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Risk factors for the diagnosis of gestational diabetes mellitus in different trimesters and their relation to maternal and neonatal outcomes (GDM-RIDMAN): a retrospective cohort and nested case-control study

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Title: Risk factors for the diagnosis of gestational diabetes mellitus in different trimesters and their relation to maternal and neonatal outcomes (GDM-RIDMAN): a retrospective cohort and nested case-control study

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ABSTRACT (300 words)

Introduction: Gestational diabetes mellitus (GDM) is often associated with adverse pregnancy outcomes. All pregnant women are usually risk stratified for GDM screening according to a clinical practice guideline (CPG) on their first antenatal clinic visit. However, the association of the risk factors with GDM diagnosis, maternal and neonatal health outcomes is less established compared to women without GDM. We aims to examine the diagnostic accuracy of the latest Malaysian CPG-based risk factors and to examine novel risk factors for a GDM diagnosis in the first and second trimester, in relation to glucose regulation and impact on maternal and neonatal health outcomes.

Methods and analysis: This retrospective cohort and nested case-control study at six public health clinics in Selangor and Putrajaya is based on medical records, and questionnaire survey of women between 2-12 month postpartum. Estimated required sample size is 876 complete records (292 cases, 584 control, at a ratio of 1:2). An oral glucose tolerance test will be used to identify glucose dysregulation, and maternal and neonatal outcomes will include maternal weight gain, pre-eclampsia, polyhydramnios, mode of delivery, per-term birth, postpartum haemorrhage and perineal tear, and mode of birth, birth weight, gestational age at birth, Apgar score, congenital anomaly, congenital hypothyroidism, neonatal death or stillbirth, hypoglycaemia and hyperbilirubinemia. Psychosocial measures include the World Health Organization Quality of Life: Brief Version Questionnaire, mother-infant bonding (14-item Postpartum Bonding Questionnaire and 19-item Maternal Postnatal Attachment Scale), anxiety (7-item Generalized Anxiety Disorder), depression (9-item Patient Health Questionnaire), and stress (Perceived Stress Scale symptoms). Sociodemographic data and clinical variables will be analysed descriptively. Comparative incidences of maternal and neonatal health outcomes and the comparative prevalence of the psychosocial outcomes between women with GDM and without GDM will be reported. The current and novel GDM risk factors and outcomes will be modelled using multivariable regression analysis.

Keywords: gestational diabetes mellitus, risk factors, diagnosis, maternal and neonatal outcomes, antenatal care, postpartum, Malaysia
Article summary:

**Strengths and limitations of this study**

- This study provides an opportunity to confirm and explore the conventional CPG-based and potential new risk factors to better predict the diagnosis of GDM, either at the first or/and second trimester, and on maternal and neonatal outcomes.
- The effect of multiple pregnancies among other novel risk factors on the diagnosis of GDM which were often excluded from earlier studies will be examined.
- Results will suggest the best modelled risk profiles that predict the diagnosis of GDM that may lead to improved identification of at-risk women and allow earlier treatment initiation.
- Participants are mainly from the urban areas of Selangor and Putrajaya, and may not be representative of a larger population.
- Recruitment of fewer participants than expected could be due to the movement restriction and clinic operation caused by Covid-19 pandemic, reduced number of pregnancies and postpartum women, and limited by the study duration.
INTRODUCTION

Gestational diabetes mellitus (GDM) is a form of hyperglycaemia, where pregnant women experience glucose intolerance for the first time during the pregnancy\(^1-3\). Efficient GDM screening and accurate diagnosis allows early management and treatment could reduce adverse pregnancy outcomes for both mother and child\(^4-6\).

Asian women is at a higher risk for GDM compared to Caucasian women\(^7,8\). A systematic review and meta-analysis reported that the prevalence of GDM in Malaysia is in the top five Eastern and Southeast Asian countries with approximately one in nine pregnant women had GDM (11.8%)\(^8\). The latest National Obstetric Registry 2016-2017 reported the prevalence of GDM with adverse outcomes in Malaysia range from 10.8% to 19.3%\(^9\). Spontaneous miscarriage and caesarean section are the most frequently reported adverse outcomes in GDM women compared to healthy women, 5.9% vs. 2.6% and 28.5% vs. 18.8%, respectively\(^10\). Other adverse maternal outcomes include birth trauma, postpartum haemorrhage, pre-eclampsia, and hypertension (≥140/90 mmHg) after 20\(^{th}\) week of gestation with proteinuria\(^10,11\). Common neonatal adverse outcomes include foetal macrosomia, hypoglycaemia, prematurity, shoulder dystocia, hyperbilirubinemia and admission to intensive care units\(^11,12\). Prevalence of macrosomic babies and neonatal hypoglycaemia among GDM mother in Malaysia in 2018 are 4.8%, and 1.7%, respectively\(^12\). Post-diagnosis postprandial glucose levels are associated with macrosomia and large for gestational age (LGA), premature delivery, gestational hypertension and hyperbilirubinemia\(^13-15\).

At both the local and international level screening methods and diagnosis of GDM remains debatable. High fasting plasma glucose (FPG) level significantly increases the risk for LGA foetus, primary caesarean section and development of GDM in later pregnancy\(^16\). Several studies from Israel and Asian population supports FPG ≥6.10 mmol/L at first trimester as the predictor tools for GDM development in later pregnancy\(^17,18\). Another study in China suggested FPG 6.1-6.9 mmol/L were more accurate and reliable at early pregnancy (before 24\(^{th}\) week) for GDM diagnosis. This differs from the International Association of Diabetes and Pregnancy Study Group (IADPSG) cut-off values of FPG ≥5.1 mmol/L\(^18,19\). However, this is less well accepted because many perceive FPG ≥5.1 mmol/L is a false alarm, as pregnancy advance in week, FPG level decreases\(^18\). Glycosylated hemoglobin A1c (HbA1c) is not widely used in practice as the value can be unreliable due to many confounding conditions such as hemoglobinopathy\(^20\) although studies have shown the predictive value of HbA1c ≥6.0% of GDM development\(^5\) and adverse neonatal outcomes\(^10,21,22\).

Malaysia practices selective risk-based screening and one-step diagnosis for GDM for early diagnosis and management. All pregnant women will be risk stratified according to the Malaysia 2017 Clinical Practice Guidelines (CPG) on Management of Diabetes in Pregnancy\(^23\). Women who are perceived to be at risk of GDM will undergo 75g oral glucose tolerance test (OGTT) as immediately
as in the next appointment between 24th to 28th week of gestation\textsuperscript{23}. The test requires women to stay fasted from food and drink for at least 8 – 12 hours for FPG and 2 hours after the oral glucose intake. The one-step diagnosis approach of GDM will diagnose GDM when at least any one single abnormal reading is observed at fasting or 2-hour from 75g OGTT\textsuperscript{19,23,24}. There are some challenges in full OGTT compliance which include long hours of fasting, drinking of glucose water, vomiting and defaulting the 2-hour post-prandial (2-HPP) plasma glucose test\textsuperscript{25–27}. However, there is uncertainty in terms of the state of OGTT compliance and completion rate at the first or second trimester. Similarly, there is a lack of information about the completion rate of OGTT and its association with adverse pregnancy outcomes among pregnant women before the GDM diagnosis\textsuperscript{11}. Therefore, adherence of OGTT is equally important during and after pregnancy for GDM women.

The common risk factors of GDM include age \(\geq\)25 years old, body mass index >27 kg/m\(^2\), previous history of GDM, first degree relative with diabetes mellitus, history of macrosomia (birth weight >4 kg), bad obstetric history (unexplained intrauterine death, neural tube defects, cardiac defects and shoulder dystocia), glycosuria >2+ on two occasions, current obstetric problems (essential hypertension, pregnancy-induced hypertension (\(\geq\)140/90 mmHg), polyhydramnios and current use of corticosteroids\textsuperscript{23} (see Table 1). Other potential risk factors for GDM include polycystic ovarian syndrome (PCOS) (OR 2.33, 95% CI 1.72-3.17), multiple pregnancies (OR 1.37%, 95% CI 1.24-1.52), pre-term birth (OR 1.93, 95% CI 1.21-3.07)\textsuperscript{24}, maternal gestational weight gain (aOR 3.38%, 95% CI 1.83-6.24)\textsuperscript{28}, and maternal smoking status (OR 1.22, 95% CI 1.08 – 1.38)\textsuperscript{29}. The prevalence of PCOS among Malaysian working women age 18 – 49 years was 12.6%\textsuperscript{30} but PCOS is not consider as a risk factor in the Malaysian CPG. Multiple pregnancies is associated with higher risk for GDM due to a higher weight gain rather than the number of foetus\textsuperscript{31}. The rate of multiple pregnancies deliveries among GDM women in Malaysia range approximately from 12% to 30\%\textsuperscript{32,33}. Many GDM studies have excluded multiple pregnancies in their eligibility criteria, so the risk of multiple pregnancies on GDM is not clear. There are conflicting evidence on smoking and GDM\textsuperscript{34,35}.

**Psychosocial aspects in the postpartum period**

There is increasing evidence demonstrating that psychosocial factors, such as depressive symptoms, anxiety, high perceived stress, poor quality of life (QoL) and weakened mother-child bonding play an important role in GDM and adverse neonatal outcomes\textsuperscript{12,36–38}. A systematic review demonstrated that GDM respondents consistently showed significantly lower quality of life both short- and long-term compared to healthy pregnant participants\textsuperscript{37} and whereas the QoL scores significantly improved after pregnancy in healthy women, general health perception in GDM women remained significantly lower\textsuperscript{39,40}. The estimated prevalence of depression, anxiety, stress symptoms and poor QoL in GDM women in Malaysia ranges from 10.2% to 39.9\%\textsuperscript{12}. 
Additionally, the odds of GDM were found to be 13 folds higher among women experiencing high rates of perceived stress during pregnancy compared to those with low perceived stress among Indian women\textsuperscript{41}, suggesting that high perceived stress is a potential risk factor for GDM development. Similarly, a recent systematic review and meta-analysis investigating 62 studies indicated that there was an increased risk of depression and anxiety symptoms around the time of GDM diagnosis and in the postnatal period\textsuperscript{42}. Weakened mother-child bonding was previously shown to have a statistically significant association with mother’s depression and anxiety symptoms and these variables also affected mother-child bonding\textsuperscript{36}. Mother-child bonding is crucial to the mental growth and development of infants\textsuperscript{43}. Given the potential link between GDM and psychosocial factors, investigation and integration of physical and mental health factors in empirical studies and interventions with women experiencing GDM in Malaysia is therefore vitally important and could improve short- and long-term outcomes for women and their children\textsuperscript{42}.

**Conceptual framework**

The independent variables are risk factors of GDM including both the CPG-based (Table 1) and the potential risk factors (Table 2) based on the literature. The first dependent variables is the diagnosis of GDM in the first or second trimester as recorded on the maternal records. The second separate dependent variables in this study is the maternal and neonatal health outcomes including the maternal psychological wellbeing. The effect of glycaemic patterns after GDM diagnosis on the maternal and neonatal health outcomes is believed to be present and will be examined. Additionally, we aim to describe the incidences of the maternal and neonatal outcomes during pregnancy and in the postpartum period in women with GDM and without GDM. Figure 1 show the overall conceptual framework of this study.

Since there are uncertainties about the differences in risk factor profiles and the antenatal hyperglycaemia patterns, and also the difference on pregnancy outcomes of those who completed the OGTT in the first or second trimester with a GDM diagnosis, this study aims to examine and quantify the effects of the current recommended CPG-based risk factors for GDM diagnosis and to compare the risk factor profiles between those associated with GDM diagnoses at the first and second trimester. We will also examine the effects of other potential new risk factors on the actual diagnosis of GDM. Additionally, we will investigate the impacts of all the risk factors and the post-diagnosis blood sugar profiles on the maternal and neonatal outcomes.
METHOD AND ANALYSIS

This retrospective cohort and nested case-control study will be based on antenatal and postnatal medical records, and a questionnaire survey of postpartum women who delivered within the past 2-12 months. The five study objectives are:

1. To compare the risk factor profiles of women who undergone OGTT and diagnosed with GDM in the first and second trimesters.
2. To describe the occurrences of the maternal health outcomes during pregnancy and in the postpartum period between those with GDM and without GDM.
3. To describe the incidence of the neonatal health outcomes of mothers with GDM and without GDM.
4. To identify and quantify risk factors (including blood sugar profiles) that are associated with any maternal complications.
5. To identify and quantify risk factors (including blood sugar profiles) that are associated with any neonatal complications.

Settings

Data will be collected from six participating public health clinics in Selangor and Putrajaya over an approximately 5 months. These health clinics are attended by pregnant women of different ethnicities, provide maternal and childcare services with in-house laboratory services, and availability of GDM registry. The standard care processes in these clinics are that women will be seen by nurses and medical officers or a family medicine specialist when needed for a further care. GDM women usually have a follow-up appointment every two weeks for blood sugar level monitoring and pregnancy progress consultation. In post-partum, the appointment ranges from four to six weeks for family planning counselling and a repeat for the OGTT\textsuperscript{10,44}.

Pre-prandial and post-prandial glucose tests are blood sugar profile tests used for GDM monitoring. A pre-prandial plasma glucose should be ≤5.3 mmol/L\textsuperscript{23,45}, and post-prandial values at 1-hour and 2-hour are ≤7.8 mmol/L and ≤6.7 mmol/L to be considered as optimal, respectively\textsuperscript{23}.

Participants

The eligible participants are Malaysian women age ≥18 years old, had undergone OGTT during the last pregnancy, both singleton and multiple pregnancies, with a baby age at least two months and above (include pre-term birth between 23 – 37 week of gestation but chronological age at least two months) or has any miscarriage during last pregnancy, receiving most antenatal care at the participating clinics in the last pregnancy and return for a postnatal follow-up at the participating clinics. Malaysian women with pre-existing type 1 or type 2 diabetes and overt diabetes will be excluded from this study.

Instruments
GDM screening and diagnosis are based on the Malaysian 2017 CPG on Management of Diabetes in Pregnancy\textsuperscript{23}. Pregnant women with either one of the abnormal OGTT results, FPG $\geq 5.1$ mmol/L or 2-HPP $\geq 7.8$ mmol/L will be diagnosed as GDM\textsuperscript{23}. All data will be retrieved from the antenatal home-based record, and if necessary from the baby’s record book, clinic-based record, GDM registry book, healthcare electronic medical records and laboratory records that are available at each participating centre. If there is insufficient or missing data from the records, we may call the participants for clarification. All variables will be recorded in a structured case record form. All data retrieved will be labelled, stored safely in hard drive and locked with password. The independent and dependent variables include the following:

a. Mother’s risk factors: age $\geq 25$ years old, at booking BMI $> 27$ kg/m$^2$, history of GDM, first degree family with diabetes mellitus, previous baby with birth weight $> 4$ kg, bad obstetrics history (unexplained intrauterine death, congenital abnormalities as such neural tube defects, cardiac defects and shoulder dystocia), glycosuria $\geq 2+$ on two occasions, medical disorders (hypertension $\geq 140/90$ mmHg, polyhydramnios and on corticosteroid medication), multiple pregnancies, smoking status, miscarriage happens before 23 week on previous or most present pregnancy, and history of PCOS.

b. OGTT result, all blood sugar profiles (blood glucose testing performed at the clinic or home-monitoring) and HbA1c level.

c. Delivery records include:
   i. maternal outcomes (gestational weight gain, pre-eclampsia, polyhydramnios, mode of delivery, gestational age at birth (pre-term birth) and complication in pregnancy includes postpartum haemorrhage and perineal tear).
   ii. neonatal outcomes (mode of birth, birth weight, gestational age at birth (LGA or SGA), Apgar score, congenital anomaly, congenital hypothyroidism from TSH and T4 levels, neonatal death and stillbirth, hypoglycaemia from plasma glucose level, and hyperbilirubinemia from serum bilirubin level).

d. Psychosocial measures include quality of life\textsuperscript{46}, mother-infant bonding\textsuperscript{47–49}, anxiety and depression symptoms\textsuperscript{50,51}, and perceived stress\textsuperscript{52} (Table 3).

Cultural adaptation and validation process for questionnaires

The 14-item Postpartum Bonding Questionnaire (PBQ-14) and 19-item Maternal Postnatal Attachment Scale (MPAS-19) will be translated from English to Malay by bilingual translators. Two forward translations from English to Malay will be produced and then another bilingual translator will translate the scale back into English while being blinded to the original English version of the questionnaires\textsuperscript{63}. The two Malay versions for the scale will be compared with the original and back-
translated English version. Based on discussion and consensus by an expert committee, the most appropriate Malay version will be developed and chosen in this study. The expert committee comprises three Malay women with a history of GDM, bilingual (English and Malay) two family physicians, two psychologists and one obstetrician & gynaecologist.

Principal component analysis (PCA) will be used, utilising the Orthogonal rotation (Varimax) to determine the subscales. Preliminary analysis of the PCA output will be made to investigate multicollinearity, sampling adequacy using the Kaiser-Meyer-Olkin statistic and Bartlett’s test of sphericity. Internal consistency will be calculated with Cronbach’s alpha values for all subscales and 2-week test-retest reliability will be examined with intra-class correlation coefficients (ICC). A Cronbach’s alpha value of at least 0.75 indicates good internal consistency of the questionnaire. ICC of at least 0.7 is preferred for a sample size of >50 subjects to estimate the test-retest reliability.

To check for construct validity (hypothesis-testing validity), associations with GDM status, maternal outcomes (weight gain, pre-eclampsia, polyhydramnios, mode of delivery, pre-term birth, postpartum haemorrhage, perineal tear, retained placenta, postnatal OGTT result), neonatal outcomes (mode of birth, birth weight, Apgar score, congenital abnormalities, shoulder dystocia, neonatal hypothyroidism, neonatal hypoglycaemia, neonatal hyperbilirubinemia, admission to NICU) and the other psychosocial measures (WHOQOL-Bref, GAD-7, PHQ-9, and PSS-10) will be examined. Lastly, PBQ-14, and MPAS-19 will be examined against each other. We hypothesis that maternal feelings of bonding are moderately correlated ($r \geq 0.5$) and associated with maternal mood. All statistical analyses will use Statistical Package for Social Sciences (SPSS) version 26.0 (IBM, Chicago, IL) and p value >0.05 will be considered statistically significant.

**Sampling process**

Study will start at all six participating health clinics at the same time. All eligible participants will be invited to participate in the study. All women with GDM will be the study case. For every case of GDM, we will sample two control of women who had undergone OGTT in same clinic at about the same period of gestation but without a diagnosis of GDM. Women who consented and signed the consent form will leave their home-based health record for the researcher for a period of 1 – 2 months. They will self-administer the questionnaires (about 30 minutes to complete) in either Malay or English according to their preference and return it before they leave the clinic. A trained research assistant will be at each participating clinic to facilitate the data collection and to clarify query on the questionnaire. Every booklet will be inserted a bookmark with a unique code and kept in safe spaces in the clinics until collected data retrieval. In return, the participating women will receive a copy of the Participant Information Sheet, signed consent formed, and the same duplicate bookmark with the same code attached to their health record. The bookmark contains the study and the researcher contact information. Participants can request for early return of their home-based record at any time during the
study period, and it shall be returned to them immediately through the clinic or registered mail. At the end of the study, all home-based records will be returned to each clinic and the women will be informed for collection. They will present the duplicate bookmark for verification to collect their health records.

At each participating clinic, we will extract data from the OGTT records, and only request access to the health records of the consented patients to verify necessary information including the history of miscarriage or pre-term birth. Figure 2 show the overview of the procedures in data collection.

We will also re-invite at least 50 participants each from both women with GDM and without GDM to complete the PBQ-14 and MPAS-19 for the 2-week intra-rater test-retest reliability testing. Assuming 50% response rate, the first 100 women with and without GDM (total n= 200) will be invited to participate in this reliability test. The same questionnaire will be given to the selected participants in an envelope that contains a second self-addressed and stamped envelope. Completed questionnaire will be posted to the investigator. Additionally, we will send a Google form link to the questionnaires to the selected participants in the reminder message at 2-week.

**Sample size estimation**

Based on previous studies, the prevalence of GDM with adverse outcomes range from 5-27.9%. We use GPower 3.1.9.7 with 0.90 power and significance at two-sided $\alpha$ of 0.05 to estimate the smallest difference in maternal or neonatal complication rate between GDM with optimal glycaemic control and suboptimal control to be at 15%, the required sample size is 312 (104 cases, 208 control). On another estimation, the required sample size to estimate 10% (as the lowest possible proportion among all the risk factors) either the history of PCOS with the reported prevalence rate 12.6% or multiple pregnancies with reported incidence of 12-30% among GDM women with the power 0.90 and $\alpha$ 0.05 at two tails is 263. Taking into consideration of about 10% of incomplete or missing data in the home-based records, the sample size needed is 292 (263/0.90) cases and 584 (526) control at the ratio of 1:2. Knowing the average number of pregnancies at each of the six participating clinics (200-300 cases and 1500-3000 controls per year) and the required 1:10 ratio of independent variables to numbers of dependent variable to run a multiple logistic regression with 14 independent variables on GDM with any maternal or neonatal complication rate of 40%, the study is deemed feasible. Therefore, we will collect the home-based records from the postpartum women at the participating centres until at least 876 records have been collected.

**Data analysis plan**

All data analysis will use SPSS version 26.0 (IBM, Chicago, IL). Data entered will be cleaned and checked for the missing, extreme and suspicious values. These may be verified with the respondents or omitted as missing values. Once the missing data determined to be missing at random, multiple
imputations with ten runs may be conducted to replace the missing data. The complete case analysis will be conducted if the sample size achieves 789 at minimum.

We will use a descriptive analysis to summarize the sociodemographic data and clinical variables according to the diagnosis of GDM at first and second trimester at 24th to 28th weeks of gestation. All glycaemic biomarkers including blood sugar profiles will be reported in the trimesters according to the outcomes (normal vs. adverse). Comparisons of mean levels for continuous variables analyse using Student’s t-test and Chi-square test for categorical variables. The equivalent non-parametric tests will be used for data with non-normal distribution. We will report the proportion of postnatal women who had completed OGTT in the first trimester, those who completed OGTT in the second trimester and among each of this group the proportions offered OGTT twice or more (when they need to repeat the test).

To achieve the first objective, we will calculate the proportion of risk factors that are identified according to the trimester when GDM diagnosis is made. We will compare the risk factors profile of women completed OGTT and diagnosed GDM at first trimester to those undergone the OGTT but without GDM. A similar analysis will also be conducted to compare the risk factor profiles of women with and without GDM who were only offered OGTT during the second trimester and not in the first trimester. We will report the specificity, sensitivity, positive and negative predictive values of the CPG-based risk factors and to examine the novel risk factors, separately and combined, for a GDM diagnosis in the first and second trimester, respectively. Additionally, we will compare the risk factors profile of women diagnosed with GDM at the first and second trimester. We will model the risk factor profiles that best predict the GDM diagnosis at the first and second trimester, respectively, using multiple logistic regression.

We will report the comparative incidences of the maternal health outcomes during pregnancy and labour, and the comparative prevalence of the psychosocial outcomes in the postpartum period between the women with GDM and without GDM (second objective). Similarly, we will report the comparative incidences of the neonatal outcomes between the women with GDM and without GDM (third objective).

The fourth objective can be achieved by comparing the adjusted R² values of multivariable logistic regression models consisting of the CPG-based risk factors and models with the added new potential risk factors for GDM diagnosis, including the documented glycaemic biomarkers on the outcome of maternal complications as a whole or by each complication. If sample size allows, this analysis will be conducted separately for GDM diagnosed at first and second trimester to examine its effect on the maternal complications.

Analysis step to measure the fifth objective is similar as to the fourth objective by comparing the adjusted R² values of multivariable logistic regression models consisting of the CPG-based risk factors.
factors and models with the added new potential risk factors for GDM diagnosis, including documented glycaemic biomarkers on neonatal health outcomes.

The current risk factors for GDM will be assessed univariably and multivariably of their effect on the diagnosis of GDM at first and second trimester (24th to 28th weeks) using the $R^2$ and adjusted $R^2$. The factors from the demographic and clinical variables on each of the GDM diagnosis will be estimated in univariable logistic regression analyses. Any of this factor with a $P$-value $<$0.20 from will be included in the multiple logistics regression analysis. The analyses may be conducted by blocks of risk factors such as sociodemography (age, BMI and smoking), family history and past medical history, current antenatal medical problems (glycosuria, obstetric medical conditions and weight gain) if sample size is less than desirable. Multicollinearity between any independent variables will be checked according to the tolerance $<$0.4 (Variance inflation factors $\geq$2.5). In the presence of multicollinearity, the more critical or essential variable from clinical perspectives will be selected for use in the final regression analysis. All models, Q-Q plots for normality, the residual plots for linearity and homogeneity assumptions and model fitting will be checked. Same statistical strategy may be conducted to model the independent predictors on the maternal and neonatal outcomes. The maternal outcomes will be combined as a whole or separately if sample size allows, and the maternal psychosocial wellbeing measures will be analysed separately. Similarly, if sample size allows, we will analyse for the neonatal outcomes.

**Patient and Public Involvement**

This is one of non-experimental studies in the MYGODDESS Project (https://rb.gy/ccztw5) where women with GDM during pregnancy and in postpartum periods were interviewed on important barriers and facilitators of self-care. Women with a history of GDM are involved in the face and content validity testing of the PBQ-14 and MPAS-19 questionnaires. Their opinions on the study design, conduct, reporting and dissemination of results will be sought at appropriate time during the study.

**DISCUSSION**

This retrospective cohort study incorporates a nested case-control design, providing an opportunity to confirm and explore the conventional CPG-based and potential risk factors to better predict the diagnosis of GDM, either at the first or/and second trimester. This is one of the core outcomes to be included in GDM prevention and treatment research. Additionally, we will also examine multiple pregnancies on diagnosis of GDM, which was often excluded from earlier similar studies. The risk profiles that best predict the diagnosis of GDM will be modelled and examined of their impacts on the maternal and neonatal health outcomes. This evidence is imperative to improve the identification of at-risk women and earlier treatment for GDM. This study would help healthcare practitioners and women with GDM to better understand the effect of both the currently ‘recommended’ and potentially...
new' important risk factors of GDM, patterns of glycaemic control and association with health outcomes in both the women and neonates. Primarily, we may verify the diagnostic accuracy or to quantify the effect of the current CPG-based risk factors and potential risk factors on GDM diagnosis and on both maternal and neonatal health outcomes. This is potentially impactful on the decision rule of the existing practice. If a delay in the completion of OGTT is one of the possible causes of a delayed GDM diagnosis and treatment, the study would determine the level of OGTT completion, and identify the risk profiles of women and their association with any maternal and neonatal health outcomes. Additionally, the effect size of each individual risk factors and as a whole for GDM, glycaemic patterns during the pregnancy with GDM, and the maternal and neonatal health outcomes including psychosocial wellbeing will be quantified. Furthermore, this study would produce a locally culturally adapted and validated 14-item PBQ and the 19-item MPAS.

This study faces a few challenges. The incidence of some of the CPG-based and potential risk factors is low and may not getting the sufficient numbers for the multivariable regression analysis. The study expands the data source providers by including all the adjacent six public health clinics. This increases the demands of training and supervision of research assistants beside travelling time and coordinating effort between the clinics and university. In case of smaller than expected sample size recruited, we plan the multivariable regression analysis by separate blocks of risk factors. Secondly, the study participants are those receiving care at the public health clinics in the urban areas of Selangor and Putrajaya, thus they may not be representative of the larger Malaysian population. Owing to the Covid-19 pandemic and its effect aftermath, which may delay the data collection processes and a reduction in the number of participants of pregnant women visiting clinics in-person. The decreased in pregnancy in the past year would lower the number of postpartum women with a history of GDM this year. Another limitation of this study may be the quality and accuracy of the antenatal health records. However, we believe this problem is minimal with the many decades long use of the same antenatal records by all the healthcare providers in the public health clinics. The booklet is well-structured with dedicated spaces for the variables to be investigated in this study. We plan clarification and verification strategies to confirm the nature of the risk factors when present but unclear through calling up the women, checking the clinic-based or hospital-based records.

ETHICS AND DISSEMINATION

Risk Benefit Assessment

Participants are not subjected to any medications or treatments during the study period. Also there is no rescue medication or procedures involved. Therefore, there is no direct health risk or might be very least side effects to the participant as this is not an interventional study. There might be a potential risk of fatigue upon completion of the questionnaires. No direct benefit to participants and an honorarium

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of MYR 10.00 will be given. Their participation will provide data that improve understanding in the research topic that may help in the future protocol, guidelines or policymaking.

**Ethical consideration**

The study will be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Approval from the MREC ethics committee will be obtained. We will clearly explain and state the purpose of this study, also to obtain written consent in Malay or English from all study participants before data collection. Participation is voluntary. They have the right to withdraw at any stage of the research without giving any reason.

Should there be any further amendments to the protocol, other than administrative ones, further approval from the MREC ethics committee will be obtained. Any revisions of documents and amendment to the protocol originally submitted for review, unexpected events during the study period, and new information that may adversely affect the safety of participants and publication will duly be informed to the ethics committee.

**Privacy and Confidentiality**

Only researchers of this study have access to the participant’s data and it will be handled diligently only for this study’s purposes. Participant identity will not be revealed as no referencing of participants by name upon presenting the result. The identification number will be used on subject data sheets. All information in this study is confidential. Data from this study will be entered and saved on a dedicated computer that is password protected. Upon completion of the study, softcopy data in the computer will be copied to password protected pen drive and the data in the computer erased. Any hardcopy (including the consent form) and the pen drive will be keep in a locked office of the Principal Investigator’s office at UPM and maintained for a minimum of twenty years after the completion of the study. The collected data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database. The participants can write to the investigators to request access to the study findings.

**Data sharing statement**

Data sharing will be considered on a case-by-case basis upon assessment of the proposed study protocol.

**Publication Policy**

Participants personal information will not be disclosed, thus will not be identified when the findings of this research are published and presented.

**Dissemination plan**

Research findings will be published in scientific journals, may be presented in scientific conferences, and will be reported and shared with the local health stakeholders.
CONTRIBUTORSHIP STATEMENT

CBH, NIB, INS, and PY contributed to the study planning and design of the study. The study design was further developed by IP, VR, MB and CBH. PY drafted the manuscript with assistant from CBH and also input from various stages from NMN, ZAS, HH, FP, RZ, SRMA, NBIB, AF and KI. All authors critically reviewed the manuscript and approved the final version as submitted.

COMPETING INTERESTS / CONFLICT OF INTERESTS

None declared.

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DATA SHARING STATEMENT

Data are available upon reasonable request. Data sharing will be considered on a case-by-case basis upon assessment of the proposed study protocol.

ETHICAL APPROVAL

The project has been approved by the Malaysia Research Ethics Committee.
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TABLES

Table 1 The Malaysian Clinical Practice Guideline 2017 recommended risk factors for GDM screening

| Clinical Practice Guideline (CPG) Risk Factors: |
|------------------------------------------------|
| 1. Age ≥ 25 years old |
| 2. Body mass index > 27 kg/m² |
| 3. Previous history of GDM |
| 4. First degree relative with diabetes mellitus (DM) |
| 5. History of macrosomia (birth weight > 4 kg) |
| 6. Bad obstetric history (unexplained intrauterine death, neural tube defects, cardiac defects and shoulder dystocia) |
| 7. Glycosuria ≥ 2+ on two occasions |
| 8. Current obstetric problems (essential hypertension, pregnancy-induced hypertension (≥ 140/90 mmHg), polyhydramnios and current use of corticosteroids) |

Table 2 Potential new risk factors to be screened for GDM diagnosis and health outcomes

| Potential Risk Factors: |
|-------------------------|
| 1. History of PCOS |
| 2. Current multiple pregnancies |
| 3. Active or passive smoking status |
| 4. Miscarriage (before 23rd week) (previous and most present) |
| 5. Pre-term Birth (23rd to 36th week +6 days) (previous and most present) |
| 6. Gestational weight gain |
Table 3 Description of the questionnaires

| Questionnaire                                      | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Score range                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **The World Health Organization Quality of Life: Brief Version (WHOQOL-BREF Questionnaire)**[^46^] | The WHOQOL-BREF measure is an abbreviated 26-item version of the WHOQOL-100 questionnaire and measures 4 domains of quality of life (QoL): physical (7 items), psychological (6 items), social relationship (3 items) and environment (8 items) domains and 2 additional global items focusing on overall QoL. Four types of 5-point Likert interval scale are used, inquiring ‘how much’, ‘how often’, ‘how completely’, ‘how satisfied’ or ‘how good’ the respondent felt in the past 4-weeks, with different response scale distributed across the domains. Three negatively scored items are reversed scored (3, 4 and 26) and scores are summed up for each domain. Domain scores are computed by taking the mean of the scores and multiplied by 4 (and ranged from 4 to 20) to allow for direct comparison with the WHOQOL-100 scores. Higher domain scores indicate higher QoL. Malay version of this questionnaire showed high internal consistency with Cronbach’s alpha ranging from 0.82 to 0.89, which is comparable to the English-language version[^53^] Interclass Correlation Coefficient ranged from 0.58 to 0.69 across domains, indicating good test-retest reliability[^53^]. | Four types of 5-point Likert interval scale are used, inquiring ‘how much’, ‘how often’, ‘how completely’, ‘how satisfied’ or ‘how good’ the respondent felt in the past 4-weeks, with different response scale distributed across the domains. Three negatively scored items are reversed scored (3, 4 and 26) and scores are summed up for each domain. Domain scores are computed by taking the mean of the scores and multiplied by 4 (and ranged from 4 to 20) to allow for direct comparison with the WHOQOL-100 scores. Higher domain scores indicate higher QoL. Malay version of this questionnaire showed high internal consistency with Cronbach’s alpha ranging from 0.82 to 0.89, which is comparable to the English-language version[^53^] Interclass Correlation Coefficient ranged from 0.58 to 0.69 across domains, indicating good test-retest reliability[^53^]. |
| **The 14-item Postpartum Bonding Questionnaire (PBQ-14)[^47^,^48^]** | The PBQ measure will be used to assess the mother-infant relationship during the postpartum period, with a total of 14 items which are rated on a six-point Likert scale from 0 (always) to 5 (never) on four subscales indicating impaired bonding, rejection and anger, anxiety about care, and the risk of abuse. When the statement is reflecting negative emotion, the scoring is reversed. The summed total score ranges from 0 to 70, with low scores indicating good bonding. The PBQ has acceptable reliability and validity and as for its utility specifically in Asian countries, the measure has been previously tested and demonstrated high sensitivity of 83% and specificity of 96%^[^48^,^54^]. | Four types of 5-point Likert interval scale are used, inquiring ‘how much’, ‘how often’, ‘how completely’, ‘how satisfied’ or ‘how good’ the respondent felt in the past 4-weeks, with different response scale distributed across the domains. Three negatively scored items are reversed scored (3, 4 and 26) and scores are summed up for each domain. Domain scores are computed by taking the mean of the scores and multiplied by 4 (and ranged from 4 to 20) to allow for direct comparison with the WHOQOL-100 scores. Higher domain scores indicate higher QoL. Malay version of this questionnaire showed high internal consistency with Cronbach’s alpha ranging from 0.82 to 0.89, which is comparable to the English-language version[^53^] Interclass Correlation Coefficient ranged from 0.58 to 0.69 across domains, indicating good test-retest reliability[^53^]. |
| **The 19-item Maternal Postnatal Attachment Scale (MPAS-19)[^49^]** | MPAS is a 19-item self-report questionnaire designed to assess maternal emotional response towards her infant during the first year of life. There are three dimensions: 1) Quality of postnatal attachment (quality of the maternal feelings towards the infant as well as maternal confidence and satisfaction in being a mother); The three dimensions are considered to be independent but they can be combined to obtain a global attachment score (Total postnatal attachment). The scores on the “Quality” subscale range from 9 to 45, while the scores on the “Pleasure in interaction” and “Absence of hostility” subscales range from 5 to 25. Scores on the global attachment scale range from 19 to 95. Higher scores are generally indicative of stronger attachment but a specific cut-off is not provided[^49^]. | Four types of 5-point Likert interval scale are used, inquiring ‘how much’, ‘how often’, ‘how completely’, ‘how satisfied’ or ‘how good’ the respondent felt in the past 4-weeks, with different response scale distributed across the domains. Three negatively scored items are reversed scored (3, 4 and 26) and scores are summed up for each domain. Domain scores are computed by taking the mean of the scores and multiplied by 4 (and ranged from 4 to 20) to allow for direct comparison with the WHOQOL-100 scores. Higher domain scores indicate higher QoL. Malay version of this questionnaire showed high internal consistency with Cronbach’s alpha ranging from 0.82 to 0.89, which is comparable to the English-language version[^53^] Interclass Correlation Coefficient ranged from 0.58 to 0.69 across domains, indicating good test-retest reliability[^53^]. |
2) Absence of hostility (lack of resentment and negative feelings towards the infant) and 3) Pleasure in interaction (desire for proximity and interaction with the infant). Responses are scored on 1 (low attachment) to 5 (high attachment). 

| 7-item Generalized Anxiety Disorder (GAD-7)⁵⁰ | The GAD-7 is a 7-item questionnaire measuring the perceived frequency of generalised anxiety symptoms in the past 2-weeks. The items assess the most prominent diagnostic features of GAD. The items include nervousness, excessive worry, and inability to stop worrying. Restlessness, easy irritation, difficulty relaxing, and fear of something awful happening on response categories 'not at all', 'several days', 'more than half the days' and 'nearly every day' scored 0, 1, 2 and 3, respectively. The summed total score ranges from 0 to 21, with higher scores indicating more severe symptoms of anxiety. The Malay version of this questionnaire was found to be valid and reliable measure in women in Malaysia, with high sensitivity of 76% and a specificity of 94%.⁵⁶ |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| 7-item Generalized Anxiety Disorder (GAD-7)⁵⁰ | The GAD-7 is a 7-item questionnaire measuring the perceived frequency of generalised anxiety symptoms in the past 2-weeks. The items assess the most prominent diagnostic features of GAD. The items include nervousness, excessive worry, and inability to stop worrying. Restlessness, easy irritation, difficulty relaxing, and fear of something awful happening on response categories 'not at all', 'several days', 'more than half the days' and 'nearly every day' scored 0, 1, 2 and 3, respectively. The summed total score ranges from 0 to 21, with higher scores indicating more severe symptoms of anxiety. The Malay version of this questionnaire was found to be valid and reliable measure in women in Malaysia, with high sensitivity of 76% and a specificity of 94%.⁵⁶ | Scores range from 0 to 27, as each of the nine items is scored from 0 (not at all) to 3 (nearly every day). PHQ-9 scores of 5, 10, 15, and 20 represents mild, moderate, moderately severe, and severe depression, respectively. This questionnaire was found to be a valid and reliable instrument to measure depression, with high sensitivity 87% and specificity of 82% in Malaysia.⁵⁷ Good internal reliability with a Cronbach’s alpha of 0.67 and test-retest reliability of 0.73 were also demonstrated in this population.⁵⁸ |
| Patient Health Questionnaire (PHQ-9)⁵¹ | Nine items refer to symptoms experienced by patients during the two weeks prior to answering the questionnaire in making diagnosis and assessing severity of depression. The total score is calculated by reversing the responses for the 4 positively stated items (4, 5, 7 and 8) and then summing across all 10 items. The total score can range from 0 to 56, with higher score representing greater perceived levels of stress. This scale was previously utilised in Malaysian diabetic patients, medical students, working population, and female prisoners in Malaysia and showed comparable psychometric properties to the original English version, with Cronbach’s alpha from 0.63 to 0.85 and high test-retest reliability of r = .72. |
| The Perceived Stress Scale (PSS)⁵² | The Perceived Stress Scale (PSS) measure has 10 items on a 5-point Likert scale ranging from 0 (never) to 4 (very often), assessing the perceived stress levels in the past 4-weeks. The total score is calculated by reversing the responses for the 4 positively stated items (4, 5, 7 and 8) and then summing across all 10 items. The total score can range from 0 to 56, with higher score representing greater perceived levels of stress. This scale was previously utilised in Malaysian diabetic patients, medical students, working population, and female prisoners in Malaysia and showed comparable psychometric properties to the original English version, with Cronbach’s alpha from 0.63 to 0.85 and high test-retest reliability of r = .72. |
FIGURE LEGEND / CAPTION

Figure 1: Risk factors for the diagnosis of gestational diabetes mellitus in different trimester and their relation to maternal and neonatal outcomes

Figure 2: Overview of the procedure in data collection
LIST OF ABBREVIATIONS

BMI    Body Mass Index
CPG    Clinical Practice Guideline
DM     Diabetes Mellitus
FPG    Fasting Plasma Glucose
GAD-7  7-item Generalized Anxiety Disorder
GDM    Gestational Diabetes Mellitus
HBA1C  Glycosylated hemoglobin A1c
2-HPP  2-Hour Post-Prandial
IADPSG International Association of Diabetes and Pregnancy Study Group
LGA    Large for Gestational Age
MREC   Malaysia Research Ethics Committee
NMRR   National Medical Research Registration
MPAS-19 19-item Maternal Postnatal Attachment Scale
OGTT   Oral Glucose Tolerance Test
PBQ-14 14-item Postpartum Bonding Questionnaire
PCA    Principal component analysis
PCOS   Polycystic Ovarian Syndrome
PHQ-9  9-item Patient Health Questionnaire
PPH    Postpartum Haemorrhage
PSS    Perceived Stress Scale
QoL    Quality of Life
SGA    Small for Gestational Age
TSH    Thyroid Stimulating Hormone
T4     Thyroxine
WHOQOL World Health Organization Quality of Life
Figure 1: Risk factors for the diagnosis of gestational diabetes mellitus in different trimester and their relation to maternal and neonatal outcomes

Health outcomes

(Maternal outcomes)
- Weight gain
- Pre-eclampsia
- Polyhydramnios
- Mode of delivery
- Pre-term birth
- Postpartum Haemorrhage
- Perinatal tear
- Retained Placenta
- Postnatal OGTT
- Psychosocial wellbeing

(Neonatal outcomes)
- Mode of birth
- Birth Weight
- LGA or SGA
- Apgar Score
- Congenital Abnormalities
- Shoulder Dystocia
- Neonatal Hypothyroidism (TSH & T4 value)
- Neonatal Hypoglycaemia (glucose value)
- Neonatal Hyperbilirubinemia (SB value)
- Neonatal Death
- Stillbirth
- Admission to NICU

Risk factor profiles
- CPG-based risk factors
- Potential risk factors

Women Diagnosed GDM

75g OGTT done;
- at first trimester only
- at 24th – 28th week only
- at first trimester & at 24th-28th week

Glycaemic patterns in HbA1c, FPG, BG at clinic, SMBG at home

A: the association between risk factor profiles and OGTT of GDM women at different trimester
B: the association between glycaemic patterns after GDM diagnosis on maternal and neonatal health outcomes
C: the association between risk factors, blood sugar profiles on maternal and neonatal health outcomes

*CPG=Clinical Practice Guidelines, FPG=Fasting Plasma Glucose, BG=Blood Glucose, SMBG=Self-Monitoring Blood Glucose, OGTT=Oral Glucose Tolerance Test, LGA=Large Gestational Age, SGA=Small Gestational Age, TSH=Thyroid Stimulating Hormone, T4=Thyroxine, SB=Serum Bilirubin, NICU=Neonatal Intensive Care Unit
Figure 2: Overview of the procedure in data collection

All women at least two months postpartum, include women with a miscarriage who attended public health clinic (KKS, KKPch, KKP9, KKP18, KKKjg, KKB) for their postnatal check-up & baby’s immunization will be recruited.

Exclude those who do not meet the eligibility criteria

Approach for agreement & consent, collect the home-based antenatal booklet from consented participants and distribute psychosocial questionnaires

Completed psychosocial questionnaires returned and retrieve data/records (if necessary also from the clinic-based antenatal record and other records from clinic)

2-week intra-rater test-retest reliability testing for the 14-item Postpartum Bonding Questionnaire & the 19-item Maternal Postnatal Attachment Scale in a self-addressed postal envelope, to be completed and returned, or through an online form of the same questionnaires.

May call the participants for clarification on missing information from the home-based antenatal booklet, if required

Return of the home-based antenatal booklet

Data Analysis

Data Reporting

* KKP9= Klinik Kesihatan Precint 9; KKP18= Klinik Kesihatan Precint 18; KKS= Klinik Kesihatan Seri Kembangan; KKPch= Klinik Kesihatan Puchong; KKKjg= Klinik Kesihatan Kajang; KKB=Klinik Kesihatan Bangi
| Item No | Recommendation |
|--------|----------------|
| 1 | *(a)* Indicate the study’s design with a commonly used term in the title or the abstract |
| 2 | *(b)* Provide in the abstract an informative and balanced summary of what was done and what was found |
| 3 | **Title and abstract** |
| 4 | **Introduction** |
| 5 | Explain the scientific background and rationale for the investigation being reported |
| 6 | 4-7 |
| 7 | **Objectives** |
| 8 | State specific objectives, including any prespecified hypotheses |
| 9 | 8 |
| 10 | **Methods** |
| 11 | **Participants** |
| 12 | 6 |
| 13 | *(a)* Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up |
| 14 | *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls |
| 15 | *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| 16 | **Variables** |
| 17 | 7 |
| 18 | *(b)* Cohort study—For matched studies, give matching criteria and number of exposed and unexposed |
| 19 | *Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| 20 | **Data sources/measurement** |
| 21 | 8* |
| 22 | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| 23 | **Bias** |
| 24 | 9 |
| 25 | Describe any efforts to address potential sources of bias |
| 26 | **Study size** |
| 27 | 10 |
| 28 | Explain how the study size was arrived at |
| 29 | **Quantitative variables** |
| 30 | 11 |
| 31 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| 32 | **Statistical methods** |
| 33 | 12 |
| 34 | *(a)* Describe all statistical methods, including those used to control for confounding |
| 35 | *(b)* Describe any methods used to examine subgroups and interactions |
| 36 | *(c)* Explain how missing data were addressed |
| 37 | *(d)* Cohort study—If applicable, explain how loss to follow-up was addressed |
| 38 | *Case-control study*—If applicable, explain how matching of cases and controls was addressed |
| 39 | *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| 40 | *(e)* Describe any sensitivity analyses |

Continued on next page
### Results

| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | na |
| | | (b) Give reasons for non-participation at each stage | na |
| | | (c) Consider use of a flow diagram | na |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | na |
| | | (b) Indicate number of participants with missing data for each variable of interest | na |
| | | (c) Cohort study—Summarise follow-up time (eg, average and total amount) | na |
| Outcome data | 15* | Cohort study—Report numbers of outcome events or summary measures over time | na |
| | | Case-control study—Report numbers in each exposure category, or summary measures of exposure | na |
| | | Cross-sectional study—Report numbers of outcome events or summary measures | na |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | na |
| | | (b) Report category boundaries when continuous variables were categorized | na |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | na |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | na |

### Discussion

| Key results | 18 | Summarise key results with reference to study objectives | na |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 13-14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | na |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | na |

### Other information

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 22 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.
**Study protocol on Risk factors for the diagnosis of gestational diabetes mellitus in different trimesters and their relation to maternal and neonatal outcomes (GDM-RIDMAN)**

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| Keywords:               | Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Clinical chemistry < PATHOLOGY, Depression & mood disorders < PSYCHIATRY |
RevisedGDM-RIDMAN study protocol_bmjopen-2021-052554.R1

Title: Study protocol on Risk factors for the diagnosis of gestational diabetes mellitus in different trimesters and their relation to maternal and neonatal outcomes (GDM-RIDMAN)

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ABSTRACT (299/300 words)

Introduction: Gestational diabetes mellitus (GDM) is often associated with adverse pregnancy outcomes. However, the association of risk factors with GDM diagnosis, maternal and neonatal health outcomes is less established when compared to women without GDM. We will aim to examine the diagnostic accuracy of the conventional and novel risk factors for a GDM diagnosis, and their impact on maternal and neonatal health outcomes.

Methods and analysis: This retrospective cohort and nested case-control study at six public health clinics is based on medical records, and questionnaire survey of women between 2-12 months postpartum. The estimated required sample size is 876 complete records (292 cases, 584 control, at a ratio of 1:2). Oral glucose tolerance test results will be used to identify glucose dysregulation, and maternal and neonatal outcomes include maternal weight gain, pre-eclampsia, polyhydramnios, mode of delivery, pre-term or post-date birth, complications in labour, birth weight, gestational age at birth, Apgar score, congenital anomaly, congenital hypothyroidism, neonatal death or stillbirth, hypoglycaemia and hyperbilirubinemia. Psychosocial measures include the World Health Organization Quality of Life: Brief, mother-infant bonding (14-item Postpartum Bonding Questionnaire and 19-item Maternal Postnatal Attachment Scale), anxiety (7-item Generalized Anxiety Disorder), depression (9-item Patient Health Questionnaire), and stress (Perceived Stress Scale symptoms) questionnaires. The comparative incidences of maternal and neonatal health outcomes, the comparative prevalence of the psychosocial outcomes between women with GDM and without GDM, specificity, sensitivity, positive and negative predictive values of the risk factors, separately and combined, will be reported. All GDM risk factors and outcomes will be modelled using multivariable regression analysis and the receiver operating characteristics curve will be reported.

Ethics and dissemination: This study was approved by the Malaysia Research and Ethics Committee, Ministry of Health Malaysia. Informed consent will be obtained from all participants. Findings will be submitted for publications in scientific journals.

Keywords: gestational diabetes mellitus, risk factors, diagnosis, maternal and neonatal outcomes, antenatal care, postpartum, Malaysia
Strengths and limitations of this study

- This study provides an opportunity to confirm and explore the conventional risk factors to better predict the diagnosis of GDM.
- Quality of life, mental health and maternal-infant bonding will be assessed during the COVID-19 pandemic.
- Participants are mainly from the urban areas of Selangor and Putrajaya and may not be representative of a larger population.
- The incidence of some of the risk factors may be low and insufficient for inclusion into multivariable regression analysis.
- Recruitment of fewer participants than expected due to the COVID-19 pandemic and the reduced number of pregnancies and postpartum women visiting clinics in-person may introduce challenges in data collection, analysis and interpretation.
INTRODUCTION

Gestational diabetes mellitus (GDM) is a form of hyperglycaemia, where pregnant women experience glucose intolerance for the first time during the pregnancy. Efficient GDM screening and accurate diagnosis allows for early management and treatment which could reduce adverse pregnancy outcomes for both mother and child.

Asian women are at a higher risk for GDM compared to Caucasian women. A systematic review and meta-analysis reported that the prevalence of GDM in Malaysia is in the top five Eastern and Southeast Asian countries where approximately one in nine pregnant women had GDM (11.8%). The latest National Obstetric Registry 2016-2017 reported the prevalence of GDM with adverse outcomes in Malaysia range from 10.8% to 19.3%. Spontaneous miscarriage and caesarean section are the most frequently reported adverse outcomes in GDM women compared to healthy women, 5.9% vs. 2.6% and 28.5% vs. 18.8%, respectively. Other adverse maternal outcomes include birth trauma, postpartum haemorrhage, pre-eclampsia, and hypertension (≥140/90 mmHg) after the 20th week of gestation with proteinuria. Common neonatal adverse outcomes include foetal macrosomia, hypoglycaemia, prematurity, shoulder dystocia, hyperbilirubinemia and admission to intensive care units. Prevalence of macrosomic babies and neonatal hypoglycaemia among GDM mothers in Malaysia in 2018 are 4.8%, and 1.7%, respectively. Post-diagnosis postprandial glucose levels are associated with macrosomia and large for gestational age (LGA), premature delivery, gestational hypertension and hyperbilirubinemia.

At both the local and international level, screening methods and diagnosis of GDM remains debatable. High fasting plasma glucose (FPG) level significantly increases the risk for LGA foetus, primary caesarean section and development of GDM in later pregnancy. Several studies from Israel and Asian population supports FPG ≥6.10 mmol/L at first trimester as the predictor tools for GDM development in later pregnancy. Another study in China suggested FPG 6.1-6.9 mmol/L were more accurate and reliable at early pregnancy (before the 24th week) for GDM diagnosis. This differs from the International Association of Diabetes and Pregnancy Study Group (IADPSG) cut-off values of FPG ≥5.1 mmol/L. However, this is less well accepted because many perceive FPG ≥5.1 mmol/L to be a false alarm, as when pregnancy advances in a week, FPG level decreases. Glycosylated haemoglobin A1c (HbA1c) is not widely used in practice as the value can be unreliable due to many confounding conditions such as hemoglobinopathy. Although studies have shown the predictive value of HbA1c ≥6.0% of GDM development and adverse neonatal outcomes.

Malaysia practices selective risk-based screening and one-step diagnosis for GDM for early diagnosis and management. All pregnant women will be risk stratified according to the Malaysia 2017 Clinical Practice Guidelines (CPG) on Management of Diabetes in Pregnancy. Women who are perceived to be at risk of GDM will undergo 75g oral glucose tolerance test (OGTT) as soon as the
next appointment between the 24th to 28th week of gestation. The test requires women to stay fasted from food and drink for at least 8 – 12 hours for FPG and 2 hours after the oral glucose intake. The one-step diagnosis approach of GDM will diagnose GDM when at least any one single abnormal reading is observed at fasting or 2-hour from 75g OGTT. There are some challenges in full OGTT compliance which include long hours of fasting, drinking of glucose water, vomiting and defaulting the 2-hour post-prandial (2-HPP) plasma glucose test. However, there is uncertainty in terms of the state of OGTT compliance and completion rate during the first or second trimester. Similarly, there is a lack of information about the completion rate of OGTT and its association with adverse pregnancy outcomes among pregnant women before the GDM diagnosis. Therefore, adherence of OGTT is equally important during and after pregnancy for GDM women.

The common risk factors of GDM include age ≥25 years old, body mass index >27 kg/m², previous history of GDM, first degree relative with diabetes mellitus, history of macrosomia (birth weight >4 kg), bad obstetric history (unexplained intrauterine death, neural tube defects, cardiac defects and shoulder dystocia), glycosuria ≥2+ on two occasions, current obstetric problems (essential hypertension, pregnancy-induced hypertension (≥140/90 mmHg), polyhydramnios and current use of corticosteroids (see Table 1). Other potential risk factors for GDM include polycystic ovarian syndrome (PCOS) (OR 2.33, 95% CI 1.72-3.17), multiple pregnancies (OR 1.37%, 95% CI 1.24-1.52), pre-term birth (OR 1.93, 95% CI 1.21-3.07)²⁴, maternal gestational weight gain (aOR 3.38%, 95% CI 1.83-6.24)²⁸, and maternal smoking status (OR 1.22, 95% CI 1.08 – 1.38)²⁹. The prevalence of PCOS among Malaysian working women age 18 – 49 years was 12.6 % but PCOS is not considered to be a risk factor in the Malaysian CPG. Multiple pregnancies is associated with higher risk for GDM due to a higher weight gain rather than the number of foetus. The rate of multiple pregnancy deliveries among GDM women in Malaysia range approximately from 12% to 30%. Many GDM studies have excluded multiple pregnancies in their eligibility criteria, so the risk of multiple pregnancies on GDM is not clear. There is conflicting evidence on smoking and GDM.

Psychosocial aspects in the postpartum period

There is increasing evidence demonstrating that psychosocial factors, such as depressive symptoms, anxiety, high perceived stress, poor quality of life (QoL) and weakened mother-child bonding play an important role in GDM and adverse neonatal outcomes. A systematic review demonstrated that GDM respondents consistently showed significantly lower quality of life both short- and long-term compared to healthy pregnant participants. Although the QoL scores significantly improved after pregnancy in healthy women, general health perception in GDM women remained significantly lower. The estimated prevalence of depression, anxiety, stress symptoms and poor QoL in GDM women in Malaysia ranges from 10.2% to 39.9%.
Additionally, the odds of GDM were found to be 13-fold higher in women with high stress levels during pregnancy than in women with low stress levels among Indian women\textsuperscript{41}, suggesting that high perceived stress is a potential risk factor for GDM development. Similarly, a recent systematic review and meta-analysis investigating 62 studies indicated that there was an increased risk of depression and anxiety symptoms around the time of GDM diagnosis and in the postnatal period\textsuperscript{42}. Weakened mother-child bonding was previously shown to have a statistically significant association with the mother’s depression and anxiety symptoms and these variables also affected mother-child bonding\textsuperscript{36}. Mother-child bonding is crucial to the mental growth and development of infants\textsuperscript{43}. Given the potential link between GDM and psychosocial factors, investigation and integration of physical and mental health factors in empirical studies and interventions with women experiencing GDM in Malaysia is therefore vitally important and could improve short- and long-term outcomes for women and their children\textsuperscript{42}.

**Conceptual framework**

The independent variables are risk factors of GDM including both the CPG-based (Table 1) and the potential risk factors (Table 2) based on the literature. The first dependent variables are the diagnosis of GDM in the first or second trimester as recorded in the maternal records. The second separate dependent variables in this study are the maternal and neonatal health outcomes including the maternal psychological wellbeing. The effect of glycaemic patterns after GDM diagnosis on the maternal and neonatal health outcomes is believed to be present and will be examined. Additionally, we aim to describe the incidences of the maternal and neonatal outcomes during pregnancy and in the postpartum period in women with GDM and without GDM. Figure 1 shows the overall conceptual framework of this study.

There are uncertainties about the differences in risk factor profiles, the antenatal hyperglycaemia patterns, and also the difference on pregnancy outcomes of those who completed the OGTT in the first or second trimester with a GDM diagnosis. Therefore, this study aims to examine and quantify the effects of the current recommended CPG-based risk factors for GDM diagnosis and to compare the risk factor profiles between those associated with GDM diagnoses in the first and second trimester. We will also examine the effects of other potential new risk factors on the actual diagnosis of GDM. Additionally, we will investigate the impacts of all the risk factors and the post-diagnosis blood sugar profiles on the maternal and neonatal outcomes.
METHOD AND ANALYSIS

This retrospective cohort and nested case-control study will be based on antenatal and postnatal medical records, and will include a questionnaire survey of postpartum women who have delivered within the past 2-12 months. The five study objectives are:

1. To compare the risk factor profiles of women who have undergone OGTT and have been diagnosed with GDM in the first and second trimesters.
2. To describe the occurrences of the maternal health outcomes during pregnancy and in the postpartum period between those with GDM and without GDM.
3. To describe the incidence of the neonatal health outcomes of mothers with GDM and without GDM.
4. To identify and quantify risk factors (including blood sugar profiles) that are associated with any maternal complications.
5. To identify and quantify risk factors (including blood sugar profiles) that are associated with any neonatal complications.

Settings

Data will be collected from six participating public health clinics in Selangor and Putrajaya over approximately 5 months. These clinics are attended by pregnant women of different ethnicities and will provide maternal and childcare services with in-house laboratory services, and availability of GDM registry. The standard care processes in these clinics are that women will be seen by nurses and medical officers or a family medicine specialist when needed for further care. GDM women usually have a follow-up appointment every two weeks for blood sugar level monitoring and pregnancy progress consultation. In post-partum, the appointment ranges from four to six weeks for family planning counselling and a repeat for the OGTT. Pre-prandial and post-prandial glucose tests are blood sugar profile tests used for GDM monitoring. A pre-prandial plasma glucose should be \( \leq 5.3 \, \text{mmol/L} \) and post-prandial values at 1-hour and 2-hour are \( \leq 7.8 \, \text{mmol/L} \) and \( \leq 6.7 \, \text{mmol/L} \) to be considered as optimal, respectively.

Participants

The eligible participants are Malaysian women age \( \geq 18 \) years old who have undergone OGTT during the last pregnancy, both singleton and multiple pregnancies, with a baby aged at least two months and above (include pre-term birth between 23 – 37 week of gestation but chronological age at least two months) or who have had a miscarriage during last pregnancy, receiving most antenatal care at the participating clinics during the last pregnancy and who have returned for a postnatal follow-up at the participating clinics. Malaysian women with pre-existing type 1 or type 2 diabetes and overt diabetes will be excluded from this study.
Instruments

GDM screening and diagnosis are based on the Malaysian 2017 CPG on Management of Diabetes in Pregnancy\textsuperscript{23}. Pregnant women with either one of the abnormal OGTT results, FPG \( \geq 5.1 \) mmol/L or 2-HPP \( \geq 7.8 \) mmol/L will be diagnosed as GDM\textsuperscript{23}. All data will be retrieved from the antenatal home-based record, and if necessary, from the baby’s record book, clinic-based record, GDM registry book, healthcare electronic medical records and laboratory records that are available at each participating centre. If there is insufficient or missing data from the records, we may call the participants for clarification. All variables will be recorded in a structured case record form. All data retrieved will be labelled, stored safely in hard drive and password protected. The independent and dependent variables include the following:

a. Mother’s risk factors: age \( \geq 25 \) years old, at booking BMI \( >27 \) kg/m\(^2\), history of GDM, first degree family with diabetes mellitus, previous baby with birth weight \( >4 \) kg, poor obstetrics medical history (unexplained intrauterine death, congenital abnormalities as such neural tube defects, cardiac defects and shoulder dystocia), glycosuria \( \geq 2+ \) on two occasions, medical disorders (hypertension \( \geq 140/90 \) mmHg, polyhydramnios and on corticosteroid medication), multiple pregnancies, smoking status, miscarriage occurring before 23 weeks during the previous or most present pregnancy, and history of PCOS.

b. OGTT result, all blood sugar profiles (blood glucose testing performed at the clinic or home-monitoring) and HbA1c level.

c. Delivery records include:
   i. maternal outcomes (gestational weight gain, pre-eclampsia, polyhydramnios, mode of delivery, gestational age at birth either pre-term or post-date birth and complications in labour including postpartum haemorrhage and perineal tear).
   ii. neonatal outcomes (birth weight, gestational weight at birth either LGA or SGA, Apgar score, congenital anomaly, congenital hypothyroidism from TSH and T4 levels, neonatal death and stillbirth, hypoglycaemia from plasma glucose level, and hyperbilirubinemia from serum bilirubin level).

d. Psychosocial measures include quality of life\textsuperscript{46}, mother-infant bonding\textsuperscript{47–49}, anxiety and depression symptoms\textsuperscript{50,51}, and perceived stress\textsuperscript{52} (Table 3).

Cultural adaptation and validation process for questionnaires

The 14-item Postpartum Bonding Questionnaire (PBQ-14) and 19-item Maternal Postnatal Attachment Scale (MPAS-19) will be translated from English to Malay by bilingual translators. Two forward translations from English to Malay will be produced and then another bilingual translator will translate the scale back into English while being blinded to the original English version of the
questionnaires\textsuperscript{53}. The two Malay versions for the scale will be compared with the original and back-translated English version. Based on discussion and consensus by an expert committee, the most appropriate Malay version will be developed and chosen in this study. The expert committee comprises three Malay women with a history of GDM, bilingual (English and Malay) two family physicians, two psychologists and one obstetrician & gynaecologist.

Principal component analysis (PCA) will be used, utilising the Orthogonal rotation (Varimax) to determine the subscales. Preliminary analysis of the PCA output will be made to investigate multicollinearity, sampling adequacy using the Kaiser-Meyer-Olkin statistic and Bartlett’s test of sphericity. Internal consistency will be calculated with Cronbach’s alpha values for all subscales and 2-week test-retest reliability will be examined with intra-class correlation coefficients (ICC). A Cronbach’s alpha value of at least 0.75 indicates good internal consistency of the questionnaire\textsuperscript{54}. ICC of at least 0.7 is preferred for a sample size of $>$50 subjects to estimate the test–retest reliability\textsuperscript{55,56}.

To check for construct validity (hypothesis-testing validity)\textsuperscript{57}, associations with GDM status, maternal outcomes (weight gain, pre-eclampsia, polyhydramnios, mode of delivery, pre-term or post-date birth, postpartum haemorrhage, perineal tear, retained placenta, postnatal OGTT result), neonatal outcomes (birth weight, LGA or SGA, Apgar score, congenital abnormalities, shoulder dystocia, neonatal hypothyroidism, neonatal hypoglycaemia, neonatal hyperbilirubinemia, admission to NICU) and the other psychosocial measures (WHOQOL-Bref, GAD-7, PHQ-9, and PSS-10) will be examined. Lastly, PBQ-14, and MPAS-19 will be examined against each other. We hypothesise that maternal feelings of bonding are moderately correlated ($r \geq 0.5$) and associated with maternal mood\textsuperscript{58,59}. All statistical analyses will use Statistical Package for Social Sciences (SPSS) version 26.0 (IBM, Chicago, IL) and p value $>$0.05 will be considered statistically significant.

\textit{Sampling process}

The study will take place at all six participating health clinics at the same time. All eligible participants will be invited to participate in the study. All women with GDM will be the case. Two control will be sampled for each case. Women in the control group were selected based on the eligibility criteria from the same six health clinics who had undergone OGTT but without a diagnosis of GDM, at about the same period of gestation at the diagnosis of GDM to the case. Women who have consented will leave their home-based health record for the researcher for a period of 1-2 months. They will self-administer the questionnaires (about 30 minutes to complete) online or manually in either Malay or English according to their preference and return it before they leave the clinic. A trained research assistant will be at each participating clinic to facilitate the data collection and to respond to any queries relating to the questionnaire. A researcher (PPHY) will be contactable to answer queries from those who choose to complete the questionnaire online. Participants will answer the online questionnaires at their own convenience to reduce the physical contact and time spent during their clinic visit. A weekly reminder
in the form of a text message will be sent to the participants who did not complete the questionnaires for two weeks. Every booklet will have a bookmark inserted with a unique code and the booklets will be kept in a safe place in the clinics until collected data retrieval. In return, the participating women will receive a copy of the Participant Information Sheet, signed consent form, and a duplicate bookmark with the same code attached to their health record. The bookmark contains details on the study and the researcher contact information. Participants can request for early return of their home-based record at any time during the study period, and it will be returned to them immediately through the clinic or registered mail. At the end of the study, all home-based records will be returned to each clinic and the women will be informed for collection. They will present the duplicate bookmark for verification to collect their health records. Participants who have completed the questionnaires will receive a token of appreciation when they return to collect their antenatal home-based record.

At each participating clinic, we will extract data from the OGTT records, and only request access to the health records of the consented patients to verify necessary information including the history of miscarriage or pre-term birth. Figure 2 shows the overview of the procedures in data collection.

We will also re-invite at least 50 participants from both case and control group to complete the PBQ-14 and MPAS-19 for the 2-week intra-rater test-retest reliability testing\(^5\). Assuming a 50% response rate, the first 100 women with and without GDM (total n= 200) will be invited to participate in this reliability test. We will send the PBQ-14 and MPAS-19 online questionnaires to selected participants after 2-week after completing the first.

**Sample size estimation**

Based on previous studies, the prevalence of GDM with adverse outcomes range from 5-27.9\(^\%\)\(^4,11\). We use GPower 3.1.9.7\(^6\) with 0.90 power and significance at two-sided $\alpha$ of 0.05 to estimate the smallest difference in maternal or neonatal complication rate between GDM with optimal glycaemic control and suboptimal control to be at 15%, the required sample size is 312 (104 cases, 208 control). For another estimation, the required sample size to estimate 10% (as the lowest possible proportion among all the risk factors) either the history of PCOS with the reported prevalence rate 12.6\(^\%\)\(^3\) or multiple pregnancies with reported incidence of 12-30\(^\%\) among GDM women\(^32,33\) with the power 0.90 and $\alpha$ 0.05 at two tails is 263. Taking into consideration about 10% of incomplete or missing data in the home-based records, the sample size needed is 292 (263/0.90) cases and 584 (526/0.90) control at the ratio of 1:2. Knowing the average number of pregnancies at each of the six participating clinics (200-300 cases and 1500-3000 controls per year) and the required 1:10 ratio of independent variables to numbers of dependent variables to run a multiple logistic regression with 14 independent variables on GDM with any maternal or neonatal complication rate of 40\(^\%\)\(^6\), the study is deemed to be feasible.
Therefore, we will continue to collect the home-based records from the postpartum women until at least 876 records have been collected.

Data analysis plan

All data analysis will be conducted using SPSS version 26.0 (IBM, Chicago, IL). Data entered will be cleaned and checked for the missing, extreme and suspicious values. These may be verified with the respondents or omitted as missing values. Once the missing data is determined to be missing at random, multiple imputations with ten runs may be conducted to replace the missing data. The complete case analysis will be conducted if the sample size achieves 789 at a minimum.

We will use a descriptive analysis to summarize the sociodemographic data and clinical variables according to the diagnosis of GDM during the first and second trimester at 24th to 28th weeks of gestation. All glycaemic biomarkers including blood sugar profiles will be reported in the trimesters according to the outcomes (normal vs. adverse). Comparisons of mean levels for continuous variables will be analysed using Student’s t-test and Chi-square test for categorical variables. The equivalent non-parametric tests will be used for data with non-normal distribution. We will report the proportion of postnatal women who had completed OGTT in the first trimester as well as those who completed OGTT in the second trimester and among each of this group the proportions offered OGTT twice or more (when they need to repeat the test).

To achieve the first objective, we will calculate the proportion of risk factors that are identified according to the trimester when GDM diagnosis is made. We will compare the risk factors profile of women completed OGTT and diagnosed GDM at first trimester to those who have undergone the OGTT but without GDM. A similar analysis will be conducted to compare the risk factor profiles of women with and without GDM who were offered OGTT during the second trimester and not in the first trimester. We will report the specificity, sensitivity, positive and negative predictive values of the CPG-based risk factors and to examine the novel risk factors, separately and combined, for a GDM diagnosis in the first and second trimester, respectively. Additionally, we will compare the risk factors profile of women diagnosed with GDM at the first and second trimester. We will model the risk factor profiles that best predict the GDM diagnosis at the first and second trimester, respectively, using multiple logistic regression. The discrimination ability of the multiple logistic model consisting of the risk factors for GDM will be estimated with the area under the receiver operating characteristics curve with 95% confidence interval.

We will report the comparative incidences of the maternal health outcomes during pregnancy and labour, and the comparative prevalence of the psychosocial outcomes in the postpartum period between the women with GDM and without GDM (second objective). Similarly, we will report the comparative incidences of the neonatal outcomes between the women with GDM and without GDM (third objective).
The fourth objective can be achieved by comparing the adjusted $R^2$ values of multivariable logistic regression models consisting of the CPG-based risk factors and models with the added new potential risk factors for GDM diagnosis, including the documented glycaemic biomarkers on the outcome of maternal complications as a whole or by each complication. If sample size allows, this analysis will be conducted separately for GDM diagnosed at first and second trimester to examine its effect on the maternal complications.

Analysis step to measure the fifth objective is similar to the fourth objective by comparing the adjusted $R^2$ values of multivariable logistic regression models consisting of the CPG-based risk factors and models with the added new potential risk factors for GDM diagnosis, including documented glycaemic biomarkers on neonatal health outcomes.

The current risk factors for GDM will be assessed univariably and multivariably of their effect on the diagnosis of GDM at first and second trimester (24th to 28th weeks) using the $R^2$ and adjusted $R^2$. The factors from the demographic and clinical variables on GDM diagnosis will be estimated in univariable logistic regression analyses. Any of this factor with a $P$-value <0.20 from will be included in the multiple logistics regression analysis. The analyses may be conducted by blocks of risk factors such as sociodemographic information (age, BMI and smoking), family history and past medical history, current antenatal medical problems (glycosuria, obstetric medical conditions and weight gain) if sample size is less than desirable. Multicollinearity between any independent variables will be checked using correlation matrix and standard errors (SE) of each variable. Any two variables correlated $>0.9$ or/and the variable has a SE $>5.0$ will indicate the presence of multicollinearity. In the presence of multicollinearity, the variable with largest SE and less critical or essential from clinical perspectives will be excluded. This process will continue until the magnitude of the SEs for all the variables hover around 0.001 - 5.0. All final models, Q-Q plots for normality, the residual plots for linearity and homogeneity assumptions and model fitting will be checked. Same statistical strategy may be conducted to model the independent predictors on the maternal and neonatal outcomes. The maternal outcomes (abnormal gestational weight gain, pre-eclampsia, polyhydramnios, abnormal modes of delivery, gestational age at birth either pre-term or post-date birth and complication in labour includes postpartum haemorrhage and perineal tear) will be combined as a whole or separately if sample size for any of the outcome allows, and the maternal psychosocial wellbeing measures will be analysed separately. Similarly, if sample size allows, we will analyse for the neonatal outcomes (birth weight, abnormal gestational weight at birth, poor Apgar score, congenital anomaly, congenital hypothyroidism, neonatal death, stillbirth, hypoglycaemia, and hyperbilirubinemia). Confounding factors will be assessed in multiple logistic regression modelling on maternal and neonatal outcomes, and maternal psychosocial wellbeing measures. A confounding factor is present when it changes the odd ratio of GDM on the outcome by a magnitude of $>10\%$. This will be done to verify the variables
included in the final models of the maternal and neonatal outcomes, and maternal psychosocial wellbeing measures.

Strengths and Limitations

This retrospective cohort study incorporates a nested case-control design, providing an opportunity to confirm and explore the conventional CPG-based and potential novel risk factors to better predict the diagnosis of GDM, either at the first or/and second trimester. This is one of the core outcomes to be included in GDM prevention and treatment research. Additionally, we will also examine multiple pregnancies on diagnosis of GDM, which was often excluded from earlier studies. The risk profiles that best predict the diagnosis of GDM will be modelled and examined for their impacts on the maternal and neonatal health outcomes. This evidence is imperative to improve the identification of at-risk women and earlier treatment for GDM. This study would help healthcare practitioners and women with GDM to better understand the effect of both the currently ‘recommended’ and potentially ‘new’ important risk factors of GDM, patterns of glycaemic control and their association with health outcomes in both the women and neonates. This is potentially impactful on the decision rule of the existing practice. As this study will be assessing the level of OGTT completion, it will determine whether a delay in the completion of OGTT is one of the possible causes of a delayed GDM diagnosis and treatment, and the risk profiles of women and their association with any maternal and neonatal health outcomes will be identified. Additionally, the effect of each individual risk factor and as a whole on GDM, glycaemic patterns during pregnancy, and the maternal and neonatal health outcomes including psychosocial wellbeing will be quantified. Furthermore, this study would also validate locally and culturally adapted 14-item PBQ and the 19-item MPAS.

This study faces a few limitations. The incidence of some of the CPG-based and potential novel risk factors may be low and insufficient in numbers for the multivariable regression analysis. To overcome this, the study has included all the adjacent six public health clinics. Consequently, this has also increased the demands of training and supervision of research assistants, travelling time and coordinating effort. This will be taken care of by having a written study manual, a site visit to the participating clinics before the start of recruitment, and regular contact with all the research assistants until the end of recruitment. In the case of a smaller than expected sample size being recruited, multivariable regression analysis by separate blocks of risk factors will be conducted. Secondly, the six public health clinics are situated in the urban areas of Selangor and Putrajaya, thus the study participants may not be representative of the larger Malaysian population. Owing to the COVID-19 pandemic, the effects of the aftermath may delay the data collection processes and cause a reduction in the number of pregnant women visiting the clinics in-person. There may also be a decrease in pregnancy in the past year which would lower the number of postpartum women participants with a history of GDM this year. Another limitation may be the quality and accuracy of the data in the
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antenatal health records. However, we believe this problem is minimal with the long use over decades of the same antenatal records by all the healthcare providers in the public health clinics. The booklet is well-structured with dedicated spaces for the variables to be investigated in this study. We plan clarification and verification strategies to confirm the nature of the risk factors when present with doubts by contacting the participant, checking the clinic-based or/hospital-based records.

**Patient and Public Involvement**

This is one of non-experimental studies in the MYGODDESS Project (https://rb.gy/ccztw5) where women with GDM during pregnancy and in postpartum periods will be interviewed on important barriers and facilitators of self-care. Women with a history of GDM are involved in the face and content validity testing of the PBQ-14 and MPAS-19 questionnaires. Their opinions on the study design, conduct, reporting and dissemination of results will be sought at appropriate time during the study.

**ETHICS AND DISSEMINATION**

**Risk Benefit Assessment**

Participants are not subjected to any medications or treatments during the study period. No rescue medication or procedures will be involved. Since this is not an interventional study, there is therefore no direct health risk and no side effects for the participant. There might be a potential risk of fatigue upon completion of the questionnaires. No direct benefit to participants. A small token of appreciation will be given to all participants. Their participation will provide data that aims to improve and increase understanding in the research topic that may contribute to future protocol, guidelines or policymaking.

**Ethical consideration**

The study will be conducted in compliance with the ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. This study obtained approval from the MREC ethics committee. We will clearly explain, state the purpose of this study, and to obtain written consent in Malay or English from all study participants before data collection. Participation is voluntary. They have the right to withdraw at any stage of the research without giving any reason. Should there be any further amendments to the protocol, other than administrative ones, further approval from the MREC ethics committee will be obtained. Any revisions of documents and amendment to the protocol originally submitted for review, unexpected events during the study period, and new information that may adversely affect the safety of participants and publication will duly be informed to the ethics committee.

**Privacy and Confidentiality**

Only researchers of this study have access to the participants’ data and will be handled diligently only for the purpose of this study. Participant identity will not be revealed as there will be no referencing...
of participants by name upon presenting the result. The identification number will be used on subject
data sheets. All information in this study is confidential. Data from this study will be entered and saved
on a dedicated computer that is password protected. Upon completion of the study, softcopy data in
the computer will be copied to a password protected pen drive and the data in the computer will be
erased. Any hardcopy (including the consent form) and the pen drive will be kept in the Principal
Investigator’s locked office at UPM and maintained for a minimum of twenty years after the
completion of the study. The collected data will be destroyed after that period of storage. Subjects will
not be allowed to view their personal study data as the data will be consolidated into a database. The
participants can write to the investigators to request access to the study findings.

Publication Policy
Participants’ personal information will not be disclosed, thus will not be identified when the findings
of this research are published and presented.

Dissemination plan
Research findings will be published in scientific journals, may be presented in scientific conferences,
and will be reported and shared with the local health stakeholders.

Word count: 6002/4000 words from Introduction to Dissemination plan (excluding tables)

AUTHORS’ CONTRIBUTIONS
CBH, NIB, INS, and PY contributed to the study planning and design of the study. The study design
was further developed by IP, VR, MB and CBH. PY drafted the manuscript with assistant from CBH
and also input from various stages from NMN, ZAS, HH, FP, RZ, SRMA, NBIB, AF and KI. All
authors critically reviewed the manuscript and approved the final version as submitted.

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COMPETING INTERESTS / CONFLICT OF INTERESTS
None declared.

DATA SHARING STATEMENTS
Data sharing will be considered on a case-by-case basis upon assessment of the proposed study
protocol.
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TABLES

Table 1 The Malaysian Clinical Practice Guideline 2017 recommended risk factors for GDM screening

| Clinical Practice Guideline (CPG) Risk Factors: |
|-----------------------------------------------|
| 1. Age ≥ 25 years old                        |
| 2. Body mass index > 27 kg/m²                 |
| 3. Previous history of GDM                   |
| 4. First degree relative with diabetes mellitus (DM) |
| 5. History of macrosomia (birth weight > 4 kg) |
| 6. Bad obstetric history (unexplained intrauterine death, neural tube defects, cardiac defects and shoulder dystocia) |
| 7. Glycosuria ≥ 2+ on two occasions          |
| 8. Current obstetric problems (essential hypertension, pregnancy-induced hypertension (≥ 140/90 mmHg), polyhydramnios and current use of corticosteroids) |

Table 2 Potential new risk factors to be screened for GDM diagnosis and health outcomes

| Potential Risk Factors: |
|-------------------------|
| 1. History of PCOS      |
| 2. Current multiple pregnancies |
| 3. Active or passive smoking status |
| 4. Miscarriage (before 23rd week) *(previous and most present)* |
| 5. Pre-term Birth (23rd to 36th week +6 days) *(previous and most present)* |
| 6. Gestational weight gain |
Table 3 Description of the questionnaires

| Questionnaire                                      | Description                                                                                                                                                                                                                                                                                                                                 | Score range                                                                                                                                      |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| The World Health Organization Quality of Life:    | The WHOQOL-BREF measure is an abbreviated 26-item version of the WHOQOL-100 questionnaire and measures 4 domains of quality of life (QoL): physical (7 items), psychological (6 items), social relationship (3 items) and environment (8 items) domains and 2 additional global items focusing on overall QoL.                                                                                          | Four types of 5-point Likert interval scale are used, inquiring ‘how much’, ‘how often’, ‘how completely’, ‘how satisfied’ or ‘how good’ the respondent felt in the past 4-weeks, with different response scale distributed across the domains. Three negatively scored items are reversed scored (3, 4 and 26) and scores are summed up for each domain. Domain scores are computed by taking the mean of the scores and multiplied by 4 (and ranged from 4 to 20) to allow for direct comparison with the WHOQOL-100 scores. Higher domain scores indicate higher QoL. Malay version of this questionnaire showed high internal consistency with Cronbach’s alpha ranging from 0.82 to 0.89, which is comparable to the English-language version Interclass Correlation Coefficient ranged from 0.58 to 0.69 across domains, indicating good test-retest reliability.
| Brief Version (WHOQOL)-BREF Questionnaire        |                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                   |
| The 14-item Postpartum Bonding Questionnaire (PBQ-14) | The PBQ measure will be used to assess the mother-infant relationship during the postpartum period, with a total of 14 items which are rated on a six-point Likert scale from 0 (always) to 5 (never) on four subscales indicating impaired bonding, rejection and anger, anxiety about care, and the risk of abuse.                                                                                       | When the statement is reflecting negative emotion, the scoring is reversed. The summed total score ranges from 0 to 70, with low scores indicating good bonding. The PBQ has acceptable reliability and validity and as for its utility specifically in Asian countries, the measure has been previously tested and demonstrated high sensitivity of 83% and specificity of 96%. |
| MPAS is a 19-item self-report questionnaire designed to assess maternal emotional response towards her infant during the first year of life. There are three dimensions: 1) Quality of postnatal attachment (quality of the maternal feelings towards the infant as well as maternal confidence and satisfaction in being a mother); |                                                                                                                                                                                                                                                                                                                                 | The three dimensions are considered to be independent but they can be combined to obtain a global attachment score (Total postnatal attachment). The scores on the “Quality” subscale range from 9 to 45, while the scores on the “Pleasure in interaction” and “Absence of hostility” subscales range from 5 to 25. Scores on the global attachment scale range from 19 to 95. Higher scores are generally indicative of stronger attachment but a specific cut-off is not provided. |
2) Absence of hostility (lack of resentment and negative feelings towards the infant) and 3) Pleasure in interaction (desire for proximity and interaction with the infant). Responses are scored on 1 (low attachment) to 5 (high attachment)\textsuperscript{49}.

| 7-item Generalized Anxiety Disorder (GAD 7)\textsuperscript{50} | The GAD-7 is a 7-item questionnaire measuring the perceived frequency of generalised anxiety symptoms in the past 2-weeks. The items assess the most prominent diagnostic features of GAD\textsuperscript{68}. The items include nervousness, excessive worry, and inability to stop worrying. Restlessness, easy irritation, difficulty relaxing, and fear of something awful happening on response categories ‘not at all’, ‘several days’, ‘more than half the days’ and ‘nearly every day’ scored 0, 1, 2 and 3, respectively. The summed total score ranges from 0 to 21, with higher scores indicating more severe symptoms of anxiety. The Malay version of this questionnaire was found to be valid and reliable measure in women in Malaysia, with high sensitivity of 76% and a specificity of 94%\textsuperscript{69}. |
|---|---|
| Patient Health Questionnaire (PHQ-9)\textsuperscript{51} | Nine items refer to symptoms experienced by patients during the two weeks prior to answering the questionnaire in making diagnosis and assessing severity of depression. Scores range from 0 to 27, as each of the nine items is scored from 0 (not at all) to 3 (nearly every day). PHQ-9 scores of 5, 10, 15, and 20 represents mild, moderate, moderately severe, and severe depression, respectively. This questionnaire was found to be a valid and reliable instrument to measure depression, with high sensitivity 87% and specificity of 82% in Malaysia\textsuperscript{70}. Good internal reliability with a Cronbach’s alpha of 0.67 and test-retest reliability of 0.73 were also demonstrated in this population\textsuperscript{71}. |
| The Perceived Stress Scale (PSS)\textsuperscript{52} | The PSS measure has 10 items on a 5-point Likert scale ranging from 0 (never) to 4 (very often), assessing the perceived stress levels in the past 4-weeks. The total score is calculated by reversing the responses for the 4 positively stated items (4, 5, 7 and 8) and then summing across all 10 items. The total score can range from 0 to 56, with higher score representing greater perceived levels of stress. This scale was previously utilised in Malaysian diabetic patients\textsuperscript{72}, medical students\textsuperscript{73}, working population\textsuperscript{74}, and female prisoners\textsuperscript{75} in Malaysia and showed comparable psychometric properties to the original English version, with Cronbach’s alpha from 0.63 to 0.85 and high test-retest reliability of $r =.72$. |
FIGURE LEGEND / CAPTION

Figure 1: Risk factors for the diagnosis of gestational diabetes mellitus in different trimester and their relation to maternal and neonatal outcomes

Figure 2: Overview of the procedure in data collection
Figure 1: Risk factors for the diagnosis of gestational diabetes mellitus in different trimester and their relation to maternal and neonatal outcomes

Risk factor profiles
- CPG-based risk factors
- Potential risk factors

75g OGTT done;
- at first trimester only
- at 24th – 28th week only
- at first trimester & at 24th-28th week

Women Diagnosed GDM

Glycaemic patterns in HbA1c, FPG, BG at clinic, SMBG at home

Health outcomes
(Maternal outcomes)
✓ Weight gain
✓ Pre-eclampsia
✓ Polyhydramnios
✓ Mode of delivery
✓ Pre-term birth
✓ Postpartum Haemorrhage
✓ Perinatal tear
✓ Retained Placenta
✓ Postnatal OGTT
✓ Psychosocial wellbeing
(Neonatal outcomes)
✓ Mode of birth
✓ Birth Weight
✓ LGA or SGA
✓ Apgar Score
✓ Congenital Abnormalities
✓ Shoulder Dystocia
✓ Neonatal Hypothyroidism (TSH & T4 value)
✓ Neonatal Hypoglycaemia (glucose value)
✓ Neonatal Hyperbilirubinemia (SB value)
✓ Neonatal Death
✓ Stillbirth
✓ Admission to NICU

A: the association between risk factor profiles and OGTT of GDM women at different trimester
B: the association between glycaemic patterns after GDM diagnosis on maternal and neonatal health outcomes
C: the association between risk factors, blood sugar profiles on maternal and neonatal health outcomes

*CPG=Clinical Practice Guidelines, FPG=Fastig Plasma Glucose, BG=Blood Glucose, SMBG=Self-Monitoring Blood Glucose, OGTT=Oral Glucose Tolerance Test, LGA=Large Gestational Age, SGA=Small Gestational Age, TSH=Thyroid Stimulating Hormone, T4=Thyroxine, SB=Serum Bilirubin, NICU=Neonatal Intensive Care Unit
Figure 2: Overview of the procedure in data collection

All women at least two months postpartum, include women with a miscarriage who attended public health clinic (KKSK, KKPch, KKP9, KKP18, KKKjg, KKB) for their postnatal check-up & baby’s immunization will be recruited.

Exclude those who do not meet the eligibility criteria

Approach for agreement & consent, collect the home-based antenatal booklet from consented participants and distribute psychosocial questionnaires

Completed psychosocial questionnaires returned and retrieve data/records (if necessary also from the clinic-based antenatal record and other records from clinic)

2-week intra-rater test-retest reliability testing for the 14-item Postpartum Bonding Questionnaire & the 19-item Maternal Postnatal Attachment Scale through an online form of the same questionnaires.

May call the participants for clarification on missing information from the home-based antenatal booklet, if required

Return of the home-based antenatal booklet

Data Analysis

Data Reporting

* KKP9= Klinik Kesihatan Precint 9; KKP18= Klinik Kesihatan Precint 18; KKS= Klinik Kesihatan Seri Kembangan; KKPch= Klinik Kesihatan Puchong; KKKjg= Klinik Kesihatan Kajang; KKB=Klinik Kesihatan Bangi
| Item No | Recommendation | Page No |
|---------|----------------|---------|
| 1 | **Title and abstract** | |
| (a) Indicate the study’s design with a commonly used term in the title or the abstract | 3 |
| (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 3 |
| 2 | **Introduction** | |
| Explain the scientific background and rationale for the investigation being reported | 5-7 |
| 3 | **Objectives** | |
| State specific objectives, including any prespecified hypotheses | 8 |
| 4 | **Methods** | |
| Present key elements of study design early in the paper | 7-8 |
| 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 8 |
| 6 | Participants | |
| (a) **Cohort study**—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | na |
| Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | |
| Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants | |
| (b) **Cohort study**—For matched studies, give matching criteria and number of exposed and unexposed | 8 |
| Case-control study—For matched studies, give matching criteria and the number of controls per case | |
| 7 | Variables | |
| Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 9 |
| 8 | Data sources/measurement | |
| For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-10 |
| 9 | Bias | |
| Describe any efforts to address potential sources of bias | na |
| 10 | Study size | |
| Explain how the study size was arrived at | 11 |
| 11 | Quantitative variables | |
| Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 11 |
| 12 | Statistical methods | |
| (a) Describe all statistical methods, including those used to control for confounding | 12-13 |
| (b) Describe any methods used to examine subgroups and interactions | 12-13 |
| (c) Explain how missing data were addressed | 12 |
| (d) **Cohort study**—If applicable, explain how loss to follow-up was addressed | 11-13 |
| Case-control study—If applicable, explain how matching of cases and controls was addressed | |
| Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy | |
| (e) Describe any sensitivity analyses | 11-13 |

Continued on next page
### Results

| Items | Numbers | Notes |
|-------|---------|-------|
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed na |
| | | (b) Give reasons for non-participation at each stage na |
| | | (c) Consider use of a flow diagram na |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders na |
| | | (b) Indicate number of participants with missing data for each variable of interest na |
| | | (c) Cohort study—Summarise follow-up time (eg, average and total amount) na |
| Outcome data | 15* | Cohort study—Report numbers of outcome events or summary measures over time na |
| | | Case-control study—Report numbers in each exposure category, or summary measures of exposure na |
| | | Cross-sectional study—Report numbers of outcome events or summary measures na |
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included na |
| | | (b) Report category boundaries when continuous variables were categorized na |
| | | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period na |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses na |

### Discussion

| Items | Numbers | Notes |
|-------|---------|-------|
| Key results | 18 | Summarise key results with reference to study objectives na |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence na |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results na |

### Other information

| Items | Numbers | Notes |
|-------|---------|-------|
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 3 & 16 |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.