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Prevalence and Factors Associated with Postpartum Glucose Intolerance Following Gestational Diabetes Mellitus in Malaysia: A Narrative Review

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Abstract

Postpartum glucose intolerance, including pre-diabetes and type 2 diabetes (T2D), is an adverse outcome of gestational diabetes mellitus (GDM). The review aims to summarize the prevalence and factors associated with postpartum glucose intolerance in women post-GDM in Malaysia. We performed a literature search on three databases (Pubmed, Science Direct and MyJurnal) for relevant studies. Based on five studies (n = 664) that included multiple ethnicities in Malaysia, postpartum glucose intolerance in women post-GDM ranged from 12.1% to 61.7%. Factors associated with postpartum glucose intolerance included maternal age; working status; education level; infant birth weight; maternal obesity; insulin treatment during GDM; glucose and HbA1c levels during pregnancy; duration lapse after GDM; postpartum levels of triglycerides, insulin resistance and HbA1c; and gut microbiota. Insulin treatment during GDM pregnancy was the most prevalent factor associated with postpartum glucose toleranceFurther studies on sociodemographic, biological and lifestyle risk factors of

T2D in Malaysia are needed to understand the pathophysiology of T2D development in this high-risk population.
Keywords: Gestational Diabetes Mellitus, Glucose Intolerance, Pre-Diabetes, Type 2 Diabetes, Malaysia

Introduction

Gestational diabetes mellitus (GDM) is diabetes first diagnosed during pregnancy that was not clearly overt diabetes prior to gestation (American Diabetes Association, 2022). Postpartum glucose intolerance, which includes pre-diabetes (impaired fasting glucose [IFG] or impaired glucose tolerance [IGT]) and type 2 diabetes (T2D) is one of the several adverse outcomes of GDM (Pastore et al., 2018). GDM often indicates underlying pancreatic β-cell impairment, which confers an elevated risk of future diabetes (T2D) (Buchanan et al., 2007; American Diabetes Association, 2022). A nationwide study reported the prevalence of overall raised blood glucose in Malaysian adults increased from 11.2% in 2011, to 13.4% (2015) and most recently 18.3% (2019) (Institute for Public Health, 2019). In Malaysian women of reproductive age (18 – 49 years old), the prevalence of overall raised blood glucose was 4.0% to 25.2% (Institute for Public Health, 2019). However, there was no local nationwide data on T2D prevalence in women post-GDM, despite women post-GDM having a 10-fold risk of developing T2D compared to women with normoglycemic pregnancies (Vounzoulaki et al., 2020; Gadve et al., 2021). Up to 31% parous women with T2D had a previous diagnosis of GDM (Cheung & Byth, 2003). Women post-GDM also carry up to 60% lifelong risk of T2D (Noctor & Dunne, 2015), emphasizing the importance of early detection and prevention of glucose intolerance in this high-risk population.

Reviews on prevalence and factors significantly associated with postpartum glucose intolerance in women post-GDM mainly included studies conducted in the Western population (Kim et al., 2002; Cheung & Byth, 2003; Baptiste-Roberts et al., 2009; Bellamy et al., 2009; Rayanagoudar et al., 2016; Vounzoulaki et al., 2020; Li et al., 2020). Diabetes genes and lifestyle behaviour of Asian populations may widely differ from their Caucasion counterpart (Hu et al., 2011; Gujral et al., 2013; Norimah et al., 2008). There are limited reviews discussing on the prevalence and factors associated with postpartum glucose intolerance in Asian women post-GDM (Nouhjah et al., 2007; Gadve et al., 2021), and none in the Malaysian population. Hence, the current review may be useful to identify strategies for public health interventions for women post-GDM in this specific Asian population. This narrative review aims to summarize the prevalence and factors associated with postpartum glucose intolerance in women post-GDM in Malaysia.

Materials and Methods

Literature Search

A literature search was performed on three databases for relevant studies published since 1990 up to 2021: Pubmed, Science Direct and MyJurnal (Malaysian journal database). The following search terms and their combinations were used: “gestational diabetes”, “postpartum”, “Malaysia”, “pre-diabetes”, “type 2 diabetes”, “glucose intolerance” and “glucose level”. Articles yielded during the search result were screened for eligibility based on their abstract and full text.

Study Selection

This review included observational studies conducted among women with a history of GDM (post-GDM) in Malaysia at postpartum, that assessed glucose intolerance (pre-diabetes and/or T2D). We excluded non-original articles (reviews, protocol papers, guidelines, editorials, conference proceedings), animal studies, studies without diabetes-related outcomes, and studies conducted in pregnant women currently implicated with GDM. Figure 1 depicts the selection process of relevant studies.

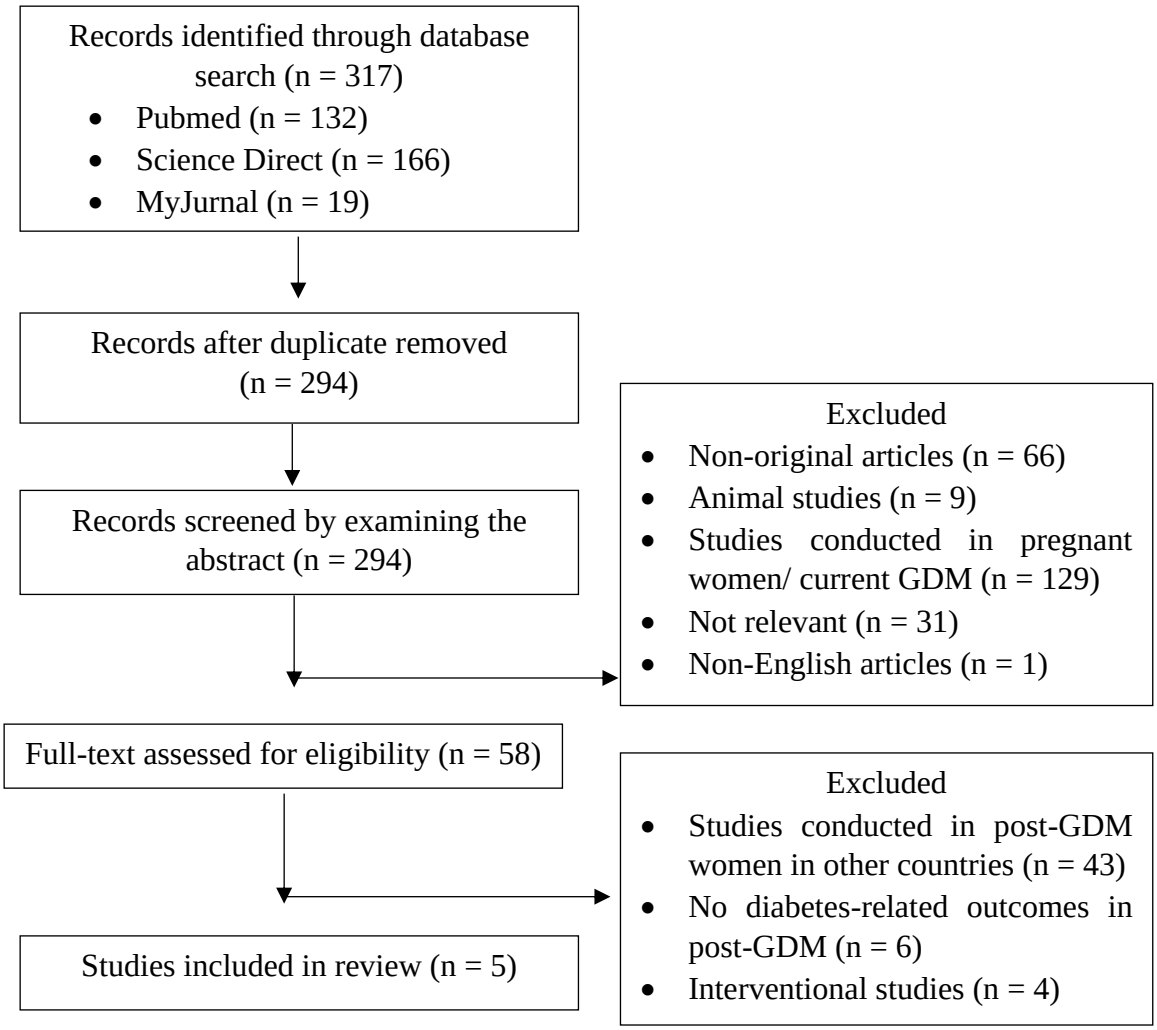

Figure 1: Selection of articles through literature search

Data Extraction

The following information was extracted from the relevant studies: study design, study site, participant characteristics and assessment of postpartum glucose intolerance (time of assessment, screening method, prevalence and factors associated with glucose intolerance).

Results

Study Characteristics

A total of five articles fit the criteria (Table 1). Three of the studies were cross-sectional (Chew et al., 2012; Logakodie et al., 2017; Fatin & Alina, 2019); one was a cross-sectional analysis of a randomized controlled trial (Shyam et al., 2014); and another was a comparative cross-sectional conducted in two groups of women post-GDM (Hasain et al., 2021). Three studies were conducted in urban setting at teaching hospitals (Chew et al., 2012; Shyam et al., 2014; Hasain et al., 2021), while the other two studies collected secondary data from antenatal records at several government health clinics (Logakodie et al., 2017; Fatin & Alina, 2019). The number of participants ranged from 24 to 342 women post-GDM, with most of the participants being Malays (48.2% - 91.7%). Two of the studies had non-Malaysians included in the analysis: 9.1% in Logakodie et al (2017), and 2.6% in (Shyam et al., 2014). On average, participants were less than 35 years old in the studies, except for Hasain et al (2021), with older mean age of 33.7 – 35.9 years old.

Assessment of Postpartum Glucose Intolerance

Glucose intolerance was determined shortly after delivery: at six weeks (Logakodie et al., 2017; Fatin & Alina, 2019) and up to six months postpartum (Shyam et al., 2014; Hasain et al., 2021). One study assessed glucose intolerance from three months up to 15 years postpartum (Chew et al., 2012). All of the studies performed a 75g, 2-hour oral glucose tolerance test (OGTT) based on various diagnostic criteria to determine glucose intolerance. Abnormal glucose tolerance, defined as the sum of pre-diabetes and T2D, ranged from 12.1% (Logakodie et al., 2017) to 61.7% (Chew et al., 2012). Pre-diabetes was either in the form of isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT) or combined IFG and IGT; and ranged from 11.5% (Fatin & Alina, 2019) to 28.6% (Shyam et al., 2014). Meanwhile, T2D ranged from 0.8% (Fatin & Alina, 2019) to 35.5% (Chew et al., 2012). In Hasain et al (2021), the glucose intolerance group (n = 14) mainly comprised of pre-diabetes (64.2%).

Factors Significantly Associated with Postpartum Glucose Intolerance

Factors significanty associated with postpartum glucose intolerance were determined using regression analysis (Chew et al., 2012; Shyam et al., 2014; Fatin & Alina, 2019) or generalized estimating equation (GEE) (Logakodie et al., 2017). Factors significantly associated with postpartum glucose intolerance assessed during GDM pregnancies include: levels of fasting plasma glucose (FPG) and 2-hour postprandial glucose (2hPG) (Chew et al., 2012); HbA1c (Fatin & Alina, 2019); insulin usage (Logakodie et al., 2017; Fatin & Alina, 2019) or pharmalogical requirements (Hasain et al., 2021); and maternal obesity (Logakodie et al., 2017). Meanwhile, factors independently associated with postpartum glucose intolerance assessed during postpartum period included duration lapse after GDM (Chew et al., 2012); levels of triglycerides (Shyam et al., 2014; Hasain et al., 2021), HbA1c (Hasain et al., 2021) and HOMA-IR (Hasain et al., 2021); gut microbiota from Proteobacteria and Bacteroidetes phyla (Hasain et al., 2021).

Sociodemographic factors significantly correlated with postpartum glucose intolerance were maternal age (Shyam et al., 2014), working mothers (Logakodie et al., 2017) and lower educational level (Hasain et al., 2021). Neonatal factors associated with postpartum glucose intolerance were infant birth weight (Shyam et al., 2014), having hospital follow-up and admission into the neonatal intensive care unit (NICU) ward (Fatin & Alina, 2019).

Table 1

Characteristics of studies investigating postpartum glucose intolerance in Malaysian women post-GDM

Authors (year)	Study design	Study site (institution)	Time of assessment	Participants	Screening of postpartum glucose intolerance	Prevalence of postpartum glucose intolerance	Factors significantly associated with postpartum glucose intolerance
Chew et al (2012)	Cross-sectional	Teaching hospital (n=1; University Malaya Medical Centre, Kuala Lumpur)	3 months to 15 years postpartum	n = 342; mean age 31.7-33.2 across groups; Malay 48.2%; Chinese 30.7%; Indian 21.1%	75g, 2-hour OGTT (WHO, 2002)	Glucose intolerance: 61.7% This included: • T2D: 35.5% • Pre-diabetes: 26.2% - Isolated IFG: 10.3 - Isolated IGT: 9.4% - Combined IFG/IGT: 6.5%	<u>During pregnancy</u>: FPG and 2hPG levels at GDM diagnosis <u>During postpartum</u>: Duration lapse after index GDM
Shyam et al (2014)	Cross-sectional analysis of RCT	Teaching hospital (n=1; Universiti Kebangsaan Malaysia Medical	2-6 months postpartum	n = 77; mean age 30.5; Malay 74%; Chinese 17%; Indian 6%; others	75g, 2-hour OGTT. IGT based on ADA (2007), IFG based on Albertl	Glucose intolerance: 28.6% This included: • Isolated IFG: 6.5%	<u>During postpartum:</u> Triglycerides level <u>Sociodemographic:</u> Age

		Centre, Kuala Lumpur)		3%. Excluded post-GDM diagnosed with T2D.	et al (2009)	• Isolated IGT: 16.9% • Combined IFG/ IGT: 5.2%	Neonatal: Infant birth weight
Logakodie et al (2017)	Cross-sectional	Public health clinics (n=72, in Selangor)	6 weeks postpartum	n = 99; 68.6% less than 35 years old; Malay 71.6%; Chinese 9.8%; Indian 7.8%; others 10.8%	75g, 2-hour OGTT (Ministry of Health Malaysia et al., 2015)	Glucose intolerance: 12.1%	During pregnancy: Maternal obesity; insulin usage during GDM Sociodemographic: Working mothers
Fatin and Alina (2019)	Cross-sectional	Public health clinics (n=13, in Johor Bahru)	6 weeks postpartum	n = 122; mean age 31 years old; Malay 64.8%; Chinese 20.5%, Indian 9.8%; others 4.9%	75g, 2-hour OGTT (Ministry of Health Malaysia et al., 2015)	Glucose intolerance: 12.3% This included: • T2D: 0.8% • IGT: 11.5%	During pregnancy: Insulin usage and abnormal HbA1c at GDM diagnosis Neonatal: Hospital follow-up; NICU admission
Hasain et al (2021)	Comparative cross-sectional	Teaching hospital (n=1; Universiti Kebangsaan Malaysia Medical Centre,	3-6 months postpartum	n = 24 (10 NGT, 14 with glucose intolerance [GI]); Malay 91.7%; others 8.3%; mean	75g, 2-hour OGTT (Ministry of Health Malaysia et al., 2015)	No prevalence as this was a comparative cross-sectional From 14 in GI group,	During pregnancy: GI group had significantly higher prevalence of pharmalogical requirement during GDM During postpartum:

		Kuala Lumpur)		age 33.7-35.9 across groups		• Isolated IGT: 57.1% • Combined IFG/ IGT: 7.1% • T2D: 35.7%	GI group had significantly higher levels of HbA1c, HOMA-IR, triglycerides; gut microbiota from Proteobacteria and Bacteroidetes phyla <u>Sociodemographic:</u> GI group had significantly lower education level

2hPG: 2-hour postprandial glucose; ADA: American Diabetes Association; AGT: abnormal glucose tolerance; FPG: fasting plasma glucose; HbA1c: glycated hemoglobin; NGT: normal glucose tolerance; NICU: neonatal intensive care unit; OGTT: oral glucose tolerance test; RCT: randomized controlled trial; T2D: Type 2 diabetes; WHO: World Health Organization

Discussion

This narrative review describes the prevalence and factors associated with postpartum glucose intolerance in women post-GDM in Malaysia. Five articles were included, with data from a total of 664 women post-GDM from various ethnicities in Malaysia.

The prevalence of overall glucose intolerance at postpartum ranged from 12.1% to 61.7%, which shows a high variance across the studies. Logakodie et al (2017) and Fatin and Alina (2019) showed a relatively lower rate of glucose intolerance at approximately 12%, which could be due to various factors. One possible reason could be due to the time point of postpartum glucose screening, which was at 6 weeks. Despite data collection being conducted at several public health clinics in Johor Bahru and Selangor, the sample size was relatively small (n = 99-122 respondents) compared to Chew et al (2012) (n = 342 respondents). Compliance rate towards the 6-week postpartum glucose screening was suboptimal at 15.0% in Logakodie et al (2017) and 35.8% in (Fatin and Alina, 2019). The studies were also conducted in both urban and rural setting, which may hinder their compliance towards postpartum glucose screening, such as having financial or time constraints (Rafii et al., 2017). Hence, the small sample size in these two studies could contribute towards the lower prevalence of postpartum glucose intolerance compared to other studies, as less women were being screened for type 2 diabetes or pre-diabetes.

Furthermore, traditional postnatal care during the confinement period practiced by Malaysian Malays, Chinese and Indians typically lasts up to 44 days or 6 weeks after delivery (Yusoff et al., 2018). During this period, mothers are encouraged to underwent certain postpartum practices such as adhering to food taboos or dietary restrictions, which are claimed to improve blood circulation, breast milk flow and return body weight to pre-pregnancy weight (Fadzil et al., 2015). We postulate that these dietary restrictions of several foods and drinks, such as cold rice, yams, sweet potatoes, sugary drinks and "cold foods" (Fadzil et al., 2015) may contribute towards an overall decrease of calorie intake and postpartum weight retention, thus decreasing their risk of glucose intolerance at this timepoint.

On the other hand, Chew et al (2012) showed a higher rate of glucose intolerance at 61.7% in women 3 months to 15 years post-GDM. This was in line with current literature that reported the cumulative incidence of T2D at 10 years post-GDM was approximately 60% (Bellamy et al., 2009). Thus, regular and longer follow-up is recommended as they may progress to pre-diabetes and eventually T2D several years after their GDM pregnancies. Screening for T2D should be performed annually in women post-GDM (Ministry of Health et al., 2015). Furthermore, the study was conducted at an urban teaching hospital. A previous local study found that respondents from urban areas reported higher prevalence of chronic illness compared to rural areas, which could be partly due to higher accessibility to healthcare services (Amal et al., 2011).

Malaysia comprises of multiple ethnic groups, mainly Malays, Chinese and Indians. A previous review had reported that Malay and Indian adults had a higher risk of T2D compared to Chinese or other ethnic groups (Jan Mohamed et al., 2014). Indian and Malay women post-GDM with pre-diabetes also had a higher body mass index (BMI) and waist circumference compared to Chinese in (Chew et al., 2012). A previous local study found that Indian adults were more likely to present with central obesity and elevated FPG compared to other ethnic groups (Khoo et al., 2011). The ethnic disparities in T2D prevalence may be partly explained by the lifestyle behaviours practiced by the different ethnic groups, including dietary intake and physical activity (Khoo et al., 2011). A large multi-ethnic cohort study also found Chinese adults had less adiposity compared to Malay and Indian adults (Abdullah et al., 2018). Thus, the development of ethnicity-specific anthropometric cut-off points for determining the risk of T2D is highly recommended (Abdullah et al., 2018).

Insulin or pharmalogical treatment during GDM was the most common factor associated with postpartum glucose intolerance (Logakodie et al., 2017; Fatin & Alina, 2019; Hasain et al., 2021), which agreed with the findings from several studies conducted in Asian countries (Herath et al., 2017; Nouhjah et al., 2017). Insulin requirement during pregnancy indicates worsening hyperglycemia and an impaired β-cell function in women diagnosed with GDM (Fatin & Alina, 2019). Therefore, women treated with insulin during their GDM pregnancies represent a high-risk population that should be targeted for early detection of glucose intolerance.

Sociodemographic factors including maternal age, lower educational level and being working mothers were associated with postpartum glucose intolerance. Advanced maternal age was an independent predictor of future T2D following GDM pregnancies in several Asian and

Caucasian cohorts (Rayanagoudar et al., 2016; Gadve et al., 2021). The landscape of female autonomy is changing, with delayed childbearing becoming more common in developed countries as the priority has shifted to pursuing educational and career goals before rearing a family (Sauer, 2015). Age-associated defects in insulin secretion, and a decline in insulin action, β-cell mass and function had been demonstrated in humans, increasing the overall risk of T2D in older age (Gong & Muzumdar, 2012). Working mothers may also lack the time, commitment and energy to engage in healthy lifestyle programs after their GDM pregnancies (Swan et al., 2007). In the European Prospective Investigation in Cancer and Nutrition (EPIC) cohorts, adults with low education level had higher BMI, lower physical activity level and higher risk of T2D (Sacerdote et al., 2012). The relationship between educational level and health could be mediated by lifestyle, access to health services and knowledge of health promotion (Sacerdote et al., 2012).

This review has a few limitations. Heterogeneity occurs across multiple variables, such as the timepoint of assessment of postpartum glucose tolerance, diagnostic criteria used and differing terms of glucose tolerance. There is no uniformity in diagnosing glucose intolerance across these studies. Two studies also included non-Malaysians in their analysis as well (Shyam et al., 2014; Logakodie et al., 2017), thus their findings must be interpreted with caution. Nevertheless, despite the various diagnostic criteria being used, the 75g, 2-hour OGTT remains the gold standard to detect pre-diabetes and T2D. There is a wide range of timepoint of assessment, from short-term (6 weeks until 6 months postpartum) to long-term (up to 15 years postpartum). All of the studies are also cross-sectional, thus unable to establish a temporal relationship between GDM diagnosis and diagnosis of glucose intolerance. Only one study assessed non-clinical factors that expedite T2D progression in women post-GDM, such as dietary intake and gut microbiota (Hasain et al., 2021). Women post-GDM at risk of T2D had distinctive features of gut microbiota (Fugmann et al., 2015). As T2D is a multifactorial disease, investigating sociodemographic, biological and lifestyle factors of T2D in addition to clinical risk factors may improve our understanding of the overall pathophysiology of T2D.

Conclusions

GDM has several adverse short- and long-term complications, including postpartum glucose intolerance. The prevalence of postpartum glucose intolerance in Malaysia following GDM is 12.1% to 61.7%, indicating that women post-GDM is at high risk of progressing towards pre-diabetes and T2D. Factors associated with postpartum glucose intolerance included maternal age; working status; education level; infant birth weight; maternal obesity; insulin treatment during GDM; glucose and HbA1c levels during pregnancy; duration lapse after GDM; postpartum levels of triglycerides, insulin resistance and HbA1c; and gut microbiota. Insulin treatment during GDM pregnancy was the most common factor associated with postpartum glucose tolerance in women post-GDM. Further studies on glucose intolerance in Malaysian women post-GDM should emphasize on sociodemographic, biological and lifestyle risk factors of T2D risk. Understanding the overall pathophysiology of T2D may facilitate in risk reduction and disease prevention.

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Conflict of Interest

The authors declare no conflict of interest.

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