

## Gestational Diabetes in Malaysia: A Systematic Review of Prevalence, Risk Factors and Outcomes

(Diabetes Gestasi di Malaysia: Suatu Kajian Sistematis Mengenai Prevalens, Faktor Risiko dan Akibat)

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### ABSTRACT

*Gestational diabetes mellitus (GDM) is glucose intolerance first diagnosed during pregnancy. In Malaysia, the prevalence, risk factors, and maternal/foetal outcomes vary somewhat among the local studies. In this systematic review of Malaysian studies, we synthesise relevant data from 13 journal articles (including 10,285 women with gestational diabetes). A meta-analysis of twelve datasets showed a prevalence of 21.5% (95% CI 17.3 to 25.9%, random effect model). Clinical factors in the mother found to increase her risk of GDM were consistent with international data. A meta-analysis of complications showed statistically significant increase for macrosomia (OR 3.08, 95% CI 1.77 to 5.36) but not for pre-eclampsia (OR 1.44, 95% CI 0.52 to 4.00) and caesarean delivery (OR 1.31, 95% CI 0.98 to 1.75). The high prevalence of gestational diabetes mellitus and documented adverse consequences support the need for universal screening of this condition in all pregnant women in Malaysia.*

*Keywords: Gestational diabetes; Malaysia; pregnancy; prevalence; risk factors*

### ABSTRAK

*Diabetes gestasi (GDM) adalah keadaan intolerans glukosa yang pertama kali dikesan semasa kehamilan. Di Malaysia, prevalens, faktor risiko dan akibat penyakit ini agak berbeza di kalangan penyelidikan tempatan. Dalam kajian sistematik ke atas penyelidikan dari Malaysia, kami menggabungkan data daripada 13 artikel jurnal (termasuk 10,285 wanita yang mengidap diabetes gestasi). Analisa meta 12 set data menunjukkan prevalens ialah 21.5% (95% CI 17.3 - 25.9%, model kesan rawak). Faktor klinikal pada ibu yang meningkatkan risiko kepada GDM adalah selaras dengan data antarabangsa. Analisa meta ke atas komplikasi akibat GDM menunjukkan peningkatan signifikan secara statistik bagi makrosomia (OR 3.08, 95% CI 1.77 - 5.36) tetapi tidak untuk praeklampsia (OR 1.44, 95% CI 0.52 - 4.00) dan pembedahan caesarean (OR 1.31, 95% CI 0.98 - 1.75). Prevalens diabetes gestasi yang tinggi dan akibat buruk yang ditunjukkan menyokong perlunya saringan universal bagi penyakit ini di kalangan ibu mengandung di Malaysia.*

*Kata kunci: Diabetes gestasi; faktor risiko; kehamilan; Malaysia; prevalens*

### INTRODUCTION

Gestational diabetes mellitus (GDM) is glucose intolerance first diagnosed during pregnancy. GDM poses a huge health burden in both the short and long term. Both mother and baby of GDM are at greater risk of complications during pregnancy and delivery. Poorly managed GDM results in higher perinatal morbidity and mortality (Contreras et al. 2008). After delivery, both mother and newborn are also at a greater risk of developing type 2 diabetes mellitus, obesity, and subsequent cardiovascular diseases (Kramer et al. 2019; Nouhjah et al. 2017). Hyperglycaemia in pregnancy is associated with macrosomia and polyhydramnios. During delivery,

these infants of poorly controlled GDM will be more susceptible to birth related complications of prolonged labour, shoulder dystocia, birth asphyxia, and increased rates of admission to neonatal intensive care unit (NICU). Caesarean delivery rates are higher in GDM for various reasons apart from estimated birth weight exceeding 4 kg (Boriboonthirunsarn & Waiyanikorn 2016).

The prevalence of GDM varies worldwide depending on the diagnostic criteria and reporting rates. A meta-analysis of 50 population-based prevalence studies showed that Asia has the highest prevalence (South Asia 11.4%, East Asia 10.8%), while lower rates were seen in Australia with 3.6%, North America with 4.5% and North

Europe with 6% (Behboudi-Gandevani et al. 2019). Locally, there is some variation in the prevalence, risk factors and maternal/foetal outcomes of this condition. Synthesised data in these domains derived from meta-analysis can help policy makers and clinicians with regard to the implementation of screening programme and clinical care of such patients.

#### MATERIALS AND METHODS

We searched PubMed (using the MESH terms ‘Diabetes’, ‘Gestational’ and ‘Malaysia’) and Scopus (using text word ‘gestational diabetes’ and ‘Malaysia’) on 31<sup>st</sup> December 2019. These searches were supplemented by a Google Scholar search using the same text words. The citations were processed using Endnote 7 citation manager. Keywords of all citations were coded for study designs, study settings (primary care, tertiary care), country of study (Malaysia, non-Malaysia), and any prevalence, risk factors or maternal or foetal/neonatal outcome data.

The inclusion criteria of eligible studies were: Original research conducted in Malaysia; Studies that provide data on prevalence, risk factors, maternal or

foetal/neonatal outcome data of GDM; for prevalence data, GDM must be diagnosed using an oral glucose tolerance test (oGTT); for risk factor assessment, the recruitment of antenatal women should be universal rather than selective; and for maternal and foetal/neonatal outcome data, both prospective and retrospective studies are acceptable.

Full text of eligible studies was retrieved. Relevant data in the included studies were extracted by a pair of investigators and checked by a senior researcher. The number of study participants (total sample and number diagnosed with GDM) and other relevant data (study setting, patient selection, oGTT method) were extracted. Meta-analysis was performed using MedCalc Statistical Software using fixed effect model if study heterogeneity ( $I^2$ ) is less than 50%, otherwise random effect model was used (MedCalc 2019). Sensitivity analysis was performed for prevalence data taking into account the study setting, patient selection and oGTT procedure.

This systematic review was prepared following PRISMA guideline (Moher et al. 2009). The quality assessment of the published studies was assessed using a checklist published by Munn et al. (2015).

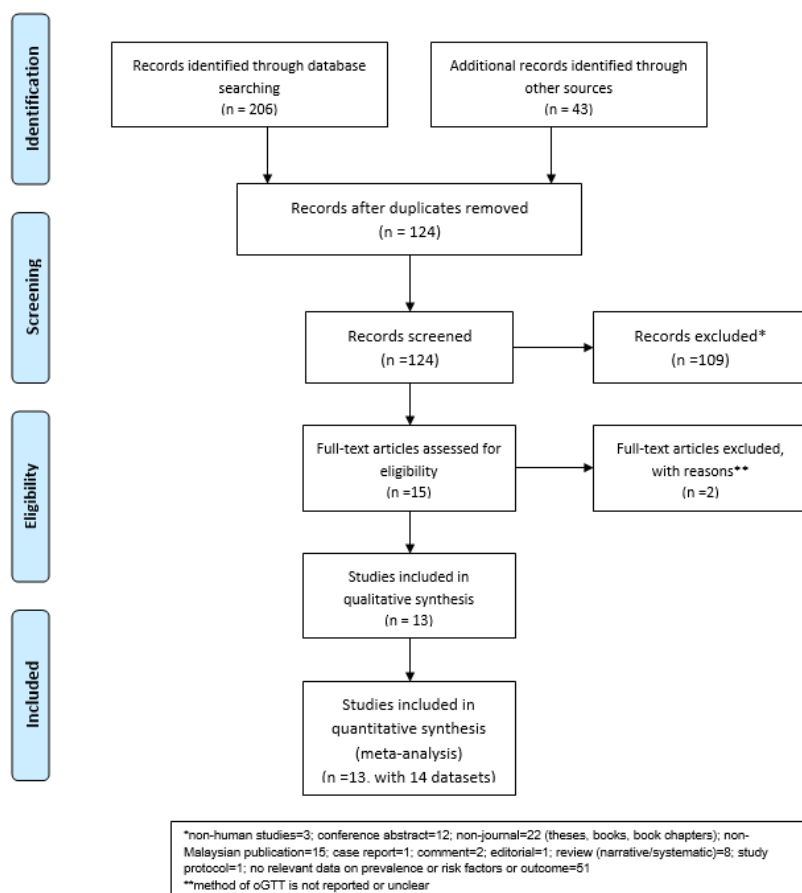


FIGURE 1. PRISMA 2009 flow diagram

## RESULTS

## SEARCH RESULTS

Of the 124 items found from the database and internet search, we included 15 publications in the qualitative analysis (Basri et al. 2018; Gill et al. 2012; Goh et al. 2018; Hasbullah et al. 2020; Idris et al. 2009; Ismail et al. 2013, 2011; Kalok et al. 2018; Kampan et al. 2013; Logakodie et al. 2018; Muniswaran et al. 2017; Nordin et al. 2006; Shamsuddin et al. 2001; Tan et al. 2012, 2007). Two publications with low quality score were excluded (lack of information on the patient recruitment and diagnostic method) (Goh et al. 2018; Muniswaran et al. 2017). Eleven publications provided prevalence data (Basri et al. 2018; Gill et al. 2012; Hasbullah et al. 2020; Idris et al. 2009; Ismail et al. 2013, 2011; Kalok et al. 2018; Logakodie et al. 2018; Shamsuddin et al. 2001; Tan et al. 2012, 2007). Four publications provided risk factors data (Gill et al. 2012; Shamsuddin et al. 2001; Tan et al. 2012, 2007), and seven publications provided maternal, foetal/neonatal complications data (Basri et al. 2018; Ismail et al. 2013, 2011; Kalok et al. 2018; Kampan et al. 2013; Logakodie et al. 2018; Nordin et al. 2006).

## QUALITY ASSESSMENT

All the included studies received a moderate to high quality rating in our critical appraisal.

## PREVALENCE OF GESTATIONAL DIABETES

Eleven publications provided data on prevalence of GDM (Table 1) (Basri et al. 2018; Gill et al. 2012; Hasbullah et al. 2020; Idris et al. 2009; Ismail et al. 2013, 2011; Kalok et al. 2018; Logakodie et al. 2018; Shamsuddin et al. 2001; Tan et al. 2012, 2007). One publication contained two separate datasets of GDM prevalence (Basri et al. 2018). These studies were conducted in various settings (primary care and tertiary care), and recruited pregnant women with and without risk factors of GDM. Although all of them used oGTT to confirm the presence of GDM, the methods employed in administering oGTT and diagnostic threshold were highly variable. 1-step procedure (75 g oGTT) was used in seven studies (eight datasets) and 2-step procedure (a 50 g glucose challenge test followed by a 75 g oGTT in selected cases) was done in three studies.

The prevalence rate of GDM in the primary studies ranged from 11.4 to 37.9%, a 3.3-fold difference. A meta-analysis of twelve datasets involving 9587 antenatal women showed very high study heterogeneity ( $I^2=95.97$ ) with a prevalence of 21.5% (95% CI 17.3 to 25.9%, random effect model) (Figure 2). Sensitivity analysis showed no difference in the prevalence by setting. However, prevalence of GDM appeared to be lower if there was less selection bias while 2-step procedure tends to under-detect GDM compared to 1-step procedure (Table 2).

TABLE 1. Malaysian studies providing prevalence data of gestational diabetes

Study	Methods			Participants				Prevalence	
	Study design*	Recruitment	oGTT method	oGTT criteria	Setting	n	Mean age, y		Primigravida, %
Basri et al. (2018)	RCT	Selective	1-step	FBS>6.1 OR 2HPP>7.8 mmol/L [WHO1999]	Tertiary care	261	31.9	32.6	37.9%
Basri et al. (2018)	RCT	Selective	1-step	FBS≥5.1 OR 2HPP≥8.5 mmol/L [IADPSG]	Tertiary care	259	31.1	42.1	38.6%

Gill et al. (2012)	RCS	Universal	2-step	GCT (50 g) 1HPP>7.2; then oGTT (75 g), FBS>6.0, 2HPP >7.8 mmol/L	Tertiary care	1997	29.0	NA	21.5%
Hasbullah et al. (2020)	PCS	Universal	1-step	FBS>5.1 OR 2HPP >7.8 mmol/L	Primary care	294	30.1	38.1	15.3%
Idris et al. (2009)	CSS	Selective	2-step	GCT (50 g) 1HPP>7.8; then oGTT (75 g), FBS<7.0 AND 2HPP ≥7.8 mmol/L	Primary care	366	30.3	30.0	18.3%
Ismail et al. (2011)	PCS	Selective**	1-step	FBS>6.0 OR 2HPP >7.8 mmol/L	Tertiary care	616	26.6	100	18.3%
Ismail et al. (2013)	PCS	Selective	1-step	FBS≥6.0 OR 2HPP ≥7.8 mmol/L	Tertiary care	279	30.9	30.1	22.6%
Kalok et al. (2018)	PCS	Selective***	1-step	FBS >6.1 OR 2HPP >7.8 mmol/L	Tertiary care	197	31.0	NA	14.2%
Logakodie et al. (2017)	RCS	Selective	1-step	FBG ≥5.6 or 2HPP ≥7.8 mmol/L	Primary care	659	NA	29.3	27.9%
Shamsuddin et al. (2001)	CSS	Universal	1-step	2HPP ≥7.8 mmol/L (no FBS)	Tertiary care	768	NA	57.7	24.9%

Tan et al. (2012)	PCS	Universal	2-step	GCT (50 g) 1HPP>7.2; then oGTT (75 g), FBS>7.0, 2HPP>7.8 mmol/L	Tertiary care	2291	29.8	NA	13.9%
Tan et al. (2007)	PCS	Universal	2-step	GCT (50 g) 1HPP>7.2; then oGTT (75 g), FBS>7.0, 2HPP>7.8 mmol/L	Tertiary care	1600	29.6	42.4	11.4%

\*CSS=cross-sectional study; PCS=prospective cohort study; RCS=retrospective cohort study; RCT=randomised controlled trial;

\*\*only recruited primigravida; \*\*\*only recruited women with low GDM risk

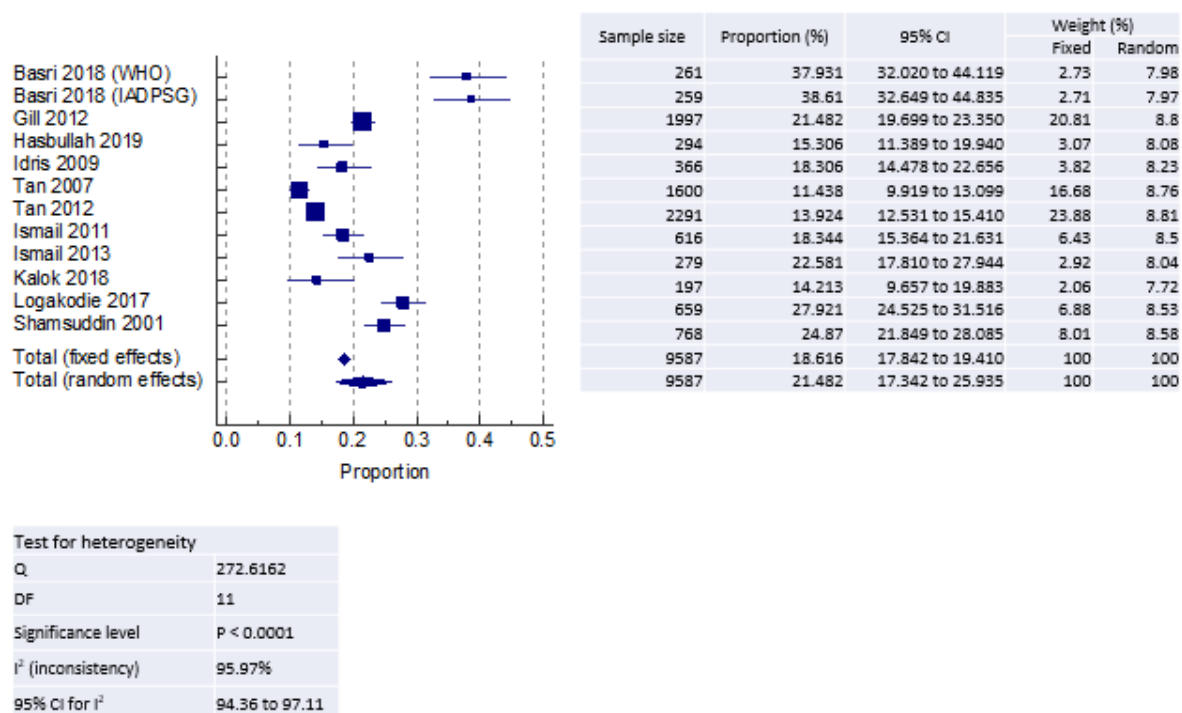


FIGURE 2. Meta-analysis of prevalence rate of gestational diabetes

TABLE 2. Sensitivity analysis of prevalence meta-analysis (all studies)

Sensitivity analysis	(n=number of datasets)	Prevalence (95%CI), [random effect]	Prevalence (95%CI), [fixed effect]	I <sup>2</sup>
Study setting	Primary care (n=3)	20.5 (13.2 to 28.8)	22.2 (20.0 to 24.6)	91.63
	Tertiary care (n=9)	21.8 (16.9 to 27.1)	18.1 (17.2 to 18.9)	96.61
Patient selection*	Universal (n=5)	17.2 (12.5 to 22.3)	16.6 (15.7 to 17.4)	96.42
	Selective (n=5)	28.7 (21.6 to 36.4)	27.9 (25.9 to 30.0)	91.77
OGTT procedure	1-step (n=8)	24.6 (19.3 to 30.2)	24.4 (23.0 to 25.9)	92.52
	2-step (n=4)	16.1 (11.6 to 21.2)	15.8 (14.9 to 16.7)	96.09

\*exclude Kalok et al. (2018) and Ismail et al. (2011) (low risk)

#### RISK FACTORS OF GESTATIONAL DIABETES

We found four studies reporting risk factors for GDM in Malaysia (Gill et al. 2012; Shamsuddin et al. 2001; Tan et al. 2012, 2007). In this analysis, we included only studies that recruited all antenatal women rather those with or

without certain risk factors. Clinical factors in the mother found to increase her risk of GDM were: older maternal age, obesity, glycosuria, abnormal GCT, family history of diabetes, previous GDM and history of stillbirth (Table 3).

TABLE 3. Malaysian studies providing risk factors data of gestational diabetes

Study	Methods			Participants		Risk factors
	Study design*	Recruitment	oGTT method	Setting	n	
Gill et al. (2012)	RCS	Universal	2-step	Tertiary care	1997	Older age, booking weight $\geq$ 80 kg, glycosuria, abnormal GCT, family history of diabetes, previous GDM, history of stillbirth
Shamsuddin et al. (2001)	CSS	Universal	1-step	Tertiary care	768	Previous GDM, maternal age $>$ 35
Tan et al. (2012)	PCS	Universal	2-step	Tertiary care	2291	Older age, abnormal GCT, maternal weight $\geq$ 70 kg
Tan et al. (2007)	PCS	Universal	2-step	Tertiary care	1600	Older age, higher maternal BMI, higher SBP, higher DBP

\*CSS=cross-sectional study; PCS=prospective cohort study; RCS=retrospective cohort study; RCT=randomised controlled trial

## MATERNAL AND FOETAL/NEONATAL COMPLICATIONS

We found seven studies that provided maternal, foetal/neonatal complications data (Basri et al. 2018; Ismail et al. 2013, 2011; Kalok et al. 2018; Kampan et al. 2013; Logakodie et al. 2018; Nordin et al. 2006). One study containing two separate datasets were analysed separately (Basri et al. 2018). Maternal complications that were associated with GDM were caesarean delivery rate, induction of labour, polyhydramnios, pre-eclampsia,

and premature labour. Foetal/neonatal, complications that were associated with GDM were birth trauma, hyperbilirubinaemia, hypoglycaemia, low Apgar score, macrosomia, NICU admission, polycythaemia, respiratory distress syndrome, and stillbirth (Table 4). A meta-analysis of complications reported in three or more datasets showed statistically significant increase for macrosomia (OR 3.08, 95% CI 1.77 to 5.36) but not for pre-eclampsia (OR 1.44, 95% CI 0.52 to 4.00) and caesarean section (OR 1.31, 95% CI 0.98 to 1.75) (Table 5).

TABLE 4. Malaysian studies providing complications data of gestational diabetes

Study	Methods			Participants		Complications	
	Study design*	Recruitment	oGTT method	Setting	n	Maternal	Foetal/neonatal
Basri et al. (2018)	RCT	Selective	1-step	Tertiary care	261	Caesarean section	Macrosomia
Basri et al. (2018)	RCT	Selective	1-step	Tertiary care	259	Gestational hypertension or pre-eclampsia	Neonatal hypoglycaemia
Ismail et al. (2011)	PCS	Selective**	1-step	Tertiary care	616	None	Hyperbilirubinaemia
Ismail et al. (2013)	PCS	Selective	1-step	Tertiary care	279	Caesarean section, assisted delivery	Macrosomia, stillbirth, birth trauma, hypoglycaemia, hyperbilirubinemia, polycythaemia
Kalok et al. (2018)	PCS	Selective***	1-step	Tertiary care	197	Labour induction, caesarean section	Macrosomia
Kampan et al. (2013)****	CCS	Selective	1-step	Tertiary care	800	Premature labour, caesarean section	Low Apgar, macrosomia, NICU admission, hypoglycaemia, respiratory distress syndrome
Logakodie et al. (2017)	RCS	Selective	1-step	Primary care	659	Non-spontaneous vaginal delivery	No data
Nordin et al. (2006)	RCS	Selective	1-step	Tertiary care	298	Polyhydramnios, pre-eclampsia, labour induction	Macrosomia

\*CCS=case-control study; PCS=prospective cohort study; RCS=retrospective cohort study; RCT=randomised controlled trial;

\*\*recruited primigravida only; \*\*\*recruited women with low GDM risk only

\*\*\*\*Some women in this study had pre-existing diabetes, it is included here as 96% of them had GDM

TABLE 5. Meta-analysis of odds ratio of complications of gestational diabetes

Outcomes	Number of datasets (references)	Number of participants		Odds ratio (95% CI), (random effect)	Odds ratio (95% CI), (fixed effect)	I <sup>2</sup>
		GDM (n/N)	No GDM (n/N)			
		Pre-eclampsia	4(9, 13, 16)			
Caesarean section	4(9, 13, 15)	96/334	227/981	1.35 (0.94 to 1.93)	1.31 (0.98 to 1.75)	30.79%
Macrosomia	6(9, 13-16)	35/797	28/1597	2.91 (1.54 to 5.47)	3.08 (1.77 to 5.36)	9.09%

n/N=number of participants with complication/number of participants in subgroup

## DISCUSSION

### PREVALENCE AND RISK FACTORS OF GDM

The pooled prevalence of GDM in Malaysia as shown in our meta-analysis is approximately 21.5% (95% CI 17.3% to 25.9%, random effect model, Table 1). There is some uncertainty in this pooled prevalence in view of high study heterogeneity, possibly as a result of differences in the patient recruitment, diagnostic methods and criteria of oGTT. In the selection of studies for this meta-analysis, we have excluded one retrospective cohort study derived from the Malaysian Obstetric Registry (Muniswaran et al. 2017). Although this study has a large sample size (n=22,044), the antenatal women were recruited at delivery from the obstetrics register of 14 public hospitals. The diagnostic method and criteria of GDM were also not clearly described.

Our pooled prevalence of GDM appeared to be higher than the pooled prevalence for Asian countries (Lee et al. 2018; Nguyen et al. 2018) (10.1-11.5%). In these meta-analyses, only two Malaysian prevalence studies were included (Lee et al. 2018; Nguyen et al. 2018). When compared to the country-specific meta-analyses of prevalence studies, our pooled prevalence is also higher than those of Iran with 3.41% (Jafari-Shobeiri et al. 2015), Turkey with 7.7% (Karaçam & Celik 2021), China with 14.8% (Gao et al. 2019), and India with 19.19% using IADPSG method of diagnosis (Li et al. 2018).

There are concerns in adopting universal screening for GDM in resource limited countries despite ACHOIS trial had shown intervention for women suffering from mild gestational diabetes did reduce some of its complications such as fetal overgrowth, shoulder dystocia, caesarean delivery, and hypertensive disorders (Landon et al. 2009). However, there appears to be some compelling evidence for the adoption of universal screening for GDM in antenatal mothers in Malaysia. Firstly, the incidence of GDM is substantially high, affecting possibly one in five pregnant women in this country. Secondly, selective screening may miss a substantial number of eligible women, e.g. Shamsuddin et al. (2001) reported 28% of GDM women in their study did not have any risk factors used in the selective screening. Furthermore, Gill et al. (2012) also did not find improved efficiency of GDM screening using a scoring system derived from nine known GDM risk factors.

Currently two Malaysian clinical practice guidelines (HTAU 2017, 2015) recommend screening of antenatal women using 75 g oGTT at booking based on the presence of risk factors, and, if negative, to repeat the same at 24-28 weeks gestation. Both these guidelines adopted the IADPSG guideline (Lapolla et al. 2011) but with some difference for the 2 h post-glucose load threshold (Type 2 Diabetes CPG: FPG  $\geq$  5.1, 2HPP  $\geq$  8.5 (Health Technology Assessment Unit 2015); DM in Pregnancy CPG: FPG  $\geq$  5.1, 2HPP  $\geq$  7.8 (Health Technology Assessment Unit



2017)). The Health Technology Assessment Unit of the Ministry of Health Malaysia, as developer of the national guideline, should initiate efforts to avoid such confusion.

#### COMPLICATIONS AND OUTCOMES OF GESTATIONAL DIABETES

Our analysis identified several complications as a result of GDM. However, in our meta-analysis, only macrosomia is a statistically significant outcome but not pre-eclampsia or caesarean section. In our literature review, we found that the above complications are by and large associated with GDM in other systematic reviews (Hosseini & Janghorbani 2018; Natamba et al. 2019; Wendland et al. 2012), however, some inconsistency is also found, e.g. Natamba's systematic review (2019) of studies in Sub-Sahara Africa also did not show an increased risk of caesarean section.

#### STUDY LIMITATIONS

This systematic review is based on a comprehensive retrieval of Malaysian journal articles on the topic of GDM. We are confident that we have identified most, if not all, relevant publications on this topic. However, publication bias cannot be excluded. In addition, pooled analysis is compounded by missing data in the original publications. Furthermore, beside the variable diagnostic methods and threshold for GDM, it is also possible there are inconsistent definitions for other outcomes such as macrosomia and pre-eclampsia. Thus, we wish to echo the call by Feig et al. (2015) for codification of the definitions and reporting of variables in future investigation on GDM.

#### CONCLUSION

This systematic review comprehensively summarises the available published literature on the prevalence, risk factors, and complications/outcomes of GDM in Malaysian women. Our study emphasised the high prevalence of GDM, summarised various risk factors associated with it and substantial complications that may result and recommend universal screening of this important health condition in pregnancy.

#### ACKNOWLEDGEMENTS

We wish to thank Dr Fauziah Zainal Ehsan for assisting in the preparation of the Malay abstract.

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Received: 14 June 2020

Accepted: 31 December 2020