EVALUATION OF KNOWLEDGE REGARDING GESTATIONAL DIABETES MELLITUS AND ITS ASSOCIATION WITH GLYCAEMIC CONTROL AMONG GDM PARTICIPANTS AT O&G WARD, HOSPITAL USM

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by

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LIST OF SYMBOLS AND ABBREVIATIONS

ACHOIS	Australian Carbohydrate Intolerance Study in Pregnant Women
BD	two-times-a-day
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
FFA	Free Fatty Acid
GDM	Gestational Diabetes Mellitus
GMDKQ	Gestational Diabetes Mellitus Knowledge Questionnaire
HPL	Human Placenta Lactogen
HOSPITAL USM	Hospital Universiti Sains Malaysia
MDG	Mean Daily Glucose
NOR	National Obstetrics Registry
O&G	Obstetrics and Gynaecology
OD	once daily
OGTT	Oral Glucose Tolerance Test
OHA	Oral Hypoglycaemic Agent
QID	four-times-a-day
SMBG	Self -monitoring blood glucose
SPSS	Statistical Package for the Social Sciences

T2DM	Type 2 Diabetes Mellitus
WHO	World Health Organisation

PERKAITAN ANTARA PENGETAHUAN DIABETES MELLITUS GESTASI DENGAN PENGAWALAN GLISEMIK DARAH DALAM KALANGAN PESERTA DIABETES MELLITUS GESTASI DI WAD O&G, HOSPITAL USM

ABSTRAK

Pengawalan glisemik darah yang baik semasa Diabetes Mellitus Gestasi (GDM) dapat mengelakkan kesan negatif kepada ibu dan bayi. Seseorang yang mempunyai pengetahuan yang mencukupi berkaitan GDM akan mempunyai kawalan glisemik yang baik. Kajian ini bertujuan untuk mengenalpasti perkaitan antara pengetahuan GDM dengan pengawalan glisemik darah dalam kalangan peserta GDM. Sebuah kajian hirisan lintang telah dijalankan ke atas 113 peserta GDM di Wad Obstetrik dan Ginekologi (O & G), Hospital USM, Kelantan dari April hingga Jun 2021. Borang soal selidik pengetahuan tentang Diabetes Mellitus Gestasi (GDM) telah diedarkan kepada peserta dengan perbimbingan dan 4 rekod glukosa darah yang terkini dalam tempoh hari yang sama telah dicatatkan berdasarkan rekod perubatan peserta. Selepas itu, purata glukosa darah telah ditentukan. Didapati bahawa jumlah purata markah pengetahuan dalam 113 peserta ialah 12.02 ± 1.81 dan jumlah markah purata glukosa darah ialah 5.22 ± 0.64 mmol/L. Antara lima domain pengetahuan, markah yang tertinggi dicatatkan pada domain pengetahuan tentang diet / nilai makanan (2.89 ± 0.40), manakala domain faktor risiko GDM mencatatkan jumlah purata markah yang terendah (1.95 ± 0.77). Tiada perkaitan yang signifikan didapati antara tahap pengetahuan dengan kawalan glisemik dalam kalangan peserta GDM ($p = 0.515$). Kajian lanjutan dicadangkan untuk mengenalpasti faktor lain yang menyebabkan pengawalan glisemik yang tidak baik, seterusnya dapat memberikan pemahaman yang lebih jelas tentang faktor yang dapat diubahsuai dalam memperbaiki pengawalan glisemik darah dan mengelakkan kesan negatif dalam GDM.

EVALUATION OF KNOWLEDGE REGARDING GESTATIONAL DIABETES MELLITUS (GDM) AND ITS ASSOCIATION WITH GLYCAEMIC CONTROL AMONG GDM PARTICIPANTS AT O&G WARD, HOSPITAL USM

ABSTRACT

A well-controlled glycaemic level in Gestational Diabetes Mellitus (GDM) will prevent unfavourable outcomes to the mother and child. An individual with adequate knowledge about GDM will has better glycaemic control. The aim of the study was to investigate the association between the extent of knowledge regarding GDM and glycaemic control in GDM participants. A cross sectional study was conducted on 113 GDM participants in the Obstetrics and Gynaecology (O&G) Ward in Hospital USM from April to June 2021. The GDM Knowledge Questionnaires (GDMKQ) was distributed to the participants with guidance and the most recent 1-day 4-times-a-day (QID) daily glucose were taken from participants' medical folder. After that, the mean daily glucose was counted. A total mean knowledge score of 113 participants was 12.02 ± 1.81 and total mean daily glucose value was 5.22 ± 0.64 mmol/L. Among five knowledge domains, highest mean score was seen for knowledge regarding diet/food values domain (2.89 ± 0.40) and lowest for risk factor of GDM (1.95 ± 0.77). The present study revealed that there is no significant association between the degree of knowledge and glycaemic control ($p = 0.515$). It is suggested that further study should be conducted to elucidate other possible determinants of poor glycaemic control, so that a clearer understanding of modifiable antecedents of GDM-related complications can be achieved and to avoid unfavourable outcomes in GDM.

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND OF STUDY

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy" (WHO, 2013) or as "any degree of glucose intolerance with onset or first recognition during pregnancy (American Diabetes Association, 2010). In a simpler definition, GDM is a high blood sugar condition that some women acquire during pregnancy and it usually starts halfway through the pregnancy between the 24^{th} and 28^{th} week of pregnancy (Niyibizi et al., 2016).

To date, there is still lack of a gold standard for the diagnosis of GDM and little evidence about the accuracy of screening strategies for GDM (Hartling et al., 2012) According to several studies conducted, it is estimated that GDM influence 7–10% approximately of all pregnancies globally (Adam & Rheeder, 2017; Ferrara, 2007; Nguyen et al., 2018; Xiong et al., 2001). Due to differences in screening strategies, testing methods as well as diagnostic for optimum GDM glycaemic thresholds, it therefore remains the subject of considerable debate (Cheung & Moses, 2018), and this cause the prevalence cannot be accurately estimated. This is because the rates differ between studies due to the prevalence of different risk factors in the population, such as maternal age and BMI, the prevalence of diabetes and ethnicity among women (Lin et al., 2016).

According to International Diabetes Federation (2017), Asia reported 26.6 % of GDM in 2017, continues rises to 27% in 2019 (International Diabetes Federation, 2019). Therefore, the prevalence of GDM is expected to keep growing over years, especially in Asia (Cho et al., 2018; Lavery et al., 2017; Tutino et al., 2014). Whereas, according to

National Obstetrics Registry (NOR), Malaysia report of 2017, the prevalence of GDM in Malaysia is 7.70% and 9.28% in 2016 and 2017 respectively (Jeganathan & Karalasingam, 2020). After that, Lee et al. (2018), claimed that the pooled prevalence of GDM in Asia was 11.5% (95% CI 10.9–12.1), reporting that Malaysia is ranked at 5th which has a prevalence of 18.5% GDM from 20 countries which involved in the study.

GDM affects the mother in the age group above 30 years old commonly (Carolan et al., 2010; Hussain et al., 2015) and therefore, it is clearly shown that advanced maternal age may serve as one of the risk factors to cause an increase in the GDM prevalence. The other contributing risk factors include a family history of diabetes (Bener et al., 2011), obesity (Bener et al., 2011) and a history of stillbirth (Egbe et al., 2018).

Abnormal levels of glucose in antenatal women can adversely affect the health of both mother and baby. For instance, women with GDM are at high risk of developing permanent diabetes in the future (Kim, 2014). Hussain et al. (2014), states that GDM is associated with a 7-fold increase in lifetime risk for developing type 2 diabetes mellitus (T2DM). Maternal complications in GDM comprise hypertension, preeclampsia, and an increased risk of caesarean delivery (Bener et al., 2011). Other than that, neonatal adverse events due to the consequence of GDM include macrosomia, neonatal hypoglycaemia and respiratory disorders (Mitanchez, 2015). Macrosomia is defined as a birth weight > 4000 g or above the 90th percentile (Kc et al., 2015) and contributed about 13.5 % by GDM mothers (Jeganathan & Karalasingam, 2017). It occurred generally in GDM as a higher amount of blood glucose passes through the placenta into the fetal circulation and extra glucose in the fetus is stored as body fat causing macrosomia as a result (Kc et al., 2015).

Well-controlled GDM is significant in the reduction of these unfavourable outcomes (Khan et al., 2013). Hence, proper management of GDM becomes the thumb of rule factor for better health outcomes. Management of GDM is principally dependent on active care measures taken by women to keep their glycaemic levels at normal range (Hussain et al., 2015). Thus, one has to be knowledgeable regarding disease and practice management strategies to avoid unfavorable maternal and fetal outcomes. This is because patients which have adequate knowledge about GDM are believed to have well-controlled on their glycaemic level to avoid the incidence of the complications of the disease.

1.2 PROBLEM STATEMENT

Knowledge is conceptualized as a set of information individuals need to master to administer their health condition (Islam et al., 2017). Inadequate health literacy is associated with limited knowledge about the disease itself. As a consequence, it results in limited adherence to disease management strategies which in turn leads to unfavorable maternal and fetal outcomes (Hunt et al., 2014).

There were several studies reported in which knowledge and attitude in GDM patients were evaluated. Based on a study conducted by Carolan et al. (2010) which was conducted in Australia, suggested that the majority of people from different ethnicities had appropriate knowledge, but they had a negative attitude toward GDM. These results are consistent with findings which shown that 76.6% of GDM patients in Hospital Pulau Pinang, Malaysia had adequate knowledge, but only 23.3% had a positive attitude (Hussain et al., 2014). However, another study conducted in Bangladesh reported that a high percentage of 60.7% have poor knowledge, but they showed a positive attitude regarding GDM control (Islam et al., 2017). The controversies among available studies

lead intention to access the association between the extent of knowledge and glycaemic control of study participants.

Based on Hussain et al. (2015), women with GDM have an increased risk of developing diabetes after pregnancy when compared to the general population, with a conversion rate of up to 7-folds. Hence, another highlighted point to conduct this study is to evaluate participants' awareness regarding complications of GDM and T2DM. Awareness of the condition among GDM antenatal mothers will translate into proper management of GDM and reduce the incidence of T2DM consequently.

There is only limited study on GDM related research in Kelantan. The most recent and related studies were carried out in 2016 to 2017, which the incidences of diabetes in pregnancy in Kelantan were collected by the National Obstetric Registry (NOR), Malaysia. Among the pregnant women affected by diabetes, 93.2% of them has GDM in 2016. Furthermore, it increases to 96.6 % in 2017 (Jeganathan & Karalasingam, 2020). Realizing the scarcity of GDM- related studies in Kelantan, this present study aimed to evaluate knowledge of participants suffering from GDM from different aspects of the disease including general knowledge about the disease, risk factors, diet, food, complications, prognosis and health outcomes.

The results of findings from this study may provide new educational strategies for the healthcare provider such as organizing routine health care education, regular physical activity, and regular clinic visits. These are believed to aid in improving pregnancy outcomes of GDM mothers.

1.3 RESEARCH QUESTIONS

1. What are the demographic characteristics of GDM participants at Obstetrics and Gynaecology (O&G) Ward, Hospital USM?
2. What is the level of knowledge regarding gestational diabetes mellitus of GDM participants at O&G Ward, Hospital USM?
3. Is there any association between the extent of knowledge regarding GDM and glycaemic control of GDM participants at O&G Ward, Hospital USM?

1.4 RESEARCH OBJECTIVE

1.4.1 GENERAL OBJECTIVE

The general objective is to evaluate the knowledge regarding GDM and its association with glycaemic control among GDM participants at O&G Ward, Hospital USM.

1.4.2 SPECIFIC OBJECTIVES

1. To determine the demographic characteristic of GDM participants at O&G Ward, Hospital USM.
2. To determine the level of knowledge of GDM participants at O&G Ward, using the Gestational Diabetes Mellitus Knowledge Questionnaire (GDMKQ).
3. To investigate the association between the extent of knowledge regarding GDM and glycaemic control of GDM participants at O&G Ward, Hospital USM.

1.5 RESEARCH HYPOTHESIS

H_0: There is no significant association between the extent of knowledge regarding GDM and glycaemic control of GDM participants at O&G Ward, Hospital USM.

H_A: There is a significant association between the extent of knowledge regarding GDM and glycaemic control of GDM participants at O&G Ward, Hospital USM.

1.6 SIGNIFICANCE OF STUDY

This study is important to evaluate the knowledge of participants suffering from GDM about different aspects of the disease including general knowledge about GDM, its risk factors, diet, complication, prognosis and health outcomes. Furthermore, the results are important to determine the evaluation of knowledge regarding gestational diabetes mellitus (GDM) and its association with glycaemic control among GDM participants at O&G Ward, Hospital USM. All of the findings in this study could furnish or update the GDM related data among GDM participants in Hospital USM. The findings will be useful for healthcare providers in developing better strategies to tackle the increasing prevalence of GDM in Kelantan and reduce the turn-over rate of GDM to T2DM.

1.7 CONCEPTUAL FRAMEWORK

Knowledge of GDM is predicted to be significantly associated with glycaemic control. Demographic characteristics, medical therapy for GDM, and response to the GDMKQ items are related to the knowledge of GDM. Other than that, glycaemic control is also being affected by the demographic characteristics of the GDM participants.

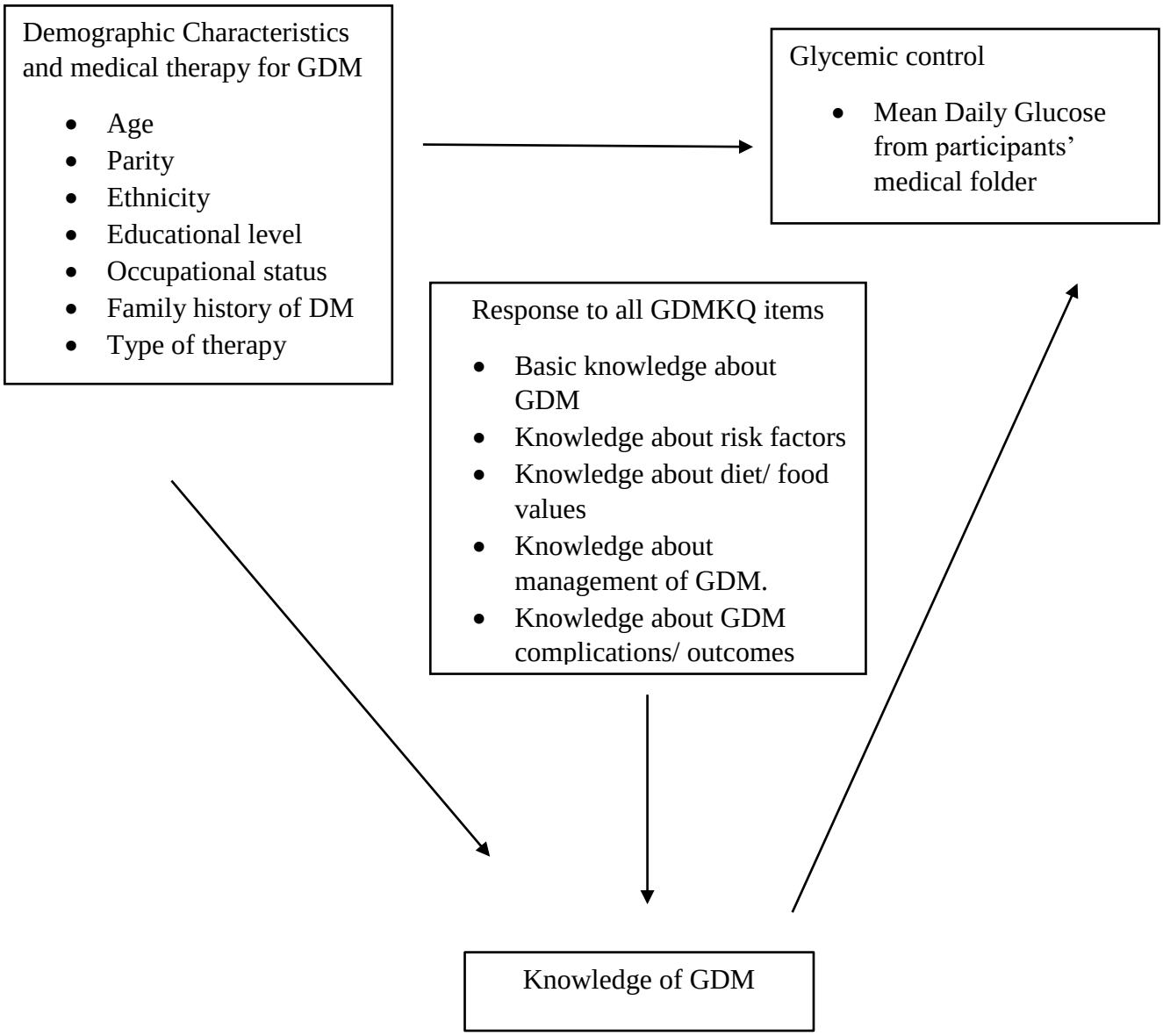

Figure 1.1: Conceptual framework of the study

1.8 OPERATIONAL DEFINITION

Caesarean Delivery: Operation to deliver the baby through the mother's belly.

Diabetes Mellitus: A group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both.

Gestational Diabetes Mellitus: Carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy or as any degree of glucose intolerance with onset or first recognition during pregnancy.

Macrosomia: Birth weight > 4000 g or above the 90th percentile.

Shoulder dystocia: The need for additional obstetrical maneuvers to effect delivery of the shoulders when gentle downward traction on the fetal head fails.

Type 2 Diabetes Mellitus: It can range from predominant insulin resistance with relative insulin deficiency to prevailing defective secretion with insulin resistance. It is also frequently associated with other problems of the so-called metabolic syndrome

CHAPTER 2

LITERATURE REVIEW

2.1 PATHOPHYSIOLOGY OF GDM

2.1.1 PANCREATIC ß CELL DYSFUNCTION AND GDM

Pancreatic ß cells are responsible for the storage and secretion of insulin to regulate blood glucose concentration. The term of 'ß cells dysfunction' is defined when ß cells lose their ability to adequately detect blood glucose concentration, or to release sufficient insulin in response to glucose load (Plows et al., 2018).

Most commonly, assessment of beta-cell function is usually conducted by measuring the fasting insulin concentration or the response to glucose infusion. Based on Yogev (2016), fasting plasma insulin will increase gradually during pregnancy and insulin level during the third trimester being the most significantly which shows twofold higher than before pregnancy.

During normal pregnancy, oral and intravenous glucose tolerance deteriorates slightly, regardless of the reduction in insulin sensitivity (Yogev, 2016). This phenomenon could be due to the gradual increase in insulin secretion by the pancreatic ß cells. Moreover, Saisho et al. (2010) reported a hyperbolic relationship between insulin sensitivity and beta-cell responsiveness to glucose in both pregnant as well as nonpregnant women, pointing to a role for the beta cells in pathological states such as GDM and demonstrating the magnitude of the change in insulin secretion that is necessary to maintain glucose tolerance. In a simpler explanation, higher insulin secretion by the pancreatic ß cells is required in response to low insulin sensitivity (insulin resistance) which is commonly happening in pregnant women.

Cerf et al. (2012), claimed that an increase in beta-cell mass in terms of both hyperplasia and hypertrophy is believed to be the major contributing factor for the increased insulin secretion during pregnancy. The increased beta-cell mass contributed to the increased fasting insulin concentration despite normal or lowered fasting glucose concentrations in late pregnancy, and the enhanced insulin response to glucose during pregnancy. Therefore, it showed that deceased in beta cell mass lowers insulin secretion and leads to the incidence of GDM (Yogev, 2016).

Over time, insulin resistance will exacerbate ß cell dysfunction (Plows et al., 2018). The reduced insulin-stimulated glucose uptake further contributes to hyperglycaemia, overburdening the ß cells, and leads to further produce additional insulin in response. The direct contribution of glucose to ß cells failure is described as glucotoxicity (Ashcroft et al., 2017). Hence, once ß cells dysfunction begins, a malicious cycle of hyperglycaemia, insulin resistance, and further ß cells dysfunction is set in motion (Plows et al., 2018).

2.1.2 CHRONIC INSULIN RESISTANCE AND GDM

Commonly, insulin resistance occurs when cells are no longer adequately respond to insulin secretion (Plows et al., 2018). According to Catalano (2010), the occurrence of insulin resistance is commonly higher in women with GDM than in normal pregnant women. This is because additional resistance is taken place in glucose uptake (predominantly skeletal muscle), glucose production (primarily liver), and fatty acid levels (adipose tissue) for women with GDM.

After pregnancy, abatement of the physiological insulin resistance rises to a greater extent in normal women than in women with GDM. In addition, serial measurements of insulin sensitivity starting before pregnancy demonstrate insulin

resistance before conception and at the beginning of the second trimester in women with GDM (Buchanan & Xiang, 2010). Therefore, most women with GDM have a separate, chronic form of insulin resistance as compared with normal women (Buchanan et al., 2012).

Mechanisms that lead to chronic insulin resistance can be varied. However, pre-pregnancy obesity is believed as a common antecedent that leads to GDM as many of the biochemical mediators of insulin resistance that occur in pre-pregnancy obesity have been identified in several studies of women with GDM or a history thereof. These mediators include inflammatory markers such as tumor necrosis factor alpha (TNF- α) and interleukin (IL)-6 will cause decrease levels of adiponectin, which subsequently result in increased fat in the liver and muscle (Plows et al., 2018). Other than that, the increased circulating levels of leptin (hyperleptinemia) will lead to insulin resistance by activation of SOCS (suppressor of cytokine signaling) proteins, which, ultimately, attenuate leptin and insulin receptor (IR) signaling (Buchanan & Xiang, 2010).

Insulin resistance develops when there is a failure of insulin signaling, resulting in inadequate plasma membrane translocation of glucose transporter 4 (GLUT4). GLUT4 is the primary transporter that is responsible to facilitate glucose to enter into the cell in, thus glucose can be utilized as an energy source. In a normal insulin signaling pathway, adiponectin has the responsibility of promoting insulin receptor substrate-1 (IRS-1) activation through AMP-activated protein kinase (AMPK). The IRS-1 will then activates phosphatidylinositol-3-kinase (PI3K), which phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5-phosphate (PIP3). Furthermore, PIP3 activates Akt2, which promotes GLUT4 translocation and glucose uptake into the cell (Plows et al., 2018).

The normal insulin signaling pathway is interrupted when there is a decreased level of adiponectin, as the activation of IRS-1 will be lowered. Nevertheless, the increased level of inflammatory markers such as TNF-alpha in turn activates protein kinase C (PKC) and serves to inhibit IRS. The combined effect of lowered adiponectin and an increased inflammatory marker will bring the process of insulin signaling to a halt. This in turn contributes to the incidence of GDM. Lastly, the increased proportion of saturated fatty acid will increase intracellular concentrations of diacylglycerol within myocytes, activating protein kinase C (PKC) and inhibiting tyrosine kinase, IRS-1 and PI3K (Plows et al., 2018).

2.1.3 HORMONAL CHANGES DURING PREGNANCY AND GDM

The placenta is a fetal organ with widespread functions located at the interface between mother and fetus. It is responsible for transporting maternal nutrients to sustain fetal growth, synthesize hormones and growth factors to facilitate maternal adaptation to pregnancy. Hence, a proper function of the placenta is essential to guarantee a better pregnancy outcome (Hiden & Desoye, 2010).

As gestational age progress, the size of the placenta increases. Consequently, there is a rise in the levels of pregnancy-associated hormones like estrogen, progesterone, cortisol and placental lactogen in the maternal circulation accompanied by increasing insulin resistance (Kamana et al., 2015). The increase of these hormones usually begins between 20 and 24 weeks of gestation, where usually GDM is being diagnosed. However, as the mother goes through parturition and delivers the fetus, the placental hormone production stops, and the incidence of GDM is relieved, which strongly suggests that these hormones cause GDM (Kamana et al., 2015).

2.1.3.1 HUMAN PLACENTA LACTOGEN (HPL)

Human placental lactogen raises approximately 10-fold in the second half of the pregnancy. The increase of HPL causes a decrease in phosphorylation of insulin receptor substrate (IRS)-1 and profound insulin resistance. Other than that, it is also discovered that overnight infusion of HPL will result in abnormal glucose tolerance even though there is an increased insulin concentration (Yogev, 2016).

Besides that, HPL also stimulates lipolysis which increases the free fatty acid (FFA) in the blood. The action of inducing lipolysis is to provide a different fuel to the mother and to preserve the glucose and amino acid for the fetus. In turn, the increase in free fatty acid (FFA) creates a mild insulin resistance that directly interferes with the insulin-directed entry of glucose into cells. Therefore, HPL is considered as a potent antagonist of insulin action during pregnancy (Chyad & Faris Shalayel, 2011).

2.1.3.2 PROGESTERONE

Progesterone is an essential sex steroid hormone that increased steadily in the advance of pregnancy to guarantee an optimum pregnancy outcome. However, progesterone is one of the potential causes implicated in insulin resistance during pregnancy and consequently leads to GDM (Wada et al., 2010).

Based on an experiment, the result claimed that progesterone administration for 8 weeks reduced whole-body glucose uptake in humans in a hyperglycaemic hyperinsulinemic clamp study (Wada et al., 2010). This result was in a line with Kunju & L (2019), which demonstrated that there is a decrease in both maximum glucose transport and insulin binding in albino females rat treated with progesterone, suggesting the role of progesterone induce insulin resistance.

The multiple mechanisms by which progesterone causes insulin resistance are described below. First, progesterone suppressed the PI 3-kinase-mediated pathway by promoting IRS-1 degradation and suppressed the subsequent phosphorylation of Akt. Second, progesterone inhibited GLUT4 translocation and glucose uptake in a step distal to Akt phosphorylation. Lastly, progesterone inhibited TC10 activation by suppressing insulin-induced Cbl phosphorylation (Wada et al., 2010).

2.2 SCREENING AND DIAGNOSTIC CRITERIA OF GDM IN MALAYSIA

GDM is related to significant maternal and fetal implications. Screening hence plays a significant role in the primary care level, allowing active interventions which significantly improve pregnancy outcomes. Despite FIGO, National Institute of Clinical Excellence (NIcE) and World Health Organization (WHO) recommendations for universal screening especially among the high-risk population; Malaysia currently adopts a selective risk-based screening for GDM.

According to Nurain et al. (2019), in a revised updated version of Clinical Practise Guidelines Management of Diabetes in Pregnancy defined women which have (1) body mass index (BMI) >27 kg/m², (2) previous history of GDM, (3) first-degree relative with diabetes mellitus (DM), (4) history of macrosomia (birth weight >4 kg), (5) Poor obstetric history such as unexplained intrauterine death, congenital anomalies, (6) glycosuria ≥2+ on two occasions, or (7) current obstetric problems such as essential hypertension, pregnancy-induced hypertension, polyhydramnios and current use of steroids, are associated with high risk for developing GDM. Hence, women which have the above criteria/ criterions, should do screening at booking as early as possible to identify the underlying diagnosis of GDM. If the test is negative, it should be repeated at 24 - 28

weeks of gestation. Meanwhile, women aged 25 years and above with no other risk factors should be also screened at 24 - 28 weeks of gestation.

Malaysia currently using a modified version for the diagnosis of GDM in the Malaysian population. On a 75g Oral Glucose Tolerance Test (OGTT), a patient which has fasting plasma glucose (FPG) ≥ 5.1 mmol/L (American Diabetes Association, 2015; International Association of Diabetes and Pregnancy Study Groups Consensus Panel, 2010; WHO, 2013) or a two-hour plasma glucose OGTT ≥ 7.8 mmol/L (NICE, 2015) is classified as diagnosis of GDM. These levels are adopted because T2DM is diagnosed in Asians at lower A1c, body mass index and waist circumference levels compared to the West (Malaysian Endocrine & Metabolic Society and Ministry of Health Malaysia, 2015).

2.3 RISK FACTOR OF GDM

2.3.1 OVERWEIGHT / OBESITY

It is well known that high maternal BMIs have been consistently associated with an increased risk of GDM. It is discovered that the risk of developing GDM is approximately 2, 3, and 6 times higher among overweight, obese, and severely obese women, respectively, as compared with normal-weight pregnant women based on meta-analyses of 20 relevant studies published between 1980 and 2006 (Zhang, 2010). Furthermore, this statement is supported by Fathy et al. (2018), which reported that GDM was found to be significantly more prevalent among women with higher BMI (>30 kg/m2) and higher pre-pregnancy weight. They had 15 times more risk for GDM than did non-obese women.

Chronic subclinical inflammation and dysregulation of adipokines are the two pathologic sequelae of obesity that emerged as processes that may potentially link

adiposity with the development of GDM (Retnakaran, 2010). McIntyre et al. (2018), claimed that there is an increase in circulating proinflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and C-reactive protein in obese pregnancy. The balance between proinflammatory and anti-inflammatory cytokines is altered in obese pregnant women, and this may contribute to increased maternal insulin resistance, for example, by differentially regulating phosphorylation of the insulin receptor and its substrates (McIntyre et al., 2018). Furthermore, adiponectin functions to enhance insulin signaling and inhibits gluconeogenesis. Hence, the low concentration of plasma adiponectin due to obesity leads to insulin resistance and causes GDM (Plows et al., 2018).

2.3.2 FAMILY HISTORY OF DM

Yang et al. (2009), found that women with a positive family history of diabetes had about twice the increased risk of GDM as compared to those without GDM history. Other than that, Moosazadeh et al. (2017), stated that the odds of GDM in women with positive familial history was 3.46 folds greater than that in those without, based on the systematic review and meta-analysis studied between 2000 to 2016. Hence, studies have consistently shown that an increased risk of GDM is contributed by the family history of diabetes mellitus.

The influence of the family history of diabetes mellitus towards the incidence of GDM and is proven by Martin et al. (1985), which emerging evidence suggesting that gravidas with gestational diabetes mellitus are more likely to have mothers with diabetes than are pregnant women with pre-gestational insulin-dependent diabetes mellitus or normal glucose regulation. This is due to gravidas may have been exposed to an abnormal environment during their own intrauterine development by virtue of their mother's

diabetes. As a result, it leads to a vulnerability to the β- cells. The β- cells will replicate poorly, but also are notoriously subject to proliferation and premature secretory maturation in utero as a result of increased stimulation with nutrient secretagogues in maternal diabetes. Excessive nutrient challenges during β-cell functional maturation could predispose to premature senescence or functional deterioration during later life. Therefore, an increased vulnerability of their β-cells may have become established in utero on nongenetic grounds and subsequently unmasked as gestational diabetes mellitus in the course of the normal diabetogenic challenges of pregnancy.

In addition, researchers have illustrated that GDM shares some genetic risk factors with T2DM (Kwak et al., 2012; Li et al., 2020). Several susceptible T2DM genes which affect insulin secretion function such as TCF7L2 and KCNQ1, seem to be associated with GDM in different populations. For example, the rs7903146 of TCF7L2 was shown to be associated with GDM in various populations (Cho et al., 2009; N. Shaat et al., 2007; Pappa et al., 2011)

2.3.3 PREVIOUS HISTORY OF STILLBIRTH

Several studies have shown the association between the history of stillbirth and the incidence of GDM. Egbe et al. (2018), claimed that past history of unexplained stillbirth (OR 5.7: 95% CI 2.5-12.9, P<0.001) was associated with the occurrences of GDM. This result is consistent with Muche et al. (2019), who reported that women with a history of stillbirth had three times (OR = 2.92; 95% CI = 1.23, 6.93) higher risk of developing GDM in future pregnancies.

There is increasing evidence to show that placental pathology may be the cause of singleton stillbirth in pregnancies at a gestation of 24 weeks or more (Pásztor et al., 2014; Redline, 2008). Villous immaturity is one of the placenta histologic lesions which

resulting in 10.1 % of fetal death cases compared to the controls in the USA (Bukowski et al., 2017).

The hallmark of villous insufficiency is characterized by insufficient development of the terminal villi, reduced vascularization of the chorionic villi, and lack of vasculo-syncytial membranes (Benirschke et al., 2006; Gordijn et al., 2010). Consequently, the diminution of vasculo-syncytial membranes and increased thickness of the placenta barrier in terms of placentas with villous immaturity resulting in placental dysfunction and fetal hypoxia, places the fetus at risk of fetal death (Gordijn et al., 2010; Higgins et al., 2011; Redline, 2012).

The phenotype of villous immaturity is also commonly seen in GDM. Villous immaturity may reflect maternal hyperglycaemia leading to fetal hyperinsulinemia. Furthermore, insulin binds to placental insulin and insulin-like growth factor receptors which then stimulating accelerated fetoplacental growth in GDM pregnancy further increases the risk of stillbirth (Pinar & Carpenter, 2010). This statement is supported by Daskalakis et al. (2008), which described villous immaturity as an indication of chronic fetal hypoxia leading to stillbirth that was significantly increased in the placentas of women with diabetes. Hence, villous immaturity is shown to be involved in the pathogenesis of stillbirth and is significantly related to the history of stillbirth occurrence and become a risk factor that may contribute to GDM.

2.3.4 POOR DIETARY FACTORS

There is substantial evidence indicates that diet has a significant relationship with the development of glucose intolerance. According to Zhang (2010), it stated that diet before and/or during pregnancy is a potentially modifiable contributor to the development of GDM.

From the study conducted by Zhang (2010), it is found that there is a strong association between the dietary pattern (Prudent versus Western) and GDM risk. The Prudent pattern was represented by a high intake of fruits, green leafy vegetables, poultry, and fish, whereas the Western pattern was characterized by a high intake of red meat, processed meat, refined grain products, sweets, french fries, and pizza. The association with the Western pattern was largely explained by a rich intake of red and processed meat products. Pre-gravid intake of red and processed meats was both significantly and positively associated with GDM risk. For instance, compared with those women who consumed less than two servings of red meat per week, those who consumed more than six servings of red meat per week had a 1.74-fold increased risk of GDM (Zhang, 2010).

The Western pattern which represents higher consumption of foods that are high in energy, saturated fat and sugar is a risk factor for obesity, which in turn is a strong risk factor for GDM. BMI might, therefore, be an intermediate in the association between the meats, snacks and sweets pattern and GDM risk (Schoenaker et al., 2015). It is commonly known that foods high in sugar and saturated fat have been shown to promote oxidative stress and inflammation. By contrast, vegetables, legumes, nuts and whole grains are low in energy and fat and have a high content of dietary fiber, magnesium, vitamin E and other antioxidants that may contribute to reducing markers of oxidative stress and inflammation, and subsequently reduces the risk of GDM.

Besides that, pre-gravid consumption of dietary total fiber in cereal and fruit was significantly and inversely associated with GDM risk (Zhang, 2010). It is reported that each 10-g/day increment in total fiber intake was associated with a 26% reduction in risk of GDM; while each 5-g/day increment in cereal or fruit fiber was associated with a 23% or 26% reduction in risk of GDM, respectively.

The association between fiber consumption and lower risk of GDM could be explained by several potential mechanisms. First, fruits and vegetables are rich in dietary fiber, which may reduce adiposity and improve insulin sensitivity (Hu et al., 2019). Furthermore, dietary fiber intake could delay gastric emptying and slows food digestion and absorption, thus decreasing postprandial plasma glucose levels (Hu et al., 2019). Moreover, vegetables and fruits are rich in polyphenols and other antioxidant components such as vitamin C, vitamin E, and carotenoids (Bahadoran et al., 2013; Du et al., 2017) and these compounds may decrease the risk of GDM by mitigating the oxidative stress that interferes with glucose uptake in cells. Thus, it is clearly shown that the importance of fiber consumption in preventing the incidence of GDM.

2.4 FETAL COMPLICATIONS TO GDM

2.4.1 MACROSOMIA

In Malaysia, macrosomia is typically defined as a birth weight above >4,000g (Jeganathan & Karalasingam, 2017). Modified Pedersen's hypothesis can be appropriate to explain the relationship between GDM mothers and macrosomia infants. In GDM mothers, glucose crosses the placenta when there is impairment of maternal glycaemic control and high maternal serum glucose. However, the maternal-derived or exogenously administered insulin does not cross the placenta. The fetal pancreas responds to hyperglycemia and secretes insulin in an autonomous manner (hyperinsulinemia) during the second trimester. Hence, the combination of hyperinsulinemia and hyperglycemia leads to an increase in protein and fat stores in the fetus, resulting in macrosomia (Kamana et al., 2015).

Several studies reported that there is a significant association between GDM and macrosomia infants (Alberico et al., 2014; He et al., 2015). Kc et al. (2015), claimed that infants born to GDM mothers have a 3-fold higher rate to develop macrosomia, comparing with non-GDM mothers and a higher proportion of infants with macrosomia, born to GDM mothers (8.6%) when compared to non-GDM mothers (2.2%) (Goh et al., 2018).

Good glycaemic control helps in reducing the incidence of GDM complications (Buhary et al., 2016) and macrosomia occurrence can be as high as 20%–45% in poor glycaemic control (Langer, 2016). In recent study discovered that the combination of both GDM and maternal obesity has a greater effect on macrosomia by showing that macrosomia in GDM plus obesity has shown a higher incidence of 33% compared to 26% of macrosomia caused solely by GDM (Kamana et al., 2015). Thus, other than efforts made to improve glycaemic control during GDM pregnancies, counseling and treatment for overweight and obese women is needed, encouraging them to aim for a BMI below 25.0 kg/m² before becoming pregnant to reduce the incidence of macrosomia (Olmos et al., 2012).

2.4.2 SHOULDER DYSTOCIA

Shoulder dystocia is characterized as the need for additional obstetrical maneuvers to effect delivery of the shoulders when gentle downward traction on the fetal head fails (Guberman & Kjos, 2010). This incidence is usually attributed to macrosomia as macrosomia fetus in GDM pregnancy develop a unique pattern of overgrowth, involving the central deposition of subcutaneous fat in the abdominal and interscapular areas. As a result, macrosomia infants have larger shoulder and extremity circumferences,

significantly higher body fat and thicker upper-extremity skinfolds, but with a decreased head-to-shoulder ratio (Kamana et al., 2015).

Based on a study conducted by Langer (2016), the rate of shoulder dystocia in three groups which are untreated GDM, treated GDM, control group was 1.6%, 1.2% and 0.4% respectively in women with normal body weight. Nevertheless, the rate is nearly doubled, contributed 3.2%, 0.7% and 0.8% in overweight or obese women (Langer, 2016). Moreover, data from the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), also demonstrated a positive relationship between the severity of maternal fasting hyperglycemia and the risk of shoulder dystocia, with a 1-mmol increase in fasting glucose leading to a 2.09 relative risk for shoulder dystocia (Kamana et al., 2015). Again, all of these findings emphasize the importance of proper glycaemic control to reduce the adverse complications of GDM (Buhary et al., 2016).

2.5 MATERNAL COMPLICATIONS TO GDM

2.5.1 DIABETES MELLITUS

Based on Ferrara et al. (2009), about 5-10% of women developed T2DM within the first 6 months after GDM pregnancy while 10-15% will develop diabetes within the subsequent 1-2 years postpartum in Northern California. However, in Malaysia, the prevalence of postnatal DM among GDM mothers was 12.1 %. In addition, it also reported that working GDM mothers were at higher risk of developing postnatal DM (Logakodie et al., 2017).

Several predictors of diabetes among women with a history of GDM include maternal antepartum and early postpartum glycemia, pancreatic β-cell compensation for higher insulin resistance, GDM recurrence and family history of

diabetes, especially having a mother with diabetes. However, among the risk factors stated, pre-pregnancy obesity, gestational weight gain, postpartum weight gain, and subsequent pregnancies have been associated with a higher risk of diabetes years later (Gunderson et al., 2011).

Greater central obesity has been reported in women who developed type 2 diabetes after GDM pregnancy in a cross-sectional study (Gunderson et al., 2011). Therefore, it is crucial that women with GDM should be advised of this increased risk and advised on weight control, diet and exercise. Based on Hunt et al. (2014), obese GDM women should be advised on moderate calorie restriction to improve glycaemic control and limit maternal weight gain. Complex carbohydrate sources with a low glycaemic index, such as wholegrain breads and cereals, aids in improving overall glucose control and limit excursions of post-prandial blood glucose (change in glucose concentration from before to after a meal). In addition, light exercises such as walking, swimming or yoga are also suggested to the GDM women to improve their blood glucose level.

2.5.2 CESAREAN DELIVERY

Caesarean Delivery is an operation to deliver the baby through the mother's belly. A woman who has diabetes that is not well controlled has a higher chance of needing a Cesarean section to deliver the baby (CDC, 2020). Based on a study conducted in Thailand, the rate of cesarean delivery is significantly higher in GDM women (31.6%) compared to non GDM women (19.4%) (Boriboonhirunsarn & Waiyanikorn, 2016). The rate of cesarean section was found to be 10 times higher among diabetic women (28.5%) as compared to healthy women (18.8%) in Malaysia (Kampan et al., 2013).

Higher rates of Cesarean section may result from macrosomia associated with fetal insulin response to increased maternal glucose levels during pregnancy or changes

in the obstetrical management due to the GDM status (Boriboonhirunsarn & Waiyanikorn, 2016). This statement is proven when both Toronto Tri-Hospital and HAPO studies found an increased risk of cesarean delivery and increased birth weight or large gestational age rate with untreated increasing levels of glucose (Guberman & Kjos, 2010).

GDM women are commonly associated with obesity (BMI≥30kg/m²). The status of obesity itself markedly rises the risk of Caesarean delivery and post-partum delivery (Guberman & Kjos, 2010). Thus, it is important to provide counseling and earlier treatment for GDM women, encouraging them to practice diet and lifestyle change, to avoid excessive gestational weight gain to prevent unfavorable outcomes.

2.6 GAP OF KNOWLEDGE

Best to our knowledge, there is only one study conducted in Malaysia to access the knowledge and glycaemic control of GDM patients by Hussain et al. (2015). Based on the analysis from the study, knowledge regarding GDM shown a significant negative association with glycaemic control ($r = -0.306$, $P < 0.01$). Knowledge is an important component for the management of GDM, therefore this study emphasis on developing new educational strategies to improve the low level of health literacy.

However, there were a few studies conducted to investigate the association between knowledge and attitudes towards GDM (Carolan et al., 2010; Hussain et al., 2014; Islam et al., 2017). Based on a study conducted by Carolan et al. (2010) which was conducted in Australia, the result suggested that the majority of people from different ethnicities had appropriate knowledge, but they had a negative attitude toward GDM. Again, the findings in the study recommended that other than developing new education