



UNIVERSITI PUTRA MALAYSIA

***DETERMINANTS AND PREGNANCY OUTCOMES OF MATERNAL
GLYCEMIA***

YONG HENG YAW

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**DETERMINANTS AND PREGNANCY OUTCOMES OF MATERNAL
GLYCEMIA**

By

YONG HENG YAW

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
in Fulfillments of the Requirements for the Degree of Doctor of Philosophy**

July 2017

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the Degree of Doctor of Philosophy

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YONG HENG YAW

July 2017

Chairman : Professor Zalilah Mohd Shariff, PhD
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Both gestational diabetes mellitus (GDM) and hyperglycemia less severe than GDM are commonly associated with risk of adverse pregnancy outcomes. This study consisted of two phases. The first phase of study was to determine the cut-off point for maternal hyperglycemia for the detection of adverse pregnancy outcomes. The second phase of study was to determine the factors and outcomes of pregnancies complicated by maternal hyperglycemia.

The first phase of study was a retrospective cohort study involving 1,356 pregnant women who were registered with and attended antenatal checkups at two Maternal and Child Health (MCH) clinics in Seremban District, Negeri Sembilan. The antenatal booklet kept at the MCH clinic was used as a data source. Demographic and socioeconomic, obstetrical, anthropometric, biochemical and birth information of infants were extracted. Hyperglycemia was defined as either or both fasting plasma glucose (FPG) 4.8–5.5 mmol/l or two-hour plasma glucose (2hPG) 7.5–7.7 mmol/l. GDM was diagnosed according to the Ministry of Health's (MOH) criteria of either or both FPG ≥ 5.6 mmol/l or 2hPG ≥ 7.8 mmol/l.

The second phase of study was a prospective cohort study in which a total of 282 pregnant women with normal glycemia were recruited from three MCH clinics in Seremban District, Negeri Sembilan and followed-up until delivery. A standard 75g Oral Glucose Tolerance Test was performed between 24–32nd weeks of gestation. Socio-demographic, anthropometric, biochemical, dietary, physical activity, smoking, and other data were collected using a pre-tested, interviewer-administered questionnaire at follow-ups of women. Pregnancy and birth information were obtained from medical records.

A majority of the pregnant women were Malays (85.1%) in the age range of 18-43 years. According to pre-pregnancy Body Mass Index, 11.0%, 20.2% and 13.5% of them were underweight, overweight, and obese, respectively. About 30.1% of the women had at risk waist circumference (≥ 80 cm). Meanwhile, the mean rate of weight gain was 0.38 kg/week for the second and third trimesters. Mean fasting plasma glucose (FPG) and two-hour plasma glucose (2hrPG) were 4.35 ± 0.47 mmol/l and 5.99 ± 1.56 mmol/l, respectively. About 10.6% and 8.9% of the women were hyperglycemic, less severe than GDM and GDM, respectively.

The mean energy intake of the pregnant women was $2,135 \pm 686.26$ kcal/day. The mean percentage of energy contributed by macronutrients was 51% by carbohydrate, 17% by protein and 32% by fat. While the mean intake of folate ($47.09 \pm 28.49\%$ RNI) was below the recommended level, the mean intake of iron ($108.18 \pm 71.86\%$ RNI) and calcium ($116.52 \pm 81.93\%$ RNI) were slightly higher than the RNI recommendation. The mean for all food groups, except for grains and cereals, meat, poultry, and fish were less than the recommended servings. Three major dietary patterns were identified, namely “sweet and fatty food pattern”, “healthy pattern” and “common food pattern”. Most women consumed dietary supplements (82.6%) and did not consume alcohol (99.0%). None of them smoked. The mean daily total physical activity was 1005 minutes with a large majority of their time spent in household/caregiving activities (625 minutes/day). It may be concluded that Malaysian pregnant women are generally sedentary in their day-to-day activities, with only a small percentage being involved in sport activities or exercises.

One-fifth of infants (19.9%) were born via caesarean deliveries. The mean infant’s length, head circumference and birth weight were 49.30 ± 2.58 cm, 32.19 ± 1.44 cm, and 3.03 ± 0.44 kg respectively. More than half (56.4%) were born with a birth weight of 3.0–4.0 kg, while 9.2% were born weighing less than 2.5kg. For the birth weight percentile, 34% of infants were small-for-gestational-age (SGA), while only 10 infants (3.5%) were large-for-gestational-age (LGA).

Women with an excessive rate of gestational weight gain (GWG) at second trimester showed a higher risk of hyperglycemia. In terms of dietary intake, pregnant women with higher fat intake and high common food dietary pattern were 4 and 6 times more likely to be at risk of hyperglycemia. Only a high common food pattern was found to be significantly associated with the risk of GDM. For the pregnancy outcomes, caesarean delivery was the only one to be significantly associated with GDM.

The cut-off points for both FPG (4.8 mmol/l) and 2hPG (7.5 mmol/l) to detect adverse pregnancy outcomes were lower than the recommended criteria of MOH for diagnosis of GDM. Further well-designed clinical trials are needed to determine the cost-effectiveness of therapeutic strategies for management of hyperglycemia, less severe than GDM diagnosed by the present study on improving the adverse pregnancy outcomes. The rising prevalence of GDM in Malaysia and its adverse consequences underscore the need to identify the determinants for formulation of effective public

health strategies. Gestational weight gain and dietary intake should be the focus of the strategies as these lifestyle factors are linked to maternal hyperglycemia.



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FAKTOR PENENTU DAN HASIL KEHAMILAN YANG DISEBABKAN OLEH GLISEMIA IBU

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Kedua-dua masalah diabetes gestasi (GDM) dan hiperglisemia kurang teruk berbanding GDM biasanya dikaitkan dengan risiko komplikasi kehamilan yang buruk. Kajian ini terdiri daripada dua fasa. Fasa pertama kajian adalah untuk menentukan titik potong hiperglisemia untuk mengesan komplikasi kehamilan yang buruk. Fasa kedua kajian adalah untuk menentukan faktor-faktor dan komplikasi kehamilan yang disebabkan oleh hyperglisemia ibu.

Fasa pertama kajian adalah kohort retrospektif yang melibatkan 1,356 wanita hamil yang berdaftar and menghadiri pemeriksaan antenatal di dua Klinik Kesihatan Ibu dan Anak (KKIA) di Daerah Seremban, Negeri Sembilan. Buku antenatal yang simpan di KKIA digunakan sebagai sumber data. Maklumat demografi dan sosioekonomi, obstetrik, antropometri, biokimia serta maklumat kelahiran bayi diambil. Hiperglisemia ditakrifkan sebagai salah satu atau kedua-dua kadar glukosa plasma berpuasa (FPG) 4.8 – 5.5 mmol/l atau kadar glukosa plasma 2 jam (2hPG) 7.5 – 7.7 mmol/l. GDM telah didiagnos mengikut kriteria Kementerian Kesihatan Malaysia (KKM) dengan salah satu atau kedua-dua FPG ≥ 5.6 mmol/l atau 2hPG ≥ 7.8 mmol/l.

Fasa kedua kajian adalah kohort prospektif di mana seramai 282 wanita hamil dengan kadar glukosa darah normal telah diambil dari tiga KKIA di Daerah Seremban, Negeri Sembilan tindakan susulan dijalankan sampai bersalin. 75g Ujian Oral Toleransi Glukosa (OGTT) dilakukan antara minggu kehamilan ke 24 and 32. Maklumat antropometri sosio-demografi, biokimia, pemakanan, aktiviti fizikal, merokok, dan data lain dikumpulkan dengan menggunakan soal selidik yang telah dipra-uji dan ditemubual oleh penemuduga semasa sesi susulan. Maklumat kehamilan dan kelahiran bayi diperolehi daripada rekod perubatan.

Majoriti wanita hamil adalah Melayu (85.1%) dalam lingkungan umur 18–43 tahun. Menurut Indeks Jisim Badan pra-kehamilan, 11.0%, 20.2% dan 13.5% daripada mereka mengalami kekurangan berat badan, berlebihan berat badan dan obes, masing-masing. Sebanyak 30.1% daripada wanita mempunyai lilitan pinggang berrisiko (≥ 80 cm). Sementara itu, kadar kenaikan berat badan semasa mengandung adalah 0.38 kg/minggu untuk trimester kedua dan ketiga kehamilan. Purata kadar glukosa plasma berpuasa (FPG) dan 2-jam glukosa plasma (2hrPG) adalah 4.35 ± 0.47 mmol/l dan 5.99 ± 1.56 mmol/l, masing-masing. Kira-kira 10.6% dan 8.9% daripada wanita hiperglisemia, kurang teruk daripada GDM dan GDM, masing-masing.

Purata pengambilan kalori wanita hamil adalah 2135 ± 686.26 kcal/hari. Purata peratusan kalori disumbangkan oleh makronutrien adalah 51% daripada karbohidrat, 17% daripada protein dan 32% daripada lemak. Walaupun purata pengambilan folat ($47.09 \pm 28.49\%$ RNI) adalah di bawah tahap yang disarankan, tetapi purata pengambilan besi ($108.18 \pm 71.86\%$ RNI) dan kalsium ($116.52 \pm 81.93\%$ RNI) adalah lebih tinggi daripada saranan RNI. Purata pengambilan bagi semua kumpulan makanan, kecuali bijirin dan bijirin, daging, ayam, dan ikan kurang daripada bilangan hidangan yang disarankan. Tiga corak pemakanan utama telah dikenal pasti, dan dilabelkan sebagai “corak pengambilan makanan manis dan lemak”, “corak pengambilan sihat” dan “corak pengambilan biasa”. Kebanyakan wanita hamil (82.6%) mengambil suplemen diet dan tidak mengambil alkohol (99.0%). Tiada seorang pun daripada mereka merokok. Purata jumlah aktiviti fizikal harian adalah 1005 minit dengan majoriti menghabiskan masa dengan aktiviti kerja rumah/mengasuh (625 minit sehari).

Satu per lima daripada bayi (19.9%) dilahirkan dengan cara pembedahan caesarean. Purata panjang, lilitan kepala dan berat badan lahir bayi 49.30 ± 2.58 cm, 32.19 ± 1.44 cm dan 3.03 ± 0.44 kg. Lebih daripada separuh (56.4%) bayi mempunyai berat badan lahir 3.0 – 4.0 kg, manakala 9.2% mempunyai berat badan lahir kurang dari 2.5 kg. Bagi persentil berat lahir, 34% bayi adalah kecil-untuk-umur getasi (SGA), manakala hanya 10 bayi (3.5%) besar-untuk-umur getasi (LGA).

Wanita dengan kadar kenaikan berat badan berlebihan di trimester kedua kehamilan menunjukkan risiko yang lebih tinggi untuk mengalami hiperglisemia. Dari segi pengambilan makanan, wanita hamil dengan pengambilan lemak tinggi, dan mempunyai corak makan biasa yang tinggi mempunyai 4 dan 6 kali lebih mudah mendapat hiperglisemia. Hanya corak makan biasa yang tinggi didapati berkaitan dengan risiko GDM. Bagi hasil kehamilan, bersalin dengan pembedahan caesaran merupakan satu-satunya hasil yang didapati signifikansi berkaitan dengan GDM.

Titik potongan untuk kedua-dua glukosa plasma berpuasa (FPG) (4.8 mmol/l) dan 2-jam glukosa plasma (2hrPG) (7.5 mmol/l) untuk mengesan komplikasi semasa kehamilan adalah lebih rendah daripada kriteria Kementerian Kesihatan Malaysia (KKM) untuk diagnos GDM. Kajian klinikal yang direka dengan baik amat diperlukan untuk menentukan keberkesanan kos strategi terapeutik untuk pengurusan

hiperglisemia, kurang teruk berbanding GDM disahkan oleh kajian ini untuk menurunkan komplikasi semasa kehamilan. Peningkatan prevalen GDM di Malaysia dan komplikasi semasa kehamilan menekankan keperluan untuk mengenal pasti penentu dalam membentuk strategi kesihatan awam yang berkesan. Penambahan berat badan semasa mengandung, dan pengambilan makanan adalah tumpuan strategi kerana faktor-faktor gaya hidup dikaitkan dengan hiperglisemia ibu.



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I certify that a Thesis Examination Committee has met on 31 July 2017 to conduct the final examination of Yong Heng Yaw on her thesis entitled "Determinants and Pregnancy Outcomes of Maternal Glycemia" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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LIST OF ABBREVIATIONS

ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
ACOG	American College of Obstetricians and Gynecologist
ADA	American Diabetes Association
AGEs	Advanced Glycation End Products
aHEL	alternate Health Eating Index
ALAD	Latin American Diabetes Association
ALSWH	Australian Longitudinal Study on Women's Health
aMed	alternate Mediterranean Diet
AUC	Area Under the Curve
BIGS	Born in Guangzhou Cohort Study
BMI	Body Mass Index
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
DIP	Diabetes in Pregnancy
EI	Energy Intake
ER	Energy Requirement
FFQ	Food Frequency Questionnaire
FPG	Fasting Plasma Glucose
GCT	Glucose Challenge Test
GDM	Gestational Diabetes Mellitus
GI	Glycemic Index
GUSTO	Growing Up in Singapore Towards Healthy Outcomes
GWG	Gestational Weight Gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes
HUSM	Hospital University Sains Malaysia

IADPSG	International Association of Diabetes in Pregnancy Study Groups
IGT	Impaired Glucose Tolerance
IHBR	Institute for Health Behavioral Research
IOM	Institute of Medicine
IPH	Institute of Public Health
LBW	Low birth weight
LGA	Large-for-Gestational Age
LMP	Last Menstruation Period
MET	Metabolic Equivalent
MCH	Maternal and Child Health
MDG	Malaysian Dietary Guideline
MOH	Ministry of Health
MREC	Medical Research Ethics Committee
MVPA	Moderate and Vigorous Physical Activity
NBW	Normal Birth Weight
NDDG	National Diabetes Data Group
NHANES	National Health and Nutrition Examination
NHMS	National Health and Morbidity Survey
NHS	Nurses' Health Study
NICE	National Institute for Health and Care Excellence
NOR	National Obstetric Registry
OGTT	Oral Glucose Tolerance Test
PINS	Pregnancy, Infection, and Nutrition Study
PPAQ	Pregnancy Physical Activity Questionnaire
PREGGIO	Pregnancy and Glycemic Index Outcomes
RNI	Recommended Nutrient Intakes

RR	Relative Risk
SBP	Systolic Blood Pressure
SECOST	Seremban Cohort Study
SGA	Small-for-Gestational Age
SNAP	Study of Nutrition and Pregnancy
STPM	Sijil Tinggi Pelajaran Malaysia
T2DM	Type 2 Diabetes Mellitus
TOP	Treatment of Obese Pregnant
UMMC	University Malaya Medical Centre
WATCH	Women and Their Children's Health
WC	Waist Circumference
WHO	World Health Organization
2hPG	2-hour Plasma Glucose

CHAPTER 1

INTRODUCTION

1.1 Background

Women undergo substantial physiological changes from the moment of conception until the process of delivery is completed. These physiological changes are typically seen in the cardiovascular, hematologic, endocrine, respiratory and renal systems. Metabolic alterations of glucose, protein and lipid are essential in order to meet the increased maternal and fetal demands. Normal physiology defines metabolism during the early pregnancy period, or the first 20 weeks of pregnancy, as a predominantly anabolic state with increased maternal fat stores and insulin secretion for increased peripheral glucose utilization (Lain & Catalano, 2007). The first half of pregnancy is basically the preparation period for rapid fetal growth, in which nutrients are being stored to meet fetal demands and to cope with late pregnancy and lactation (King, 2000).

In 2008, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study reported that there were significant continuous associations between maternal hyperglycemia below the diagnostic criteria for gestational diabetes mellitus (GDM) with an increased risk for fetal size at birth, cesarean delivery, neonatal hypoglycemia and fetal hyperinsulinemia (Metzger et al., 2008). This study defined maternal hyperglycemia not amounting to GDM as a condition in which there is an excessive amount of glucose circulating in blood plasma but the concentration is not high enough to be classified as GDM. The findings of the HAPO study provided the impetus for the International Association of Diabetes in Pregnancy Study Groups (IADPSG) and the American Diabetes Association (ADA) to revise and subsequently recommend new lower diagnostic criteria for GDM (Panel, 2010). However, the use of the new criteria has resulted in a dramatic increase in the number of women diagnosed with GDM (Blackwell, 2012; Coustan, 2013; Cundy, Ackermann, & Ryan, 2014). With increased healthcare costs and the lack of improvement in maternal and infant outcomes as concomitant concerns, the optimal maternal glycemia threshold to diagnose GDM remains a controversial issue (Langer, Umans, & Miodovnik, 2013).

GDM is a common metabolic disorder defined as glucose intolerance with onset or first recognition during pregnancy (American Diabetes Association, 2003; Metzger & Coustan, 1998). Globally, the prevalence of GDM varies across populations. The rate of GDM worldwide is of an incremental trend, especially in developing countries. In Western countries, the reported prevalence ranges from 1–14% of all pregnancies (Coustan, 2012). In Malaysia, the prevalence of GDM is 8.7–24.9%, depending on ethnicity and geographical location (Idris, Hatikah, Murizah, & Rushdan, 2009; Jeganathan, Karalasingam, Man, Naidu, & Fadzi, 2011; Kwapisz & Bodaghi, 2013; Shamsuddin, Mahdy, Rafiaah, Jamil, & Rahimah, 2001; Tan, Ling, & Omar, 2007).

The National Health and Morbidity Survey (NHMS) reported that the prevalence of obesity in Malaysian women aged 18 years and older increased from 5.7% in 1996 to 17.6% in 2011 (IPH, 1996, 2015). The increasing rate of obesity within women of childbearing age is paralleled by the inevitable rise in the GDM rate. As more women become overweight or obese prior to pregnancy, their risks for maternal hyperglycemia and subsequently poor pregnancy outcomes are significantly greater.

There are non-modifiable risk factors and modifiable risk factors for GDM. Maternal obesity, gestational weight gain (GWG) and lifestyle behavior factors, particularly dietary intake, physical activity, sedentary behavior, alcohol and smoking are important modifiable risk factors of elevated maternal glucose level during pregnancy (Bowers et al, 2011; Metzger et al., 2007; Park et al., 2014; Tovar et al., 2009). Advanced maternal age, height, parity, ethnicity, family history of diabetes, history of GDM and history of other insulin-resistant conditions, such as metabolic syndrome and polycystic ovary syndrome, are non-modifiable risk factors for GDM (Al-Rowaily & Abolfotouh, 2010; Branchtein et al., 2000; Dornhorst & Rossi, 1998; Innes et al., 2002; Legro, Gnatuk, Kunselman, & Dunaif, 2005; Morikawa et al., 2012). There is still a lack of research on the factors associated with maternal hyperglycemia not amounting to GDM in pregnant women. GDM poses a risk to both mother and child. There is consensus that GDM is associated with a significant risk of adverse pregnancy outcomes. However, the risk of adverse pregnancy outcomes with maternal hyperglycemia less severe than GDM is less known (Metzger et al., 2008).

1.2 Statement of Problem

In 2013, the third edition of *The Perinatal Care Manual* published by the Ministry of Health (MOH) of Malaysia reported that GDM is diagnosed by both/either the fasting plasma glucose (FPG) ≥ 5.6 mmol/l test and/or the two-hour plasma glucose (2hPG) ≥ 7.8 mmol/l oral glucose tolerance test (OGTT) test (MOH of Malaysia, 2013). In 2015, the MOH of Malaysia reviewed the clinical practice guidelines (CPG) on the management of type 2 diabetes mellitus (T2DM) and proposed lower diagnostic criteria for GDM, having one or more abnormal value of FPG ≥ 5.1 mmol/l, and 2hPG ≥ 7.8 mmol/l in the OGTT (CPG, 2015). Both guidelines were derived by consensus of the taskforce members, using the findings from the literature, without any experimental study in the Malaysian population. However, whether these guidelines are applicable to pregnant women in areas of the world where women are substantially shorter or thinner than Western women remains unknown.

Both maternal pre-pregnancy obesity and GWG are important modifiable risk factors of GDM. Obese pregnant women are more susceptible to GDM, as obesity increases the risk of glucose tolerance impairment (Pirjani et al., 2016; Scott-Pillai, Spence, Cardwell, Hunter, & Holmes, 2013). Women presenting with higher GWG are 2–2.54 times more at risk of impaired glucose tolerance in pregnancy (Herring et al., 2009; Saldana, Siega-Riz, Adair, & Suchindran, 2006). Furthermore, previous studies showed that the combination of pre-pregnancy obesity and excessive GWG will contribute to an even higher risk for negative pregnancy outcomes (Bowers et al., 2013;

Guelinckx, Devlieger, Beckers, & Vansant, 2008; Heude et al., 2012a). Although an optimal rate of GWG is associated with better maternal and fetal health outcomes, the actual rate of GWG defined as optimal remains controversial. At present, data on the rate of GWG and its association with GDM in Malaysian women are limited.

Maternal dietary intake during pregnancy, particularly higher intakes of energy and fat, could increase the risk for GDM (Bowers, Tobias, Yeung, Hu, & Zhang, 2012; Zhang & Ning, 2011). An adoption of the Western dietary pattern, which is characterized by high intakes of red meat, processed meats and refined foods, could also increase the risk of GDM (Zhang, Schulze, Solomon, & Hu, 2006). The major components of red meat and processed meat, such as saturated fat, cholesterol and heme iron, are associated with insulin resistance and subsequent risk of GDM (Qiu, Zhang, et al., 2011). Furthermore, high intakes of heme iron can result in high body iron stores, which may impair insulin sensitivity and glucose hemostasis (Aregbesola, Voutilainen, Virtanen, Mursu, & Tuomainen, 2013; Bao, Rong, Rong, & Liu, 2012). Most studies on dietary pattern have been limited to Western populations. As there are differences in diet and lifestyle behaviors, the dietary pattern of Malaysian pregnant women could be different from that reported in Western populations.

Apart from dietary intake, physical activity level, sedentary behavior, alcohol consumption and smoking are other lifestyle factors associated with GDM. Pregnant women in the high quartile of moderate-intensity activity and occupational activity during early pregnancy had about a 50% decreased risk of abnormal glucose tolerance (Chasan-Taber et al., 2014). Smoking has been associated with an increased risk of central obesity or abdominal fat, which is an established risk factor for insulin resistance and diabetes (Hu, 2011). It is well established that excessive alcohol drinking and smoking are associated with insulin resistance and T2DM (Dode & dos Santos, 2009; Pietraszek, Gregersen, & Hermansen, 2010; Zhang et al., 2011); however, the role of alcohol drinking and smoking in the risk of GDM remains unknown. Besides, little is known about the actual lifestyle patterns, particularly physical activity level, alcohol consumption and smoking, of Malaysian pregnant women.

Many studies have established that women with GDM are more predisposed to poor pregnancy outcomes, such as cesarean delivery, pregnancy-induced hypertension and preeclampsia (Catalano et al., 2012; Lowe et al., 2012; Nordin, Wei, Naing, & Symonds, 2006). These new mothers are more likely to give birth to asphyxiated, hypoglycemic or large-for-gestational age (LGA) infants (Leary, Pettitt, & Jovanovič, 2010; Lowe et al., 2012; Polin, Fox, & Abman, 2011). These conditions can subsequently cause other long-term health problems to the child, such as obesity, T2DM, cancer and cardiovascular disease in later life. GDM mothers themselves are more susceptible to developing cardiovascular disease and overt diabetes, particularly T2DM, during the ensuing courses of their lives (Carr et al., 2006; Gilmartin, Ural, & Repke, 2008; Negrato & Gomes, 2013). General consensus associates GDM with a significant risk of adverse pregnancy outcomes. However, the risk of adverse

pregnancy outcomes associated with maternal hyperglycemia less severe than GDM is still controversial.

To date, optimal diagnostic criteria to detect GDM are of much debate. In Malaysia, the GDM diagnostic criteria were derived by consensus of the taskforce members, using the findings from the literature (MOH, 2013). Epidemiological differences of maternal hyperglycemia between Asian and Western populations may inevitably result in different distributions of maternal glycemia during pregnancy. However, such information in Malaysia is unavailable at present. Previous studies have shown that GDM can have immediate and long-term health risks to women and offspring (Carr et al., 2006; Catalano et al., 2012; Innes et al., 2002; Ismail et al., 2011; Leary et al., 2010; Lowe et al., 2012; Nordin et al., 2006). The risk of adverse pregnancy outcomes of maternal hyperglycemia less severe than GDM, which is characterized by an intermediate glucose tolerance value between normal and GDM, as well as its associated factors, remains unclear.

Thus, this study aims to address the following questions:

- i. What is the distribution of maternal glycemia during pregnancy among Malaysian pregnant women?
- ii. What is the cut-off for maternal hyperglycemia for the detection of adverse pregnancy outcomes?
- iii. What are the lifestyle behaviors (dietary intake, physical activity level, sedentary behaviors, smoking and alcohol) and gestational weight gain of women during pregnancy?
- iv. Is there any relationship between socio-demographic factors, obstetrical factors, lifestyle behaviors and gestational weight gain with maternal glycemia?
- v. Is there any relationship between maternal glycemia and pregnancy outcomes?

1.3 Objectives of Study

General Objective

To identify the determinants and pregnancy outcomes of maternal hyperglycemia

Specific Objectives

Phase 1 study

1. To determine the cut-off for maternal hyperglycemia for adverse pregnancy outcome detection
2. To identify the distribution of maternal glycemia during pregnancy among Malaysian pregnant women

Phase 2 study

1. To assess
 - a. socio-demographic factors
 - b. obstetrical factors
 - c. lifestyle behaviors
 - d. weight gainof women during pregnancy
2. To determine the relationship between
 - a. socio-demographic factors
 - b. obstetrical factors
 - c. lifestyle behaviors
 - d. weight gainand maternal glycemia
3. To determine the relationship between maternal glycemia and pregnancy outcomes

1.4 Study Hypotheses

The hypotheses tested in this study are:

1. There are significant associations between socio-demographic factors, obstetrical factors, lifestyle behaviours and gestational weight gain with maternal hyperglycemia.
2. There are significant associations between maternal hyperglycemia and adverse pregnancy outcomes.

1.5 Research Framework

The research framework for this study is presented in Figure 1.1. This study consisted of two phases. Phase 1 was a retrospective study and phase 2 was a prospective study. Phase 1 of study focused on determining the maternal hyperglycemia cut-off for detection of adverse pregnancy outcomes. The resulting findings were then used for sample size calculation and defined the maternal hyperglycemia cut-off for the second phase of the study. Maternal glycemia was then classified into 3 groups, namely normal glycemia, hyperglycemia less severe than GDM and GDM.

The present study examined 3 groups of independent factors, namely demographic and socioeconomic, obstetrical, and lifestyle factors. Studies have shown that advanced maternal age was associated with increased risks of hyperglycemia (Morikawa et al., 2012). Socio-economic status was also established as a contributing factor to GDM incidence (El-Hazmi & Warsy, 2000; Keshavarz et al., 2005), with Keshavarz et al. (2005) showed that lower socio-economic status was associated with the development of GDM. These differences in socio-economic statuses did not pertain to lifestyle behaviors only; it also encompassed factors of general health, awareness, education and accessibility to medical care.

Several studies found that the risk of maternal hyperglycemia was substantially increased with maternal body mass index (BMI) (Chu et al., 2007; Farah et al., 2012; Teh et al., 2011). Previous history of GDM has been acknowledged as one of the strongest predictors of GDM, with the GDM recurrence rates of 48% (Schwartz, Nachum, & Green, 2015). Additionally, there was growing evidences suggest that unhealthy lifestyle behaviors (dietary intake, physical inactivity, sedentary behaviors, alcohol and smoking) during pregnancy were significant determinants of hyperglycemia (Chasan-Taber et al., 2014; Khosravi-Boroujeni et al., 2012; Malik, Popkin, & Bray, 2010; Risérus, Willett, & Hu, 2009). Smoking in particular has been associated with increased risk of central obesity, which was an established risk factor for insulin resistance and diabetes (Hu, 2011).

Maternal hyperglycemia was associated with increased placental transfer of glucose, resulting in an increase in insulin mediated fetal growth and pregnancy complications. Maternal hyperglycemia has been reported to be a predictor of caesarean section and macrosomia (Wahi et al., 2011; Yang et al., 2002). The pregnancy outcomes explored in this study were mode of delivery, birth weight, and fetal size (SGA and LGA).

Phase 1 (Retrospective study)

To determine maternal hyperglycemia cut-off for detection of adverse pregnancy

Phase 2 (Prospective study)

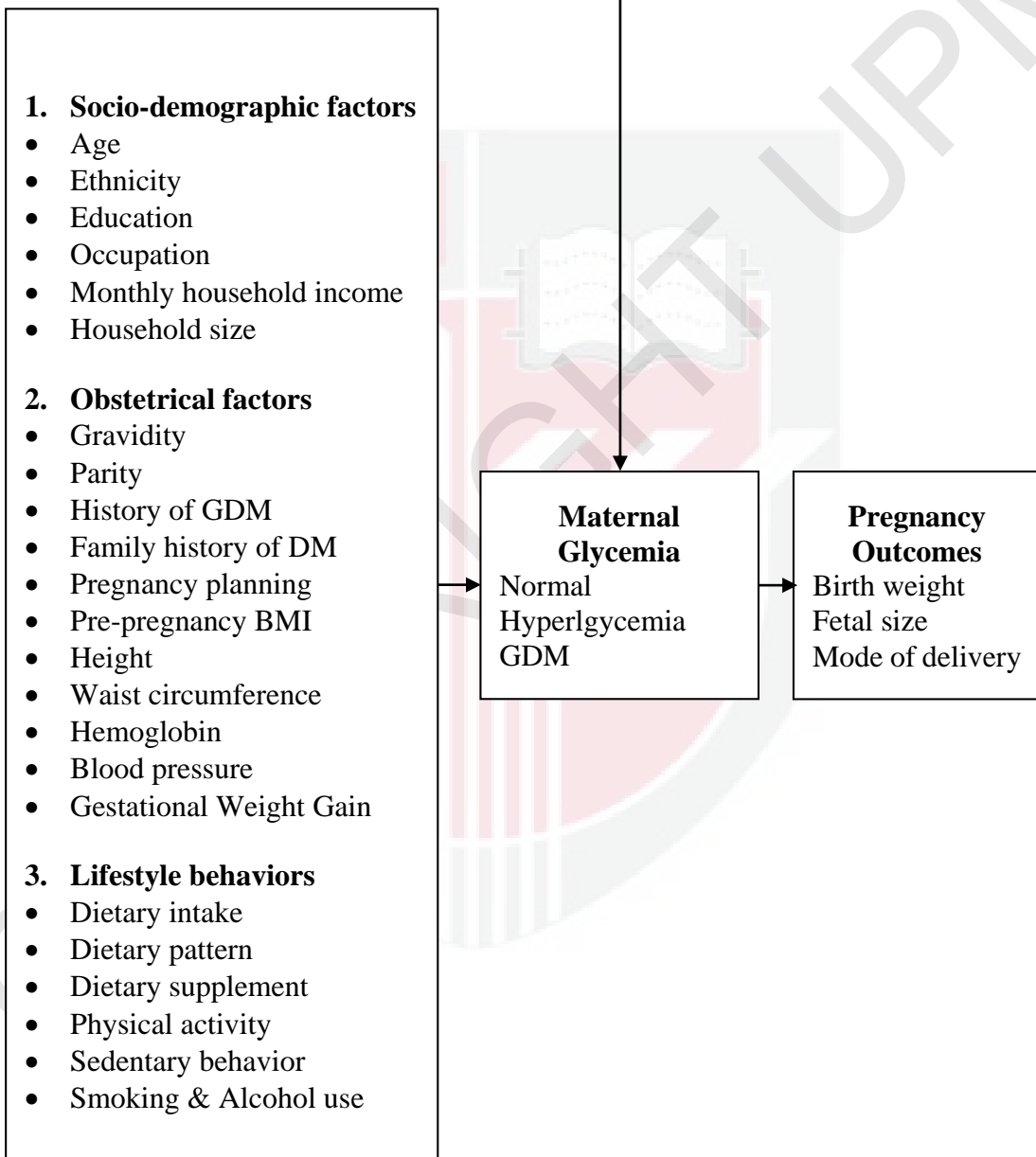


Figure 1.1 : Research framework

1.6 Importance of Study

The rising worldwide prevalence of diabetes mellitus (DM), particularly in developing countries, is worrisome, as nearly 382 million adults aged 18 years and older are afflicted by it (Aguiree, Brown, Cho, & Dahlquist, 2013). In Malaysia, the NHMS 2015 showed that the prevalence of DM increased from 11.6% in 2006 to 18.3% in 2015 (3.6 million) (IPH, 2006, 2015). If the current trend continues, Malaysia is predicted to double the percentage to 30% by 2030, which amounts to 5 million diabetic patients. As diagnosis of GDM is associated with an increased risk of maternal DM during the later course of life, maternal hyperglycemia or GDM necessitates primary prevention steps to be taken to ensure both maternal and fetal well-being. This study will contribute to the existing literature on maternal hyperglycemia during pregnancy.

The HAPO study established a strong association between maternal hyperglycemia below levels diagnostic of GDM with an increased risk of adverse pregnancy outcomes. However, no clear threshold showing the level of maternal hyperglycemia that dramatically increases the risk for poor pregnancy outcomes is currently available. Furthermore, understanding the different levels of maternal hyperglycemia associated with adverse pregnancy outcomes is crucial. It could influence T2DM-screening protocols and identify populations at risk of adverse perinatal and long-term offspring outcomes. This is the first study in Malaysia to quantify the relationship between maternal glucose levels and pregnancy outcomes.

Healthy lifestyle behaviours, specifically dietary intake and physical activity, have long since been associated with successful pregnancy. Despite Loy and Hamid's (2013) study on pregnant women's dietary intake, physical activity, sedentary lifestyle, smoking and alcohol consumption during pregnancy in Malaysia is an uncharted field of knowledge. Thus, developing a profile for pregnant women's lifestyle could initiate the identification of appropriate interventions to improve pregnancy outcomes according to needs and resources. This may enhance awareness on nutrition and GWG status during pregnancy for these mothers-to-be and be a source of motivation in achieving the recommended GWG through lifestyle behavior changes, particularly through diet and physical activity. Governmental bodies and related agencies, such as the MOH and the Ministry of Women and Family Development, could also find it beneficial for policy and program development.

The effects of excessive GWG or inadequate GWG have been frequently reported, but most data are exclusively from Western populations. Differences in population characteristics (demographics, socioeconomics, culture and health) between Asian and Western countries may influence patterns of GWG. However, data on GWG specifically applicable for Malaysian women are non-existent at present. As determining GWG could significantly prevent adverse maternal and child health outcomes, the anticipated findings could help in addressing inappropriate GWG during pregnancy. Effective strategies should be developed to focus on the high-risk population (those presenting with excessive or inadequate GWG) via lifestyle

adjustment. These findings could also provide information that rejects or supports the findings of previous studies.

Maternal hyperglycemia also amplifies the risk of complications during pregnancy. Women presenting with poor pregnancy outcomes are often saddled with higher healthcare expenditure than their peers with normal pregnancies. A large proportion of such expenses are attributable to treatments for complications of pregnancy, such as low birth weight (LBW). As well-controlled glycemic levels keep these complications at bay, early diagnosis and prompt treatment of maternal hyperglycemia will lessen both visible and hidden medical costs. This form of primary prevention strategy would prove to be very cost-effective, particularly for developing countries like Malaysia.

1.7 Definition of Terms

1. Hyperglycemia, less severe than GDM is defined as high blood sugar in which an excessive amount of glucose circulates in the blood plasma but not high enough to be classified as GDM (Metzger et al., 2008).
2. Gestational diabetes mellitus (GDM) is defined as glucose intolerance in the second or third trimester of pregnancy that is not clearly overt diabetes (American Diabetes Association, 2015).

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