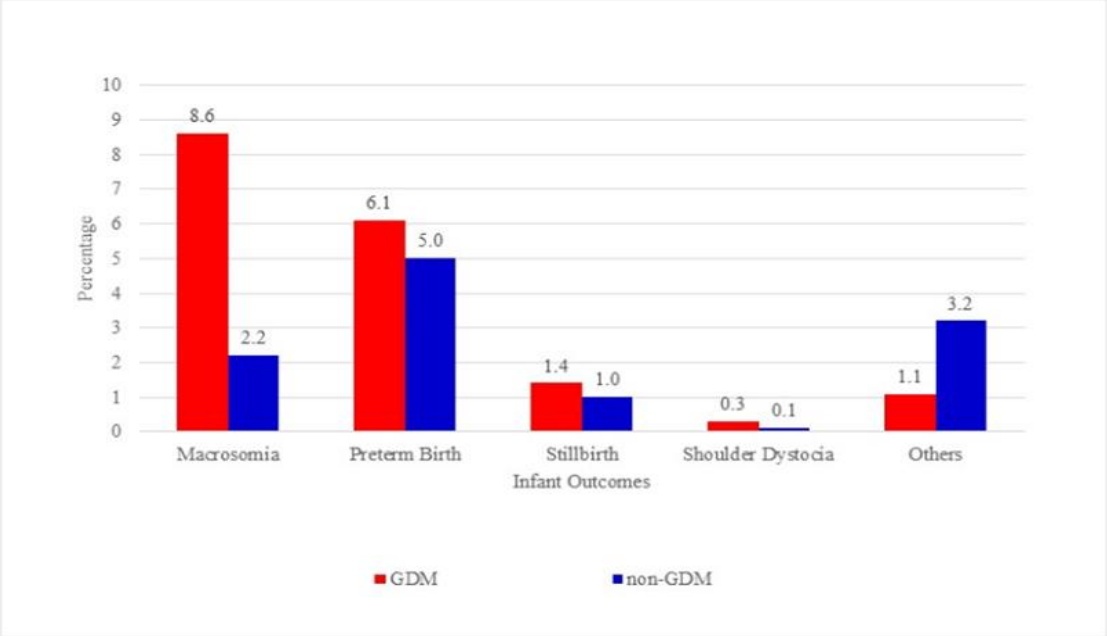

Figure 1: Proportion of infant outcomes according to GDM status

There was a higher proportion of infants with macrosomia, preterm birth, stillbirth and shoulder dystocia born to GDM mothers when compared to non-GDM mothers, these were 8.6%, 6.1%, 1.4% and 0.3% vs 2.2%, 5.0%, 1.0% and 0.1% respectively. However, a higher proportion of other outcomes (including cord prolapse, foetal anomaly, oligohydramnios and intrauterine growth restriction) were detected among infants born to non-GDM mothers (3.2%). The distribution of cases according to GDM status is available in Figure 1.

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3.3 Factors associated with macrosomia

Table 2: Factors associated with macrosomia among infants born in HUSM (n=1077)

Variables		Simple Logistic Regression		Multiple Logistic Regression	
	Crude β	Crude OR (95%CI)	*p*- value	Adjusted OR (95% CI)	*p*-value
GDM Status					
No		1		1	
Yes	1.42	4.15 (2.24, 7.69)	<0.001*	4.09(2.20, 7.58)	<0.001*
Fetal Sex					
Female		1		1	
Male	0.91	2.49 (1.28, 4.85)	0.007*	2.41(1.23, 4.74)	0.010*
Maternal Age					
≥24 years old		1			
25 - 29 years old	-0.02	0.98 (0.38, 2.56)	0.966		
30 - 34 years old	-0.42	0.66 (0.23, 1.85)	0.428		
≥35 years old	0.26	1.30 (0.49, 3.44)	0.595		
Parity					
1		1			
2 – 4	0.82	2.26 (1.03, 4.99)	0.043*		
≥ 5	1.06	2.88 (1.09, 7.63)	0.033*		
History of Miscarriage					
0		1			
1	0.43	1.54 (0.75, 3.18)	0.242		
2	-0.45	0.64 (0.09, 4.78)	0.661		
≥ 3	0.45	1.57 (0.20, 12.23)	0.666		
Status of PIH					
No		1			
Yes	-0.04	0.97 (0.29, 3.19)	0.953		

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For macrosomia at univariate level, GDM status, foetal sex and parity were significantly associated with macrosomia. However, in multivariable analysis, only maternal GDM status and male foetal sex were found to be significantly associated with macrosomia (Table 2). Infants born to GDM mothers had four times the odds of developing macrosomia, as compared to infants born to non-GDM mothers (AOR 4.09, 95% CI: 2.20, 7.58, p <0.001). Male foetus had 2.4 times the odds of developing macrosomia, as compared to female foetus (AOR 2.41, 95% CI: 1.23, 4.74, p =0.010) after adjusting for other confounders.

3.4 Factors associated with preterm birth

Table 3: Factors associated with preterm birth among infants born in HUSM (n=1077)

Variables	Simple Logistic Regression			Multiple Logistic Regression	
	Crude β	Crude OR (95%CI)	*p*- value	Adjusted OR (95% CI)	*p*-value
GDM Status					
No		1		1	
Yes	0.21	1.24 (0.72, 2.14)	0.446	1.16(0.67, 2.03)	0.593
Fetal Sex					
Female		1		1	
Male	0.24	1.27 (0.74, 2.18)	0.39	1.22(0.70, 2.10)	0.482
Maternal Age					
≤24 years old		1			
25 – 29 years old	-0.09	0.91 (0.39, 2.13)	0.836		
30 – 34 years old	-0.53	0.59 (0.23, 1.47)	0.255		
≥35 years old	0.16	1.17 (0.49, 2.76)	0.725		
Parity					
1		1			
2 - 4	-0.34	0.71 (0.40, 1.29)	0.263		
≥5	0.27	1.31 (0.61, 2.79)	0.485		
History of Miscarriage					
0		1			
1	0.17	1.18 (0.58, 2.40)	0.64		
2	0.01	1.01 (0.24, 4.31)	0.993		
≥3	0.19	1.21 (0.16, 9.35)	0.857		
Status of PIH					
No		1		1	
Yes	1.57	4.79 (2.45, 9.37)	<0.001*	4.68(2.39, 9.19)	<0.001*

For preterm birth, maternal status of PIH was the only factor with significant association in simple logistic regression analysis. In multivariable analysis, GDM status and foetal sex were retained in the model as these were the factors of interest in this study. In the final model, maternal status of PIH remained as the only statistically significant independent factor. Both GDM status and foetal sex were statistically not significant (Table 3). Infants born to mothers with PIH had 4.7 times the odds of being delivered preterm, as compared to infants born to mothers with no PIH (AOR 4.69, 95% CI: 2.39, 9.19, p <0.001).

4.0 Discussion

a. Main findings

In this study, a male predominance in infant outcomes such as macrosomia, preterm birth and stillbirth was observed among GDM mothers. For macrosomia, the proportion was comparable to other studies where among macrosomic infants, almost two third were males (Koyanagi et al., 2013; Li et al., 2014; Sojo et al., 2010; Yadav & Lee, 2014). This was also true for preterm births (Di Renzo et al., 2007; Khalil & Alzahra, 2013; Vatten & Skjærven, 2004). This may be due to women who carried male foetuses were accompanied by higher weight, poorer maternal beta cell function, and a higher risk for GDM (Di Renzo et al., 2007; Khalil & Alzahra, 2013; Retnakaran & Shah, 2015).

The higher proportion of macrosomia infants born to GDM mothers might be due to maternal glucose intolerance which lead to increased feto-placental availability of nutrients such as glucose, amino acids and free fatty acids in late gestation, thus contributing to macrosomia (Yogev & Visser, 2009). In this study, both GDM status and male foetal sex were statistically significantly associated with macrosomia. Other authors have also demonstrated similar findings (Li et al., 2014; Yadav & Lee, 2014). During pregnancy, the mothers experienced about 40 to 50% more insulin insensitivity, so as to meet the increase demand of nutrient for the growing foetus (Ehrenberg, Mercer, & Catalano, 2004; Yogev & Visser, 2009). In pregnancy complicated with diabetes, foetal sex influenced the effect of birth weight predictors, where sexual dimorphism in birth weight has been attributed to differences in cytokines, insulin, growth hormone or insulin-growth factor (IGF-1) axis, and genomic imprinting (Sojo et al., 2010). Insulin acts as the main growth hormone during intrauterine life. According to the gender insulin hypothesis, male foetuses are more insulin-sensitive compared to female foetuses, thus achieve a higher birth weight (M. J. Murphy et al., 2004; Sojo et al., 2010). Maternal diabetic status and/or obesity, resulting in high circulating glucose level, in turn leads to increase insulin and other growth factors secretion in foetus, thus accelerated foetal growth (Ehrenberg et al., 2004).

This study also demonstrated that there was a bigger proportion of preterm infants born to GDM mothers when compared to non-GDM mothers. But this proportion was smaller when compared to other studies (Khan et al., 2013; Nayak et al., 2013; Xiong et al., 2001). This was 25.2%, 9.6% and 10.6% respectively as compared to 6.1% in this study. In contrast, some studies found no difference in percentage of preterm birth among infants born to GDM and non-GDM mothers (Hediger, Scholl, Schall, & Krueger, 1997; Srichumchit, Luewan, & Tongsong, 2015). In the multiple logistic regression model, GDM status and foetal sex were not associated with preterm birth, after controlling for maternal age, parity, history of

miscarriage and PIH status. GDM status did not pose higher risk for preterm birth (Lu, Qu, Tang, Chen, & Mu, 2015; Mitrovic et al., 2014; Nordin, Wei, Naing, & Symonds, 2006). Preterm birth among infants born to GDM mothers were usually due to early induction of delivery to reduce perinatal complications associated with GDM status in other studies (Crowther et al., 2005; Mitrovic et al., 2014; Nayak et al., 2013). In this study's local context, the mode of delivery for all pregnant mothers will be dependent on maternal's height, previous obstetric history or complications (e.g. previous baby's weight, birth trauma, previous history of one lower segment Caesarean section etc.) and current clinical scenario (e.g. pelvic size, position of foetus, size of foetus) judged by the obstetricians. In addition, GDM mothers were not allowed to deliver post-date or deliver at 38 weeks gestation for those on insulin (NICE, 2015). Yet most studies suggested that male foetal sex was significantly associated with preterm birth, as compared to female foetal sex (Di Renzo et al., 2007; Gardosi & Francis, 2000; Khalil & Alzahra, 2013; D. J. Murphy, 2007; Vatten & Skjærven, 2004). Despite a higher incidence of preterm birth occurring among male foetuses, this is a constructive finding to encourage health care workers to focus on other modifiable factors rather than foetal sex alone as the predictor of preterm birth. The most important predictor for preterm birth among GDM mothers was vascular complications such as PIH (Mitrovic et al., 2014) as demonstrated in this study. Another study also noted significant association between neonatal birth weight, preterm birth and pregnancy-induced hypertension, as well as weight gain during pregnancy and pre-pregnancy body mass index (He et al., 2014). Chronic placental ischemia due to pre-eclampsia may lead to intrauterine growth restriction, thus small for gestational age infants or preterm birth may results (Thilaganathan, Khalil, & Melchiorre, 2015). Therefore, antenatal care should focus on women with PIH to reduce the incidence of preterm birth.

A higher proportion of stillbirth was born to GDM mothers in this study, which could be due to accelerating teratogenicity secondary to altered metabolism in foetus of GDM mothers, leading to defective foetal gene expression, metabolic acidosis and placental insufficiency (Mitrovic et al., 2014; Silver et al., 2007). Maternal complications increased the risk of stillbirth, but only a small proportion of stillbirth was found in this group of mothers. This was because two third of stillbirth were observed in women without any maternal complication at the time of birth (Zhu et al., 2016). Women with GDM have similar stillbirth rates as general population, whilst some women with GDM diagnosed during pregnancy actually entered the pregnancy with undiagnosed type II diabetes, thus posed the same risk of foetal loss as women with type II diabetes (Silver et al., 2007). In fact, pre-pregnancy obesity, advanced maternal age and stress have been found to be associated with higher stillbirth rates (Silver et al., 2007). In uncomplicated pregnancies, there was a 50% increase risk for stillbirth only with maternal age 35 years or older, and the risk rose rapidly as gestational age increased beyond 37 weeks (Silver et al., 2007).

b. Strength and limitations

There are a few limitations to this study. This study utilized secondary data from a Birth Registry. Many variables such as maternal socio-economic status, maternal weight, and maternal weight gain throughout pregnancy or level of glycaemic control in pregnancy which may add value to this study were not recorded in the Birth Registry. The infant outcomes documented in the Birth Registry were also limited to those commonly occurred during intrapartum and immediate postnatal period in the Labour Room. This study also included both iatrogenic preterm birth and spontaneous preterm birth as 'preterm birth', as the Birth

Registry did not document the classification of preterm birth according to its causes. Nevertheless, the fact that the clinical findings were recorded in the Birth Registry by an experienced team of nurses in the labour room increased the reliability of the data. Secondly, ethnicity was not included in the model of this study due to the extreme proportions, despite the random sampling technique. Based on the Department of Statistics Malaysia (2011), Malaysian citizens consist of the ethnic groups *Bumiputera* (67.4%), Chinese (24.6%), Indians (7.3%) and others (0.7%). Conversely in *Kelantan*, the *Malays* is the predominant ethnic group (92.3%) (Department of Statistics Malaysia, 2015). Other outcomes such as cord prolapse, foetal anomaly, intrauterine growth restriction and oligohydramnios were also found in this study, despite in a smaller proportion. Expanding the sample size maybe helpful in determining the predictors of these other outcomes.

5.0 Conclusion and recommendation

In the life course, adverse infant outcomes have been associated with lifelong health issues. This study demonstrated that foetal sex and maternal GDM status, predicted poorer outcome for these foetuses. The proportion of macrosomia, preterm birth and stillbirth were higher among infants born to GDM mothers in this study. GDM status and male foetal sex were significant predictors only for macrosomia but not for preterm birth. Although foetal sex is a non-modifiable risk factor, early screening, specifically for maternal GDM, may offer better antenatal services and detection of potential complications, to ensure better infant outcomes.

This study demonstrated that knowledge of GDM status and male foetal sex adds value to the risk assessment of pregnancies, especially in term of macrosomia. Therefore, proper documentation of foetal sex based on ultrasound finding is recommended, as well as foetal growth monitoring with clinical and ultrasound assessment should be available for all pregnant women. More vigilant monitoring and management of GDM mothers carrying male foetuses should be carried out. For preterm birth, focus should be stress on optimum management of those with pregnancy-induced hypertensive disorders.

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Declaration

Author(s) declare that no conflict of interest pertaining to this research.

Authors contribution

All authors have contributed to this article, including proof reading and approval of the final version of this manuscript. SN was involved in data collection, literature search and review, data analysis and interpretation, and writing of the manuscript. WRW was in-charged of data collection and critical revision of the manuscript. NA was responsible for data collection, data analysis and interpretation, and critical revision of the manuscript. All authors accept responsibility for the paper as published.

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