ASSOCIATION BETWEEN PRE-PREGNANCY BODY MASS INDEX AND GESTATIONAL DIABETES MELLITUS AMONG PREGNANT WOMEN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SYMBOLS AND ABBREVIATIONS

ATM	Adipose Tissue Macrophages
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CPG	Clinical Practice Guidelines
GDM	Gestational Diabetes Mellitus
GWG	Gestational Weight Gain
Hospital USM	Hospital Universiti Sains Malaysia
NHMS	National Health and Morbidity Survey
O & G	Obstetrics and Gynaecology
OGTT	Oral Glucose Tolerance Test
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
USM	Universiti Sains Malaysia
WHO	World Health Organization

PERKAITAN ANTARA INDEKS JISIM BADAN SEBELUM MENGANDUNG DAN DIABETES SEMASA HAMIL DALAM KALANGAN WANITA MENGANDUNG DI HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRAK

Diabetes semasa hamil (GDM) adalah keadaan di mana intoleransi glukosa atau diabetes yang pertama kali disahkan ketika mengandung. Indeks jisim badan (BMI) sebelum mengandung merupakan satu faktor risiko GDM. Kajian ini bertujuan untuk mengetahui status BMI sebelum mengandung, dan prevalen GDM serta mengenalpasti perkaitan antara BMI sebelum mengandung dan GDM dalam kalangan wanita mengandung. Kajian ini merupakan sebuah kajian hirisan lintang yang melibatkan seramai 104 orang wanita mengandung di wad Obstetrik dan Ginekologi (O & G), Hospital Universiti Sains Malaysia (Hospital USM), Kelantan. Soal selidik yang mengandungi maklumat sosio-demografi, antropometri dan keadaan kesihatan ibu telah digunakan dan maklumat diperoleh melalui kaedah lapor diri dan merujuk kepada rekod obstetrik klinikal atau perubatan. Berat badan sebelum mengandung telah dilapor oleh subjek dan BMI sebelum mengandung telah dikira dengan menggunakan berat badan dalam kilogram dibahagi dengan kuasa dua ketinggian dalam meter. BMI tersebut telah dikategorikan mengikut pengkelasan BMI oleh Pertubuhan Kesihatan Sedunia (WHO). Hasil kajian menunjukkan bahawa terdapat 8.7%, 43.3%, 26.9% dan 21.2% subjek mempunyai BMI sebelum hamil masing-masing kekurangan berat badan, berat badan normal, lebih berat badan dan obes. Prevalen GDM dalam kalangan wanita mengandung ialah 29.8%. BMI sebelum mengandung tidak mempunyai perkaitan dengan GDM ($p = 0.398$). Walaubagaimanapun, sejarah diabetes dalam kalangan saudara mara kelas pertama dan umur ibu mempunyai perkaitan dengan GDM (p=0.021; p=0.033). Kesimpulannya, BMI sebelum mengandung tidak mempunyai perkaitan yang signifikan dengan GDM dalam kalangan wanita mengandung yang menghadiri wad O & G di Hospital USM. Keputusan ini disebabkan oleh prevalen obesiti atau lebih berat badan yang tinggi dalam kedua-dua kumpulan ibu mengandung dengan GDM dan tanpa GDM, prevalen sejarah diabetes dalam kalangan saudara mara kelas pertama dan faktor ibu yang lanjut usia yang tinggi mungkin menyembunyikan kesan BMI sebelum mengandung terhadap GDM.

ASSOCIATION BETWEEN PRE-PREGNANCY BODY MASS INDEX AND GESTATIONAL DIABETES MELLITUS AMONG PREGNANT WOMEN IN HOSPITAL UNIVERSITI SAINS MALAYSIA

ABSTRACT

Gestational Diabetes Mellitus (GDM) is a condition of glucose intolerance or diabetes with onset or first recognition during pregnancy. Pre-pregnancy body mass index (BMI) is a risk factor for GDM. This study aimed to determine the pre-pregnancy BMI status, the prevalence of GDM, and to identify the association between pre-pregnancy BMI and GDM among pregnant women. This cross-sectional study involved 104 pregnant women at Obstetrics and Gynaecology (O&G) ward in Hospital Universiti Sains Malaysia (Hospital USM), Kelantan. A questionnaire consisted of socio-demographic, anthropometric, and maternal health condition information of the subject was used and the data was collected by self-reporting and referring to the clinical obstetric or medical records. Pre-pregnancy weight was self-reported by the subject and pre-pregnancy BMI was calculated by using weight in kilograms divided by the square of the height in metre. BMI classification of subjects was determined according to the World Health Organization (WHO). The results showed that 8.7%, 43.3%, 26.9%, and 21.2% of subjects had underweight, normal, overweight, and obese pre-pregnancy BMI, respectively. The prevalence of GDM among pregnant women was 29.8%. Pre-pregnancy BMI was not significantly associated with GDM ($p= 0.398$). However, family history of diabetes in first-degree relatives and maternal age were significantly associated with GDM ($p=0.021$; $p= 0.033$). In conclusion, there was no significant association between pre-pregnancy BMI and GDM among pregnant women attending O & G ward in Hospital

USM. It is suggested that the high prevalence of obesity or overweight among GDM and non-GDM mothers, high prevalence of first-degree family history of diabetes mellitus, and advanced maternal age may mask the effect of pre-pregnancy BMI on GDM.

CHAPTER 1: INTRODUCTION

1.1 Background of Study

Gestational Diabetes Mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy (Baz *et al*., 2016). GDM is diagnosed when the fasting plasma glucose is at least 5.1 mmol/L or 2-hour postprandial of Oral Glucose Tolerance Test (OGTT) is 7.8 mmol/L or above (Clinical Practice Guidelines (CPG) Management of Diabetes in Pregnancy, 2017). According to Plows *et al.* (2018), the risk factors for GDM are associated with insulin sensitivity and/or β-cell dysfunction. Overweight or obesity, high animal fat and cholesterol dietary intake, ethnicity, family history of diabetes, and advanced age are the risk factors for GDM (Baz *et al,* 2016; Bowers *et al.*, 2012; Plows *et al*., 2018).

According to American Diabetes Association (2010), GDM affected 7 % of all pregnant women. International Diabetes Federation (2020) has reported there were 223 million women who are having diabetes and 16% of live births had hyperglycemia in pregnancy and estimated 84% of this was due to GDM in 2019. The prevalence of GDM was estimated at 6 to 12% of all pregnancies in the world (Zhu & Zhang, 2016). Based on the finding from Wu *et al.* (2018), the prevalence of GDM in Huangdao, Qingdao, China was 21.8%. Meanwhile, Hashim *et al.* (2019) reported there was 19.1 % of Emirati and Arab women in the United Arab Emirates had GDM.

National Health and Morbidity Survey (NHMS) (2016) has reported the prevalence of GDM among the pregnant women in Malaysia aged 15 to 49 years old was 13.5% in 2016 and it was highest among women aged 45 to 49 years at 48.2%. The prevalence of GDM among the pregnant women in Kelantan, Malaysia was 8.9% in 2016.

It is found that Malaysia has a higher rate of GDM (7.42% to 27.9%) (Jeganathan & Karalasingam, 2017; Logakodie *et al.*, 2017; Yong *et al.*, 2020b) than other Asian countries (2.8% to 21.8%) (Chong *et al*., 2014; Lee *et al*., 2018; Wu *et al*., 2018).

Pre-pregnancy body mass index (BMI) is the BMI before pregnancy. BMI is an indicator of nutrition status in adults. BMI is used to determine whether a person is underweight, normal, overweight, or obese. It is calculated by using the weight of the person in kilograms divided by the square of the person's height in metre. BMI is further divided into few categories. BMI less than 18.5 kg/m^2 indicates underweight, BMI 18.5 to 24.9 kg/m^2 indicates normal weight, BMI 25.0 to 29.9 kg/m^2 indicates overweight and BMI 30 kg/m^2 or above indicates obesity (World Health Organization (WHO), 1998) as shown in Appendix A.

The world was estimated to have 650 million obese adults in 2016. About 39% of adults in the world were overweight and 13% of adults were obese in 2016 (WHO, 2020). According to NHMS (2019), the prevalence of underweight women was 5.7%. Meanwhile, there were 39.6 % of women with normal BMI. The prevalence of overweight and obesity in females in 2019 were 30%. and 24.7 %, respectively. It is noticed that the trend of overweight and obesity was increasing from the year 2015 to 2019 in females (NHMS, 2015; NHMS, 2019).

Yong *et al*. (2020a) reported that the prevalence of GDM among pregnant women with overweight and obese pre-pregnancy BMI in Seremban District, Malaysia were 31.3% and 12.5%, respectively. The prevalence of GDM among pregnant women who are obese before pregnancy in Selangor, Malaysia was even higher (45.7%) (Logakodie *et al.*, 2017).

The association between pre-pregnancy BMI and GDM has been assessed by many overseas studies (Hashim *et al.*, 2019; Shin & Song, 2015; Wu *et al.*, 2018) but there is still limited local studies that involve in this topic and the study locations were not in Kelantan, Malaysia (Logakodie *et al.*, 2017; Yong *et al.*, 2020a). Besides, due to overweight and obesity among Malaysian women is rising (NHMS, 2015; NHMS, 2019), it is important to create and enhance awareness of Malaysian women on healthy pre-pregnancy BMI to reduce the risk of GDM. Therefore, a cross-sectional study was carried out to identify the association between pre-pregnancy BMI and GDM among pregnant women in Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan.

1.2 Problem Statement

Pre-pregnancy BMI plays a role in determining the pregnancy outcome and development of offspring (Veena *et al.*, 2016). It was found that there is an increasing trend of the prevalence of unhealthy BMI among Malaysian women according to NHMS (2019).

GDM is defined as glucose intolerance with onset or first recognition during pregnancy. The risk factors for GDM included advanced age, family history of diabetes, ethnicity, and others. Obesity is a non-genetic factor that contributes to GDM. Obese mothers have a higher risk of abnormal blood glucose homeostasis during pregnancy (Papachatzi *et al*., 2013). The prevalence of GDM mothers who are obese before pregnancy is high based on previous studies (Logakodie *et al.*, 2017; Yong *et al*., 2020a). GDM will cause unflavoured outcomes to the mother as well as to the baby. GDM mothers might suffer from caesarean section and pre-eclampsia. The fetal complication of GDM included stillbirth, fetal hypoglycaemia, and obesity in later life (Baz *et al*., 2016).

Therefore, this study is important to determine the association between pre-pregnancy BMI and GDM among pregnant women in Hospital USM. This study is found to be important because to our best knowledge, there is no local study has been carried out to study the association between BMI before pregnancy and GDM in Kelantan. This study is also important because the prevalence of overweight and obesity among Malaysian women is rising (NHMS, 2015; NHMS, 2019) and the prevalence of GDM among Malaysian women is also high. It is found that Malaysia has a higher rate of GDM when compared to other Asian countries.

1.3 Significance of Study

By addressing the issues mentioned above, the pre-pregnancy BMI and GDM status among women in Hospital USM, Kelantan, Malaysia is expected to be identified. It is hoped that the awareness of healthy nutritional status before pregnancy could be increased or enhanced in order to minimise the risk of GDM or other pregnancy comorbidities. It is hoped that women in Kelantan, Malaysia would be able to practice a normal pre-pregnancy BMI (18.5-24.9 kg/m^2) so that they could have a safe and healthy pregnancy. Furthermore, it is also hoped that the well-being of GDM mothers and the child born to GDM mothers could be emphasized and enhanced because they are at risk of having Type 2 Diabetes Mellitus in the future. Lastly, it is hoped that this study could provide some information for future studies in order to enhance the understanding of this topic.

1.4 Research Questions:

1. What is the pre-pregnancy BMI status among pregnant women attending the Obstetrics and Gynaecology (O & G) ward in Hospital USM?
2. What is the prevalence of GDM among pregnant women attending the O & G ward in Hospital USM?
3. What is the association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM?

1.5 Research Objectives

1.5.1 General Objective:

To determine the association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM.

1.5.2 Specific Objectives:

1. To determine the pre-pregnancy BMI status among pregnant women attending the O & G ward in Hospital USM.
2. To determine the prevalence of GDM among pregnant women attending the O & G ward in Hospital USM.
3. To identify the association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM.

1.6 Research Hypothesis:

Null Hypothesis (H_0): There is no association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM.

Alternative Hypothesis (H_1): There is an association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM.

1.7 Conceptual Framework

Pre-pregnancy BMI is expected significantly associated with GDM. Overweight and obesity before pregnancy, age, ethnicity, educational level, household income, number of pregnancies (gravida), and family history of diabetes contribute to GDM among pregnant women.

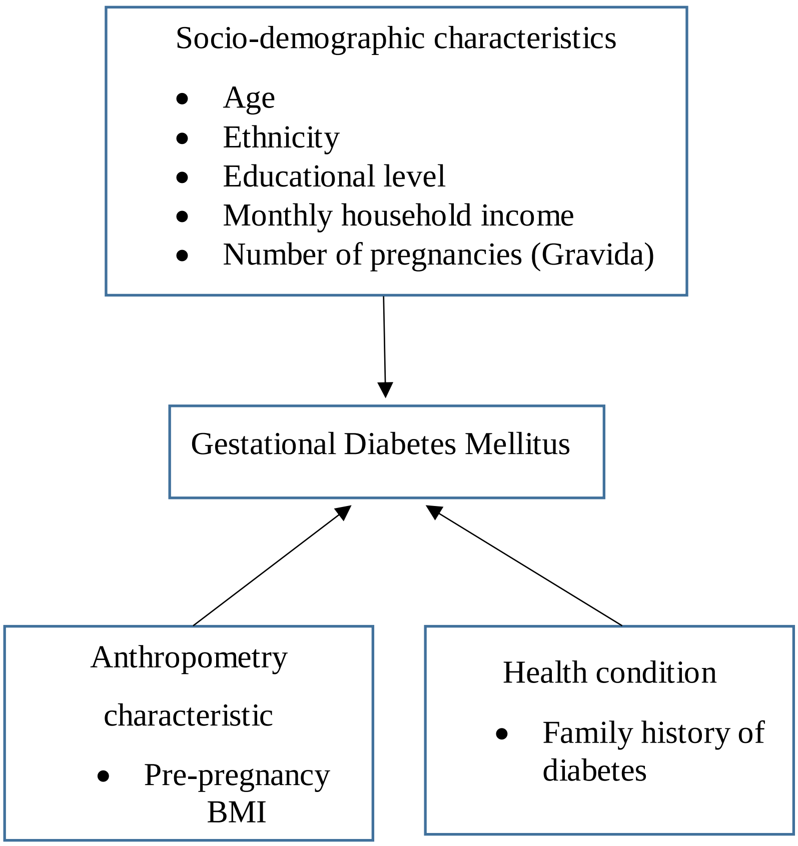

Figure 1.1: Conceptual framework of the study

1.8 Operational Definition

Gravidity: Gravidity is defined as the total number of pregnancies, including the live births or the pregnancies that terminate at less than 6 months or did not result in a live birth (Wernli *et al*., 2009).

Gestational diabetes mellitus: Gestational Diabetes Mellitus is defined as glucose intolerance with onset or first recognition during pregnancy (Baz *et al*., 2016).

CHAPTER 2: LITERATURE REVIEW

2.1 Pathophysiology of GDM

2.1.1 β-Cell Dysfunction and GDM

β-cell is responsible to store and secrete insulin to maintain the normal blood glucose level in the body. It is found that the majority of GDM cases are related to impaired β-cell function. An impaired β-cell function is due to persistent and excess insulin production in response to chronic excessive energy intake and insulin resistance, exhausting the cells over time (Plows *et al.,* 2018).

Deterioration of β-cell causes insulin resistance and deficiency which is the primary metabolic change that happens among the GDM pregnant women (Harlev & Wiznitzer, 2010). When the function of β-cell is further reduced, hyperglycaemia will become more severe and worsen. This causes β-cell to work even harder to produce more insulin in response to high blood glucose level. Thus, this can be concluded that a cycle of hyperglycaemia, low insulin sensitivity, and further β-cell function impairment will occur in the body. Reduction in the β-cell number may lead to GDM. Therefore, deterioration of β-cell and reduction in β-cell number are believed to the contributors to GDM (Plows *et al*., 2018).

2.1.2 Adipose Tissue Inflammation and GDM

Adipose tissue stores calories. There is an increase of adipose tissue mass during early pregnancy and the fat stored in the adipose tissue will be used to support fetus growth during later pregnancy. However, adipocyte differentiation is reduced and the size of adipocytes is increased in GDM. With the presence of reduced adipocyte differentiation and insulin resistance, the disposal of excess energy is affected (Plows *et al.*, 2018).

Obesity, Type II Diabetes Mellitus, and GDM are associated with an elevated number of resident adipose tissue macrophages (ATM). Pro-inflammatory cytokines are secreted by ATM. It is found that pro-inflammatory cytokines increased in GDM. The pro-inflammatory cytokines affect insulin release and signalling which contribute to insulin resistance (Plows *et al.*, 2018). Moreover, a meta-analysis has proved that GDM mothers have more tumor necrosis factor-alpha which impairs the glucose homeostasis in GDM and it is used as the most important predictor of pregnancy-induced insulin resistance (Xu *et al*., 2014).

2.1.3 Placenta and GDM

The placenta is a selective barrier between the maternal and fetal environments. The placenta secretes hormones and cytokines and it is associated with insulin resistance during pregnancy. The placenta exposes itself to hyperglycaemia. This altered placental transport of glucose, amino acid, and fatty acid from mother to fetus happens in GDM. The placenta expresses the insulin receptor and insulin signalling to influence the metabolism of glucose. Maternal hyperglycaemia is associated with abnormal growth of the fetus and macrosomia. An increase in the placental transport of amino acids is associated with GDM (Plows *et al*., 2018).

2.2 Screening and Diagnosis of GDM

GDM screening is important to identify patients with diabetes in pregnancy. There are two types of screening strategies used, namely universal strategy and selective strategy. For universal strategy, all the pregnant women are required to take the GDM screening test while for selective strategy, only women at high risk will be screened for GDM. Screening for GDM is done by using 75 grams Oral Glucose Tolerance Test (CPG Management of Diabetes in Pregnancy, 2017).

Pregnant women should be on a normal diet for 3 days before the test is carried out. She needs to fast 8-10 hours before the test. The fasting blood sugar will be recorded and glucose water will be drunk within 5 minutes. The blood sugar reading will be taken again after 2 hours (Portal Rasmi MyHEALTH Kementerian Kesihatan Malaysia, 2016).

There are different criteria used for the diagnosis of GDM. American Diabetes Association (2016) recommends GDM diagnosis criteria as fasting plasma glucose value ≥ 5.1mmol/L or one-hour plasma glucose value ≥ 10.0mmol/L or two-hour plasma glucose ≥ 8.5mmol/L of 75g-OGTT. Meanwhile, International Association Diabetes Pregnancy Study Groups (2010) recommends fasting plasma glucose ≥5.1 mmol/l (92 mg/dL) to be used to diagnose GDM. WHO (2018) has updated its criteria for diagnosis of GDM in which fasting plasma glucose 7.0 mmol/L, 2-hour 75g-OGTT plasma glucose 11.1 mmol/L or random plasma glucose 11.1 mmol/L in the presence of diabetes symptoms are used to diagnose GDM. However, in Malaysia, GDM is diagnosed when the fasting plasma glucose is at least 5.1 mmol/L or 2-hour postprandial of 75g-OGTT is 7.8 mmol/L or above (CPG Management of Type 2 Diabetes Mellitus, 2015).

2.3 Risk Factors for GDM

2.3.1 Nutritional Status and GDM

Obesity is a risk factor for GDM (Baz *et al*, 2016; Shin & Song, 2015). According to Liu *et al.* (2014), GDM mothers are more likely to have overweight or obese BMI prior to pregnancy and shorter compared to healthy women. This finding is consistent with the finding of Yong *et al.* (2020b), in which overweight or obese pregnant women were 1.44 times at higher risk of GDM as compared to healthy pregnant women. During pregnancy, there are metabolic changes and insulin sensitivity reduces in late pregnancy. Obese women were found to have a higher 40% insulin resistance compared to healthy women (Sivan *et al.*, 1997). Therefore, obese women may experience a higher risk of abnormal blood glucose homeostasis during pregnancy (Papachatzi *et al*., 2013). Besides, the study has shown that overweight and obese women are at higher risk to achieve excessive gestational weight gain (GWG) (Samura *et al.,* 2016) and GWG is associated with GDM as well (McDowell *et al*., 2018).

On the other hand, Kongubol & Phupong (2011) reported that pre-pregnancy obesity is not associated with an increased risk of GDM. This may be due to different BMI cut-off points is used to define obesity in their study.

2.3.2 Family History of Diabetes and GDM

Family history of diabetes is found to be the risk factor for GDM (Li *et al*., 2020a; Wu *et al*., 2018). Li *et al.* (2020a) reported the risk of GDM among pregnant women with a family history of diabetes in first-degree was found to be 4.94 folds higher than those who are free from the family history of diabetes in first-degree relatives.

The fetus of pre-existing diabetes mothers may have been subjected to an abnormal intrauterine environment and affect the fetus's β-cells function (Martin *et al.*, 1985). The incidence of GDM increases with both of the parents are diabetic. Maternal diabetes history is associated with a greater impact on the incidence of GDM than paternal diabetes history. This is due to abnormal maternal glucose metabolism during pregnancy and leads to fetal dysplasia during fetal growth in the womb and further development to GDM (Yaping *et al*., 2021).

2.3.3 Maternal Age and GDM

Maternal age is significantly associated with GDM. This is proven by several studies (Abu-Heija *et al*., 2017; Logakodie *et al.,* 2017; Yong *et al*., 2020b). According to the Department of Statistics Malaysia Official Portal (2015), the reproductive age of Malaysian women is in the range of 15 to 49 years old. The risk of GDM of the overall population, Asian and Europid increased by 7.9%, 12.7%, and 6.5%, respectively for each one-year increase in maternal age from 18 years old based on the finding from Li *et al.* (2020c). Meanwhile, a Selangor, Malaysia study reported that GDM risks were four times higher in women aged 35 years old and above (Logakodie *et al*., 2017). A United States study has shown that the incidence of GDM increased with age, peaked at 35-39 years old, and reduced in women with age of 40-50 years (Wang *et al*., 2012). Old maternal age shortens the time gap between the two consecutive pregnancies. Due to short inter-pregnancy intervals, women may carry along greater weight and abdominal fat during the subsequent pregnancy (Yong *et al*., 2020b). Aging is also associated with insulin resistance, results in poor glycaemic control and GDM (Chee *et al*., 2016).

2.3.4 Ethnicity or Race and GDM

Ethnicity may be defined as the social group sharing the culture, history, geographical origins, language, lifestyle, physical, genetic, and other factors (Bhopal, 2007). Ethnicity or race is an independent risk factor for GDM (Hedderson *et al.*, 2010; McDonald *et al.*, 2015). According to Hedderson *et al*. (2010), more Asian is found to have GDM when compared to other ethnicities. Among the Asian, Indian women had the highest prevalence of GDM followed by Chinese, Southeast Asian, and the Philippines. Meanwhile, non-Hispanic women had the lowest incidence of GDM in the same study. This is thought to be due to Asian pregnant women have a higher degree of insulin resistance than Caucasian women at a similar BMI, resulting in poorer glycaemic control (McDonald *et al.*, 2015).

2.3.5 Educational Level and GDM

A higher educational level reflecting the knowledge-related asset of an individual is generally associated with a better health outcome in the population (Rönö *et al*., 2020). There was an association between educational attainment and GDM (Bouthoorn *et al*. ,2015; Song *et al*., 2017). The risk of GDM was inversely associated with educational level. Bouthoorn *et al*. (2015) reported that women with the lowest educational level were three times more likely to have GDM when compared with women with the highest educational attainment. Besides, Rönö *et al.* (2019) has also found that educational attainment had a protective effect on the development of GDM among women. The mechanism that contributes to GDM among lower educational level women remains unclear. However, it is believed that it is due to limited knowledge on health risk factors among low educational level women and they display unhealthy behaviours. Women with higher educational level have better health choices and higher incomes, which provide better access to health care, thus reducing the risk of GDM (Song *et al.*, 2017).

2.3.6 Household Income and GDM

Household income is associated with GDM. It was found that income was inversely associated with occurrences of GDM (Rönö *et al.*, 2019). Bener *et al.* (2011) has reported pregnant women with low monthly income were two times more likely to have GDM. These findings are further supported by Song *et al*. (2017), in which higher household income was associated with a lower risk of GDM. Higher income enables better access to material resources, and hence promoting better health (Galobardes *et al.*, 2007). Besides, lower household income is associated with mental disorders and this is associated with GDM (Sareen *et al.*, 2011; Song *et al.*, 2017).

2.3.7 Gravidity and GDM

It was found that three or more gravida was significantly associated with GDM (Rajput *et al.*, 2014). They found that women with three or more gravida had a significantly higher GDM prevalence when compared to those with less than three gravidae. Furthermore, according to Qazi *et al*. (2016), there was 32% of GDM mothers were with three to four gravida. Meanwhile, it was found 52.3% of GDM free women were with zero to two gravida in the same study. Multigravida women have a higher risk to suffer from impaired glucose metabolism after delivery (Wang *et al*., 2019). Besides, multigravida women tend to have older maternal age which is associated with insulin resistance (Chee *et al*, 2016; Wang *et al*, 2019).

2.4 Complications of GDM

2.4.1 Macrosomia

Macrosomia is defined as a birth weight of 4.0 kg or above. It is used to describe large-for-gestational-age (birth weight > 90 th percentile) babies (Turkmen *et al*., 2018). Macrosomia is associated with higher body fat mass, larger shoulder, and higher upper-extremity skinfolds. GDM mothers are found to have higher glucose transport through placental into the fetal circulation. This causes the fetus to receive extra glucose and store it as body fat, which results in macrosomia (Kamana *et al.,* 2015). Universiti Kebangsaan Malaysia Medical Centre has proven that the mean weight of baby born with diabetic mothers was higher than healthy mothers. Their study successfully found that there were eighteen babies with diabetic mothers who had a birth weight ranged from 4.0 to 5.1 kg (Kampan *et al.,* 2013). Besides, Ornoy (2011) has suggested other causes of macrosomia, which included overweight pre-pregnancy BMI, excessive gestational weight gain, and had macrosomia baby during the previous pregnancy.

2.4.2 Cesarean Delivery and GDM

Delivery of a baby through mother's belly is known as caesarean delivery. It takes a longer time for a mother to recover from labouring (Centers for Disease Control and Prevention (CDC), 2020). Ceasarean delivery is associated with macrosomia. Large babies may face problems during vaginal delivery as the fetus may be stuck in the birth canal, results in prolonged labouring. Tear of vaginal tissues and the muscle between vagina and anus may happen when women giving birth to large babies. Therefore, caesarean delivery of a large baby may be needed to prevent negative consequences. It is also found that mothers with a history of ceasarean delivery have a higher risk of uterus tear along the scar line of previous ceasarean (Kamana *et al,* 2015). Kampan *et al*. (2013) reported the rate of caesarean delivery was ten times higher among Malaysian diabetic mothers than unaffected women.

2.4.3 Maternal Type 2 Diabetes Mellitus in Later Life and GDM

Postnatal diabetes mellitus is found to be one of the complications of GDM (Eades *et al*., 2015; Logakodie *et al*., 2017). GDM is linked to Type 2 Diabetes in predisposed women who had metabolic challenges of pregnancy (Herath, *et al*., 2017). According to CDC (2019), about 50% of GDM mothers develop Type 2 Diabetes after delivery. The progression from GDM to Type 2 Diabetes is associated with greater gestational weight gain and progressive β-cell failure to manage insulin resistance (Eades *et al*., 2015; Ratner, 2007).

2.5 Gap of Knowledge

Several studies have been carried out to identify the association between pre-pregnancy BMI and GDM in the world. Some differences could be found between this study and the pre-existing studies. For instance, when comparing to a local study that studied the GDM prevalence, associated factors, and the outcome of women attending antenatal care (Logakodie *et al*., 2017), it is found that it had the same study design (cross-sectional study) with this study. However, the study location was in public health clinic in Selangor, Malaysia which is different from this study. There are 93.8 %, 3.0 %, 0.3% and 0.6% of the Malaysian population in Kelantan are Bumiputera, Chinese, Indian, and other ethnic, respectively based on the Department of Statistics (2020a). The ethnic compositions of the Malaysian population in Selangor are 55.0 % of Bumiputera, 24.1 % of Chinese, 11.2 % Indian, and 0.8 % of other ethnicities (Department of Statistics, 2020b) which are very much different from Kelantan. The differences in ethnic composition between the two states may yield different study findings when the study was carried out in Hospital USM, Kelantan.

Besides, the study of Logakodie *et al.* (2017) applied a systematic random sampling method and required the involvement of 740 subjects while this study applied a convenient sampling method and 104 **s**ubjects were required. Furthermore, Logakodie *et al*. (2017) defined pre-pregnancy maternal obesity as BMI > 27.0 kg/m^2 while this study defined pre-pregnancy maternal overweight and obesity as BMI 25-29.9 kg/m^2 and BMI ≥30.0 kg/m^2, respectively. Therefore, it can be concluded that both of the studies are different in the term of study subject's ethnic composition, study location, sampling method, definition of pre-pregnancy obesity.

This study found there was no significant association between pre-pregnancy BMI and GDM among pregnant women which was found contradicted with several previous studies (Hashim *et al.*, 2019; Logakodie *et al*., 2017; Wu *et al*., 2018) that found there was a significant association between pre-pregnancy BMI and GDM among pregnant women.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Research Design

This study was a cross-sectional study. A cross-sectional study is a type of observational study where a sample of the individual is selected from a previously defined population and conducted at a particular period to collect information on exposure and outcome of the study interest simultaneously. The subject in this kind of study is selected based on the inclusion and exclusion criteria of the study. A cross-sectional study is effective in finding the association between two parameters but it is not suitable to study causality. It is less expensive and not time-consuming (Setia, 2016). Data included age, ethnicity, educational level, monthly household income, occupation, number of pregnancies, height, pre-pregnancy weight, pre-pregnancy BMI, first-degree family history of diabetes, and GDM status of pregnant women in Hospital USM were collected at one time using a questionnaire by self-reporting and referring to the clinical obstetrics or medical folder of the subject.

3.2 Study Area

The study was conducted at O & G ward 2 Baiduri and 2 Akik of Hospital USM.

3.3 Study Period

Data collection has started after obtaining ethical approval from the Human Research Ethics Committee USM and the director of Hospital USM. Data collection took approximately 3 weeks which started from the mid of April 2021 until the end of April

2021 every day from 2.00 pm to 5.00 pm. Data entry and analysis were started in the end of April 2021. The flow chart of research was demonstrated in Figure 3.1.

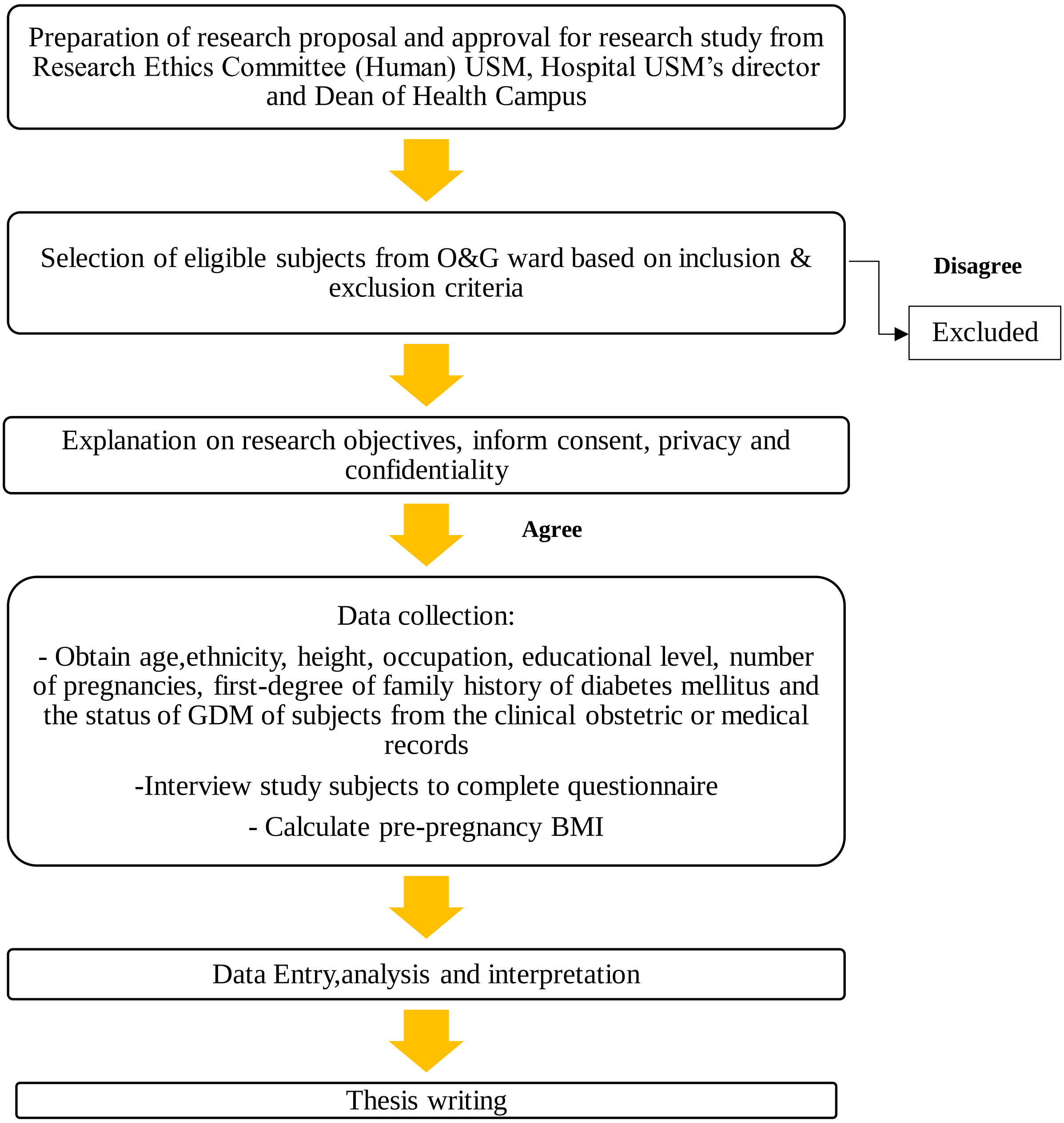

Figure 3.1: Study Flowchart

3.4 Study Population

The reference population of this study was pregnant women in Kelantan. The target population of the study was the pregnant women attending O & G ward in Hospital USM. Meanwhile, the pregnant women attending Hospital USM were the sampling pool of this study. The sampling frame of this study was the O&G ward attendance list for pregnant women.

3.5 Subject Criteria

3.5.1 Inclusion Criteria:

- Pregnant women
- Aged 18 years old and above
- Singleton pregnancy
- Have 75-g 2-h OGTT earlier or at 24 to 28 weeks of gestation
- Free from pre-existing diabetes mellitus
- Subject with complete height and pre-pregnancy weight data
- Able to give consent

3.5.2 Exclusion Criteria:

- Multiple pregnancies

3.6 Sampling Method and Subject Recruitment

The sampling strategy used in this study was the convenience sampling method. Convenience sampling is a type of non-probability sampling in which not every subject has an equal chance to be selected. The convenient sampling method is quick, cheap, and convenient to perform and it is most applicable and widely used in clinical research. The subjects were enrolled based on their availability and accessibility (Elfil, & Negida, 2017). The accessible population of this study was pregnant women attending the O&G ward of Hospital USM. Therefore, the pregnant women attending the O&G ward of Hospital USM and who met the eligibility criteria were asked to join this study, and consent was obtained from the subjects (Elfil, & Negida, 2017).

3.7 Sample Size Estimation

3.7.1 Sample Size Estimation for Specific Objective 1

Sample size to determine the pre-pregnancy BMI status among pregnant women attending the O & G ward in Hospital USM was calculated by using the formula as shown below.

$$n = \left[\frac{z}{\Delta}\right]^2 p(1-p)$$

n = sample size

z = value representing the desired confidence level

p = anticipated population proportion

Δ = precision

For this study, the level of confidence had been set at 95%. The Z-score value for the 95% confidence level was 1.96. It was estimated that the proportion of women having high pre-pregnancy BMI was 34.24 % from a previous local study (Ng *et al.*, 2019). Meanwhile, the precision rate has been set at 10%.

Sample size, n = $\left[\frac{Z}{\Delta}\right]^2 p(1-p)$

$= \left[\frac{1.96}{0.1}\right]^2 0.3424\ (1-0.3424)$

$= 86.5$

To account for potential dropouts, extra pregnant women were required to be enrolled in the study. Thus, a 20% dropout rate was applied to the sample size:

n = 86.5 + (86.5 x 20%)

= 103.8

≈ 104

3.7.2 Sample Size Estimation for Specific Objective 2

Sample size to determine the prevalence of GDM among pregnant women attending the O & G ward in Hospital USM was calculated by using the formula as shown below.

n = $\left[\frac{Z}{\Delta}\right]^2 p(1-p)$

n = sample size

z = value representing the desired confidence level

p = anticipated population proportion

Δ = precision

For this study, the level of confidence had been set at 95%. The Z-score value for the 95% confidence level was 1.96. It was estimated that the proportion of women having GDM from the previous local study was 27.9% (Logakodie *et al.*, 2017). Meanwhile, the precision rate has been set at 10%.

Sample size, n = $\left[\frac{Z}{\Delta}\right]^2 p(1-p)$

$= \left[\frac{1.96}{0.1}\right]^2 0.279(1-0.279)$

$= 77.3$

To account for potential dropouts, extra pregnant women were required to be enrolled in the study. Thus, a 20% dropout rate was applied to the sample size:

n = 77.3 + (77.3 x 20%)

= 92.76

≈ 93

3.7.3 Sample Size Estimation for Specific Objective 3

Sample size to identify the association between pre-pregnancy BMI and GDM among pregnant women attending the O & G ward in Hospital USM was calculated by using G*Power software version 3.1.9.2. Chi-square data used was based on a previous local study (Yong *et al*., 2020a). Type 1 error rate had been set at 5% and the power of the study had been set at 80%. The sample size estimation calculated by the software was 33.

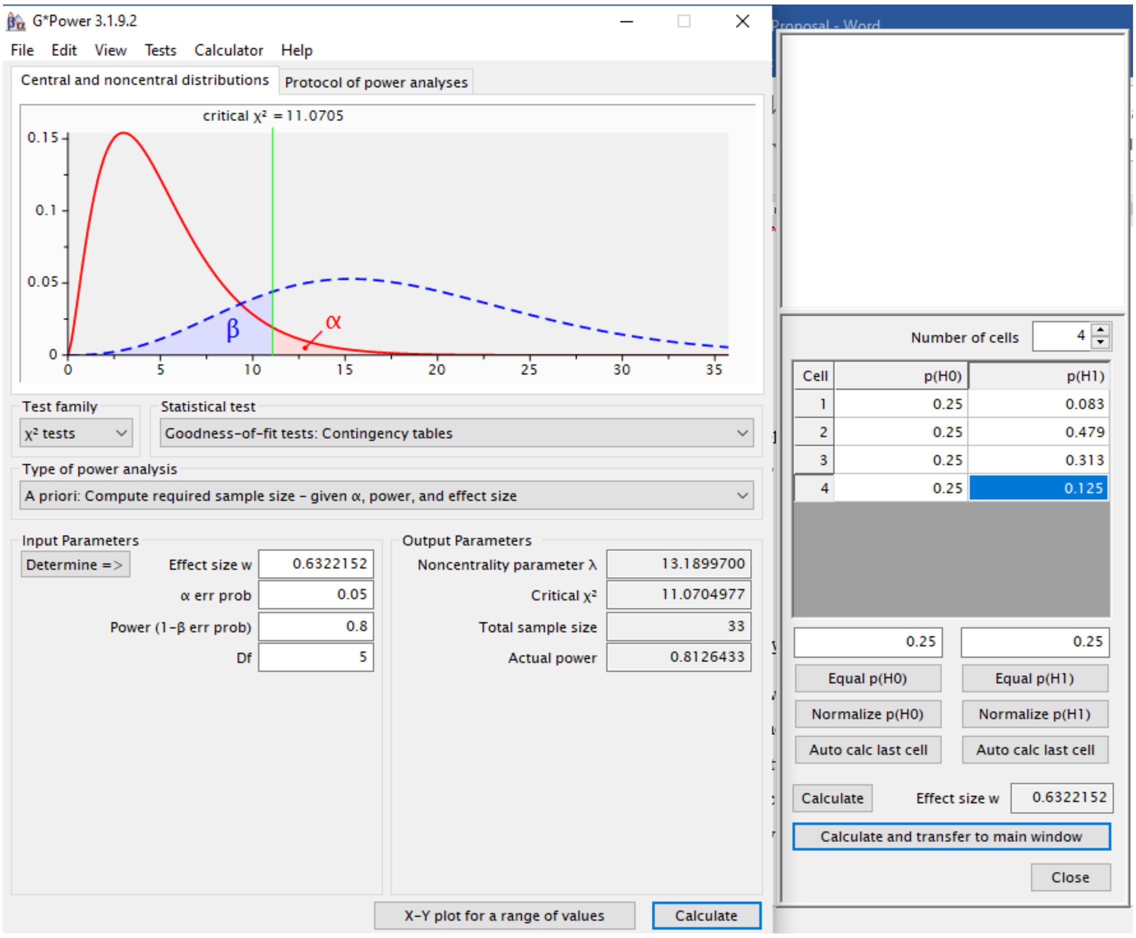

Figure 3.2: Sample size estimation by using G*Power software for specific objective 3.

To account for potential dropouts, extra pregnant women were required to be enrolled in the study. Thus, a 20% dropout rate was applied to the sample size:

$$n = 33 + (33 \times 20\%)$$

$$= 39.6$$

$$\approx 40$$

The sample size estimations for 3 specific objectives were ranged from 40 to 104. Therefore, it was decided that 104 pregnant women who fulfill the study inclusion and exclusion criteria were included in the study.