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Model design and protocol for development and validation of the PeRSonal GDM pregnancy risk model

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TITLE PAGE

Title

Model design and protocol for development and validation of the PeRSonal GDM pregnancy risk model

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ABSTRACT

Introduction

Gestational diabetes (GDM) is a common yet highly heterogeneous condition. The ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman would allow preventative and therapeutic interventions to be delivered to women at high-risk, sparing women at low-risk from unnecessary care. The PrEdiction for Risk-Stratified care for women with GDM (PeRSonal GDM) Study will develop, validate and evaluate the clinical utility of a prediction model for adverse pregnancy outcomes in women with GDM.

Methods and analysis

We undertook formative research to conceptualise and design the prediction model. Informed by these findings, we will conduct a model development and validation study using a retrospective cohort design with participant data collected as part of routine clinical care across three hospitals. The study will include all pregnancies resulting in births from 1 July 2017 to 31 December 2018 coded for a diagnosis of gestational diabetes (estimated sample size 2,430 pregnancies). We will use a non-random split-sample development and validation strategy. A multivariable logistic regression model will be fitted. The performance of this model will be assessed, and the validated model will also be evaluated using decision curve analysis. Finally, we will explore modes of model presentation suited to clinical use, including electronic risk calculators.

Results

There is a need to estimate the absolute risk of a composite of prioritised, objective and serious adverse pregnancy outcomes using clinical characteristics routinely available at the time of GDM diagnosis. We will report the results of model development and validation at study completion.

Ethics and dissemination

This study was approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). We will disseminate results via presentations at scientific meetings and publication in peer-reviewed journals.

Registration

Systematic review proceeding this work was registered on PROSPERO (CRD42019115223).

ARTICLE SUMMARY

Strengths and limitations of this study

- We have designed a prediction model to meet an established clinical need by integrating learnings from a systematic review and critical appraisal of existing models, consensus from a clinical study steering committee and consideration of consumer perspectives.
- This study will build upon relevant literature, including a systematic review of existing prediction modelling studies to formulate a composite of prioritised, objective and serious adverse pregnancy outcomes and identify a broad series of relevant candidate predictors.

- We will adopt best practice methods for model development and validation framed by learnings from a critical appraisal of existing models.
- Participants will be from multiple hospitals within a large maternity service providing universal care to an ethnically and socio-economically diverse population. however, there are attendant limitations to using routinely-collected healthcare data.
- We will use decision curve analysis to determine the suitability of the validated model as a basis for risk-stratified model-of-care.

KEYWORDS

gestational diabetes, prediction model, prognosis, pregnancy complications, adverse pregnancy outcomes, large-for-gestational-age (LGA), pre-eclampsia, neonatal hypoglycaemia

MAIN TEXT

INTRODUCTION

Gestational diabetes (GDM) is diabetes that is first diagnosed during pregnancy, typically the second or third trimester of pregnancy and not consistent with pre-existing type 1 or type 2 diabetes.[1] It is a prominent health concern as it is common, affecting 7.5% to 27.0% of pregnancies,[2] and confers an increased risk of complications with health consequences for mother and baby.[3] However, current approaches to care are based on the false premise that the diagnostic criteria used define a group of women who are all at high-risk of adverse pregnancy outcomes.[4] In reality, the identified group is highly heterogeneous with a broad and continuous range of risk related to inter-related factors, which are inadequately integrated into the current glucocentric treatment paradigm. Therefore, the ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman would support shared decision-making and a personalised approach to care. Here, the intensity of intervention could be stratified by risk of pregnancy complications such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from unnecessary intervention.

The International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria sought to translate the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study into clinical practice.[4 5] This large multi-national prospective cohort study demonstrated that the risk of two adverse pregnancy outcomes (birth of a large-for-gestational-age neonate, clinical neonatal hypoglycaemia), an obstetric intervention (primary caesarean section) and a surrogate marker for fetal hyperglycaemia (cord-blood serum C-peptide > 90th percentile) was continuously and positively associated with maternal glycaemia at 24 to 28 weeks gestation as measured by an oral glucose tolerance test (OGTT). The IADPSG diagnostic criteria dichotomise the risks related to glucometabolic dysfunction in pregnancy on serum glucose levels at a single time point in pregnancy using a threshold of an odds ratio of 1.75 for the above outcomes relative to the mean. The use of an arbitrary threshold has led to disagreement amongst experts and professional societies.[6 7] Indeed the optimal diagnostic strategy may vary depending on the characteristics of the local population.[1 8 9] Ultimately, these diagnostic criteria have had the unintended consequence of fostering a glucocentric approach to the treatment of GDM. This study will address this need for a more refined method of risk prediction and the targeting of intervention.

The need for refined and targeted approaches is strengthened by the heterogeneous population defined by current diagnostic criteria for GDM.[10] Pregnancy risk is clearly related to elevated glucose in GDM, but the relationship is complex, and an individual's risks are modified by interrelated factors including maternal weight,[11 12] gestational weight gain,[13] ethnicity, [14] and genotype.[15] For example, it has recently been shown that within the two largest maternity services in Australia, ethnic Chinese women with GDM had a lower risk of large-for-gestational-age (LGA) babies and neonatal hypoglycaemia compared to Caucasian women, even adjusting for confounders.[16] A prediction model could integrate these risk factors to estimate risk of adverse pregnancy outcome.

The feasibility of estimating an individual's absolute risk of adverse pregnancy outcomes by integrating oral glucose tolerance test results, maternal weight and pregnancy history was established in our systematic review (manuscript submitted for publication, 2020).[17] However, critical appraisal established that existing prediction models were not yet suitable

for application to clinical practice due to high risks of bias due to methodologic limitations. The Prediction for Risk-Stratified care for women with GDM (PeRSonal GDM) study will leverage the rapidly evolving methodologic advances in prediction modelling to achieve the evolution required to transform promising statistical models into useful clinical tools. In this paper, we integrate the findings of this systematic review and critical appraisal of existing models, pertinent findings from landmarks trials, clinical expertise and best practice methods from contemporary guidelines to inform the methodological design of the PeRSonal GDM study.

Objectives

The aims of the PeRSonal GDM study are to:

1. Develop a prediction model for adverse pregnancy outcomes in GDM to aid shared decision-making and stratify care;
2. Externally validate the model to demonstrate temporal transportability;
3. Evaluate the clinical utility of the model as a basis for a risk-stratified model-of-care.

METHODS AND ANALYSIS

This work was undertaken in two sequential phases to maximise the clinical acceptability and robustness of the proposed model. Phase I focussed on establishing the requirements of the model (prediction model design). Phase II focuses on the development and validation of a model to address these requirements. Here we report the methods and results from Phase I and the methods for Phase II, the study protocol for the PeRSonal GDM study, the results of which will be reported at completion.

Phase I: Prediction model design

We conducted formative research to conceptualise and design a definitive, robust and clinically acceptable prediction model. First, a systematic review and critical appraisal of existing prediction models for adverse pregnancy outcomes in women with GDM was conducted following a peer-reviewed protocol.[17] Second, the study steering committee comprising two obstetricians, three endocrinologists and a neonatologist formulated key clinical requirements of the prediction model. Finally, a multidisciplinary clinical working group was formed to provide feedback on the proposed requirements, gauge its clinical acceptability and consider its clinical application. The working group included endocrinologists (n = 9), diabetes nurse educators (n = 3), dieticians (n = 2), midwives (n = 2), administration staff (n = 2) and an obstetrician (n = 1) actively involved in the provision of GDM care at several maternity hospitals. We considered consumer perspectives throughout this process, from parallel qualitative research on GDM diagnosis and risk.[18]

Having established the fundamental clinical requirements of the prediction model the study steering committee considered (a) which outcomes should be the subject of prediction and (b) which predictors should be evaluated in model development (candidate predictors). This work was informed by relevant literature and clinical experience.

Phase II: Model development and validation

Study design

We will conduct a prediction model development and validation study using a retrospective cohort design. It will be conducted following expert guidance for model development and

validation,[19-24] and reported per the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[25]

Data sources and validation strategy

This study will use routinely collected health data for pregnancies resulting in a birth from 1 July 2017 to 31 December 2018 from an existing pregnancy outcomes database from a maternity service. Maternal, obstetric and neonatal data are collected prospectively for all women booked to deliver their baby at the service. This data is collected with consent as part of routine clinical care. This data is of high-quality and completeness as it is collected under statute with the primary aim to facilitate improvements in quality of care. We will link these data deterministically to pathology data and clinical data extracted from the medical record of the parent health service. Linked pathology data is available for approximately 70% of pregnancies, and linked clinical data is available for approximately 90% of pregnancies. All collected data will be rendered non-identifiable for all research purposes, including analysis.

The data will be split by time into two groups (analysis type 2b in TRIPOD).[26] We will develop the prediction model using pregnancies resulting in births from the first 12 months of the study period (1 July 2017 to 30 June 2018). Pregnancies resulting in births from the last six months of the study period (1 July 2018 to 31 December 2018) will be used to evaluate the predictive performance of the developed model (external validation). This strategy will evaluate the temporal transportability of the model.

Participants

Study setting

This maternity service is one of the largest in Australia, provides universal access to healthcare compromising multiple large maternity hospitals and serves an ethnically and socioeconomically diverse population within a catchment of 1.6 million in South-East Melbourne. All levels of maternity care are available across the three hospitals with shared staff and institutional protocols and practices. Maternity care is provided to more than 9,000 women each year.

Eligibility criteria

Pregnancies coded for GDM during the study period stated above will be included. There will be no exclusion criteria.

Treatment received

GDM is diagnosed and treated following institutional protocol and practices. At our service GDM is diagnosed using the International Association of Diabetes and Pregnancy Study Groups 2010 criteria,[4] as endorsed by the Australian Diabetes in Pregnancy Society with universal screening at 24-28 weeks with a one-step procedure using the 75g OGTT. [6] Early screening is based on the presence of risk factors as soon as practicable using the same testing procedure with a repeat at 24-28 weeks if negative. The treatment package for GDM consists of an initial 2-hour group education session with diabetes nurse educator and dietician. Lifestyle management involves dietary modification, physical activity and weight management. Follow up reviews occur with an endocrinologist or endocrinology specialist trainee every one to three weeks. Insulin is commenced where glucose targets (fasting < 5.5 mmol/L and 2-hour post-prandial < 7.0 mmol/L) are not met and are not amenable to further dietary modification. Metformin is used where there is evidence of significant insulin

resistance, where targets are not achieved with insulin alone or when insulin use is relatively contraindicated due to the risk of significant psychological harm.

Outcome

The outcome to be predicted will be a composite consisting of a combination of eight prioritised, objective and serious adverse pregnancy outcomes defined in Table 1.

Table 1. The adverse pregnancy outcomes to be predicted: Definition, variable type and categories.

Outcome	Definition
Maternal	
Hypertensive disorders of pregnancy	Pregnancy-induced hypertension, pre-eclampsia or eclampsia
Fetal/ Neonatal	
LGA	Birth weight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[27]
Neonatal hypoglycaemia requiring intravenous treatment	A neonate with a low blood glucose level fulfilling institutional criteria for intravenous treatment consisting of either a dextrose bolus or dextrose infusion
Shoulder dystocia	When, after delivery of the head, the baby's anterior shoulder gets caught above the mother's pubic bone
Fetal death	Death of fetus after 20 weeks gestation
Neonatal death	Death of live-born neonate
Bone fracture	Neonatal fracture (femur, humerus, clavicle or skull) suffered at birth
Nerve palsy	Neonatal nerve palsy (brachial plexus injury or facial nerve injury) suffered at birth

LGA, large-for-gestational-age

Outcome assessment

LGA assessment will be based on a population-based growth chart rather than customised centiles to avoid incorporation of predictor information such as ethnicity into outcome assessment. Blinding to the assessment of the outcome to be predicted will not be feasible.

Predictors

Definition of predictors and measurement

Candidate predictors to be evaluated for inclusion in the model are defined in Table 2. Assessment of predictors will be blinded to the outcome due to the prospective nature of data collection. There will be no blinding between the assessment of different predictors.

Table 2. Candidate predictors to be evaluated in model development: Definition, variable type and units/ categories.

Candidate predictor	Definition	Variable type	Units/ categories
Demographics			
Age	Mother's age	continuous	years
Clinical history			
Parity	Number of prior live births	continuous	number

Gestational age at diagnosis	Gestational age at diagnosis of GDM in the index pregnancy	binary	weeks' gestation
Ethnicity	Self-reported ethnicity with classification aligned to the Australian Standard Classification of Cultural and Ethnic Groups[28]	categorical	ethnicity classified into approximately 5-6 categories
Previous GDM	Previous diagnosis of GDM	binary	0 "No" 1 "Yes"
Previous LGA	Previous child with birthweight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[27]	binary	0 "No" 1 "Yes"
Previous pre-eclampsia or eclampsia	Pre-eclampsia or eclampsia in a previous pregnancy	binary	0 "No" 1 "Yes"
Previous shoulder dystocia	Shoulder dystocia in a previous pregnancy	binary	0 "No" 1 "Yes"
Family history of diabetes	Any family history of diabetes	binary	0 "No" 1 "Yes"
Height	The mother's self-reported height at about the time of conception.	continuous	centimetres (cm)
Body mass index	Body mass divided by the square of the body height	continuous	kg/m2
Weight	Mother's self-reported weight (body mass) about the time of conception	continuous	kilograms (kg)
Physical examination			
Incremental gestational weight gain	Weight at first GDM clinic appointment (at around 30 weeks gestation) minus preconception weight divided by gestational weeks completed at the time of the first GDM clinic appointment	continuous	kilograms (kg)
Laboratory investigations			
Fasting glucose from diagnostic OGTT	Glucose level from baseline or time zero of diagnostic oral glucose tolerance test	continuous	mmol/L
1h glucose from diagnostic OGTT	Glucose level 1 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L
2h glucose from diagnostic OGTT	Glucose level 2 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L

GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index

Data extraction

We will extract records for eligible participants to create a research dataset with each observation representing a pregnancy. Participants may be included more than once due to multiple pregnancy or repeat pregnancies within the study period. We will manually review eligible participant's medical record to ensure the accuracy of the diagnosis of GDM. Linked pathology and additional clinical data will be extracted and merged with the research dataset. The research dataset will be rendered non-identifiable for all subsequent analyses.

Sample size

In this study, the adequacy of the sample size of our developmental dataset will be determined by the total number of events of the composite binary outcome. Approximately 9,000 women are delivered at the institution from which the development dataset will be derived. The prevalence of GDM at this institution is 18% (unpublished data). Therefore, over the 18-month study period, we conservatively estimate that the development dataset will include 2,430 cases of women with GDM. We anticipate that at least 10% of these women will deliver neonates that have a birth weight that is LGA defined as greater than the 90th percentile for the population. As LGA is one component of the composite outcome to be predicted, we expect at least 243 events of this composite outcome. Given we envisage including up to 20 candidate predictors, our study should be adequately powered as the dataset will have at least ten events per predictor as is commonly recommended to avoiding overfitting.[29]

Missing data

We do not expect considerable missing data, but some will inevitably occur, with not all cases providing all variables of interest. Handling of missing data will be determined individually on a per predictor basis. The missing indicator method will be used for predictors where data is missing not at random. Multiple imputation by chained equations will be used to impute missing data as long as the data is missing at random.

Statistical analysis methods

To make individualised predictions for the binary composite of an adverse pregnancy outcome, we will apply a logistic regression modelling framework with the logit-probability of the composite outcome as the dependent variable.

Handling of predictors

Continuous variables will be kept as continuous in the model (rather than dichotomising), to avoid a loss of prognostic information. Those predictors that are highly correlated with others contribute little information and will be excluded from the statistical analysis.

The functional form of the relationship of continuous predictors with the outcome will be modelled with non-linear functions such as fractional polynomials (FP). As several continuous variables were included in the model, we will use the multivariable fractional polynomial algorithm. Multiple imputation and FPs will be combined using the procedure described by Morris and colleagues.[30]

Model-building procedures (including predictor selection)

Candidate predictor variables will be selected *a priori* based on existing literature and clinical expertise as described above. During modelling, predictors will be selected by using a LASSO (Least Absolute Shrinkage and Selection Operator) method, which simultaneously selects the variables and penalises the model coefficients for over-optimism.[31]

Examination of predictor interactions will be undertaken for the following groups of predictors: weight, gestational weight gain (GWG) and body mass index (BMI), and fasting, 1h and 2h glucose levels from OGTT.

Internal validation and assessment of model performance

The model performance will be assessed in terms of discrimination and calibration. We will use a bootstrap re-sampling technique to adjust for over-optimism in the estimation of model performance due to validation in the same dataset that is used to develop the model itself. We will use the area under the curve (AUC) of the receiver operating characteristic (ROC) curve with 95% confidence interval to assess the overall discriminatory ability of the developed model. We will report the apparent and adjusted for over-optimism model performance. A calibration plot will be created. This plot will facilitate the graphical assessment of calibration by putting affected women into groups ordered by predicted risk and considering the agreement between the mean predicted risk and the observed events in each risk group, usually deciles. The calibration will be summarized using the intercept and slope of the calibration plot. Internal validation, where the model's predictions are compared to the observed data, should return perfect calibration to the development data (calibration slope = 1).

External validation

External validation of the developed model will be undertaken to assess temporal transportability. We will report the predictive performance in a more recently treated cohort at the same maternity service using the same measures of discrimination and calibration as used in internal validation. Development and validation data are identical in terms of eligibility criteria, outcome and predictors.

Presentation of a simplified model for clinical use

Once a final model is identified, we will simplify and adapt the presentation of the model to facilitate its application to clinical practice. Alternative modes of presentation will be explored with a focus on maximising end-user usability and promoting translation into clinical care. Various presentation formats will be considered, including a simplified scoring system, nomogram and web or app-based electronic risk calculators.

Assessment of clinical utility

To supplement traditional measures of predictive model performance, discrimination and calibration, clinical utility will be formally evaluated. We will use decision curve analysis to explore the net benefit of developed models over the entire range of probability thresholds. [22 26 32] We will represent the net benefit as a function of the decision threshold in a decision curve plot. This will explore whether there is an overall net-benefit for using the models to stratify the population into two risk groups as a basis for a risk-stratified model of care:

1. Low-risk where the risk of adverse pregnancy outcomes is less than a pre-specified value—this group may be considered for a less intensive model-of-care;
2. High-risk where the risk is greater than a pre-specified value—this group should receive specialist-led hospital-based care.

Further formative research is planned to ascertain optimal risk thresholds. This will include engagement with stakeholders, including women affected by GDM and clinicians. A combination of focus groups and an electronic survey will be used.

Sensitivity analyses

We will conduct additional analysis to address the confounding effect of insulin treatment on predictor-outcome associations and hence the performance of the prediction model. This will consider four possible approaches with sensitivity analysis used to evaluate the robustness of each:

1. Derivation of a propensity score of being treated with insulin based on women pre-treatment characteristics. We will then weight observations by using the inverse probability of treatment weighting (IPTW). In this way, women with lower propensity to be treated will have more weight in the development of the prognostic model than those who had a higher probability of being treated.
2. Inclusion of insulin treatment as a component of the composite outcome.
3. Exclusion of cases where insulin treatment was used.
4. Exploration of the multinomial regression model framework for combinations of the composite outcome of adverse pregnancy outcome and insulin treatment.

The primary analysis will develop and validate a model based on clinical characteristics. Prognosis may also be influenced by an affected woman's capacity to implement lifestyle measures such a dietary modification and increased exercise. Therefore, we will undertake a sensitivity analysis to evaluate whether measures of socioeconomic disadvantage can improve the prediction of adverse pregnancy outcomes.

All statistical analysis will be performed using Stata version 16.1 (College Station, TX: StataCorp LLC.).

RESULTS

Phase I: Prediction model design

The fundamental clinical requirements of the prediction model were established (Table 3), and a model addressing these requirements was designed (Figure 1).

Table 3. The fundamental requirements of a prediction model for adverse pregnancy outcomes in women with gestational diabetes.[33] Framework adapted from that originally proposed by Moons and colleagues to consider in framing a systematic review of prediction modelling studies.[33]

Criteria	Specifications
1. Prognostic versus diagnostic prediction model	The aim is to predict future events (prognostic prediction model)
2. Intended scope	To inform clinicians' therapeutic decision-making and serve as a rational basis for the stratification of GDM care
3. The target population to whom the prediction model applies	Pregnant women with GDM, per diagnostic criteria in clinical practice
4. The outcome to be predicted	Pregnancy complications related to GDM affecting the mother (obstetric or maternal) or the baby (fetal or neonatal)
5. Timespan of prediction	Complications occurring during pregnancy or soon after birth

6. Intended moment of using the model	At diagnosis of GDM, typically at 24 to 28 weeks gestation but may be earlier

GDM, gestational diabetes.

Formulation of outcome(s) to be predicted

The study steering committee considered a large number of adverse pregnancy outcomes for inclusion in the composite (Online Supplementary Table S1). Outcomes predicted by existing models identified in our systematic review and predicted by a related model for insulin therapy initiation[34] were considered. The working group also considered outcomes in the final core outcome set (COS) for GDM treatment research.[35] Reference to the COS for future GDM treatment research provided objective prioritisation of outcomes from a large international multidisciplinary group of relevant stakeholders. Finally, the group considered all outcomes studied in the HAPO study,[5] the landmark international multi-centre observational study that demonstrated associations between increasing levels of glucose levels on oral glucose tolerance testing and adverse pregnancy outcomes.

From this, a composite outcome was constructed to reflect the multiple adverse pregnancy outcomes related to GDM. Construction of the composite outcome considered recommendations that components are (1) of similar importance, (2) occur with similar frequency and (3) are likely to have similar relative risk reductions (or predictive effects moving in the same direction) with similar underlying biology.[36] The rationale for inclusion or exclusion from the composite outcome to be predicted is presented in Table 4.

Table 4. The rationale for outcomes to be predicted.

Outcomes	Clinical rationale for inclusion/ exclusion
Outcomes to be predicted	
LGA (> 90th percentile)	Excess fetal growth is the central adverse pregnancy outcome in pregnancies affected by GDM with many mechanisms implicated including but not limited to the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[37] This adverse outcome is also upstream on the causal pathway to other clinically relevant complications, including those related to difficulties at delivery. LGA will be used rather than macrosomia as it is a measure of birth weight corrected for gestational age and is also less variably defined.[38]
HDP	Significant association with GDM and if at high-risk, then closer monitoring during pregnancy may be required.
Shoulder dystocia	Associated with GDM and clinically significant.
Nerve palsy	May be associated with GDM and clinically significant.
Bone fracture	May be associated with GDM and clinically significant.
Perinatal (fetal and neonatal) death	Rare but of utmost clinical significance.
Neonatal hypoglycaemia	This is the central marker of the maladaptive metabolic response of the neonate exposed to hyperglycaemia in utero as per the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[39] Severe cases requiring intravenous treatment are likely to be most clinically relevant.
The requirement for insulin therapy	A treatment for GDM that reduces the risk of some adverse outcomes.
Outcomes excluded from prediction	
Preterm birth	Not directly related to GDM and may be more related to IUGR; strongly clinician-driven.
Adherence to the intervention	Possible predictor.
GWG	Possible predictor.
Caesarean delivery	Highly clinician-driven and institution dependent.
SGA (<10th percentile)	Not directly related to GDM, more related to IUGR.
GA at birth	May be clinician-driven.
Neonatal jaundice	Only severe cases are clinically relevant and may be more closely related to prematurity rather than the maternal hyperglycaemia of GDM.
Neonatal adiposity	Not routinely assessed in clinical practice.

Neonatal hyperinsulinaemia	Neonatal hypoglycaemia is a more meaningful clinical outcome.
Admission to the NICU	Highly clinician-driven and institution dependent.
Malformations	Associated with pre-gestational diabetes and less relevant in gestational diabetes.
Neonatal hypocalcaemia	As its severity is related to the level of hyperglycaemia unlike in pre-gestational diabetes, it is rarely seen in GDM and if present is usually asymptomatic and resolves spontaneously.[40]
Neonatal respiratory distress syndrome	Only severe cases are clinically relevant and may be more closely related to prematurity rather than hyperglycaemia.[41]
Cord-blood serum C-peptide level above the 90th percentile	Not routinely assessed in clinical practice and clinical relevance unclear.

GDM, gestational diabetes; LGA, large-for-gestational-age; HDP, hypertensive disorders of pregnancy; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational-age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit

Identification of candidate predictors

Candidate predictors were identified from those selected for the final models included in the systematic review of models for pregnancy complications in women with GDM, selected in a model for GDM diagnosis previously developed by our group,[42] and selected in a related model for insulin therapy initiation.[34] (Online Supplementary Table S2) Thirteen of the 16 predictors from these existing related models will be evaluated for inclusion in this prediction modelling study (Table 2). Three predictors selected for related models (poor glycaemic control, enlarged abdominal circumference and HbA1c at diagnosis) could not be evaluated in this study as the data are not routinely collected at our service.

One previous studyselected history of macrosomia as a predictor for LGA. [43] Indeed, in clinical practice, past history is often seen as a major risk factor for future occurrence. Therefore, this study will evaluate previous histories of components of the composite outcome for inclusion in the model. Such data is available for macrosomia, LGA, pre-eclampsia and eclampsia, and shoulder dystocia, and therefore, these four predictors will be evaluated as candidate predictors.

In addition to the candidate predictors identified from their use in existing related models, ethnicity and GWG were identified as potential predictors requiring formal evaluation due to the emergence of evidence supporting their role as significant prognostic factors. Chinese women affected by GDM were at a lower risk of a range of adverse pregnancy outcomes including LGA and neonatal hypoglycaemia compared to affected Caucasian women in an Australian cohort,[16] and South Asian babies exposed to GDM were smaller across gestation than babies of White European in an English cohort.[44] Emerging physiologic data suggests highly variable degrees of beta-cell function and insulin resistance amongst women diagnosed with GDM,[45] and that classifying women with GDM by these physiologic defects may stratify women by their risk of adverse pregnancy outcomes.[46] Ethnicity may serve as a surrogate marker for these physiologic defects avoiding the need for additional investigations. Hence, ethnicity is an appealing candidate predictor for models to predict the development of adverse pregnancy outcomes.

GWG has also been shown to be a risk factor for adverse pregnancy outcomes, independent of BMI.[13] Specifically, GWG is associated with an increased proportion of LGA over and above that which is associated with GDM and overweight or obesity, in a general obstetric population.[47] BMI, parity and GWG together, better predict adverse pregnancy outcomes than BMI alone in a cohort attending a general antenatal clinic (women with GDM and normoglycaemia).[48] The effect of GWG is likely to be modified by other predictors, including ethnicity, supporting its integration within a multivariable model rather than a single prognostic factor-based approach.

Phase II: Model development and validation

The results from Phase II will be reported at the completion of this proposed study.

DISCUSSION

Strengths

The formative research undertaken established the clinical need for a robust prediction model for adverse pregnancy outcomes in GDM to support therapeutic decision-making and stratification of care. Engagement with stakeholders in the model design stage should

improve the clinical acceptability of the model and support future implementation efforts. The composite outcome of prioritised, objective and serious adverse events was formulated with reference to a systematic review and critical appraisal of existing models (manuscript submitted for publication, 2020), the relevant core outcome set,[49] and clinical expertise of endocrinologists, obstetricians and a neonatologist. This composite will be composed of LGA, neonatal hypoglycaemia, hypertensive disorders of pregnancy, shoulder dystocia, severe birth trauma (nerve palsy and bone fracture) and perinatal death. The transportability of the developed model will also be enhanced by the selection of candidate predictors using existing literature and clinical expertise, independent of the predictor-outcome association in the development dataset.

Prediction of a composite outcome will more accurately quantify the multiple adverse pregnancy outcomes related to GDM and therefore, will be more translatable into clinical practice. This composite will be valid and clinically useful because the component outcomes are of similar importance, the three main components (LGA, neonatal hypoglycaemia and hypertensive disorders of pregnancy) occur with a similar frequency (approximately 10%), [50] and the predictive effects are likely to move in the same direction due to similar underlying biology.[36]

A method to estimate the absolute risk of adverse pregnancy outcomes for an individual woman affected by GDM would be of great benefit to affected woman, their clinicians and the health system. It would allow affected woman to better understand the implication of GDM on their pregnancy and facilitate shared-decision making with clinicians regarding the relative risks and benefits of interventions. At a system-level these individualised risk estimates would support a risk-stratified model-of-care which recognises the breadth and continuum of pregnancy risk attributable to GDM such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from low-value care. Ultimately, a robust prediction model would facilitate the transition from a glucocentric model-of-care to an individualised and holistic approach to this widespread public health problem.

Translating prediction models into clinical care is challenging.[51-53] Previous efforts of addressing this clinical prediction problem have been hampered by the use of methods, which increase the risk of biased predictions limiting the transportability of developed models to new but related populations (manuscript submitted for publication, 2020). Thus, rigorous and robust methods have been adopted for model development and validation in this study. Methods have been framed by the learnings from our critical appraisal of existing models and will be guided by Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement.[25]

Limitations

Use of routine-collected healthcare data

The development dataset was created using routinely-collected healthcare data. This data was collected contemporaneously, and in a prospective fashion, however, they were not collected specifically for the purposes of this study. In prediction modelling studies, the use of routinely collected data enables the accruement of a greater number of events, which increases power to consider a greater number of candidate predictors without risking overfitting. However, the retrospective direction of enquiry creates the possibility of poor-quality data for both predictors and outcome, potential unmeasured predictors and as such

careful evaluation of missing data and application of appropriate methods to address it are essential to minimise the effect on performance and applicability of developed models. [33]

Maternal death during pregnancy or any other complications that preclude delivery at the hospital will not be captured within the source perinatal outcomes database.

Varying diagnostic criteria

Diagnostic criteria used for GDM are controversial. Some professional societies endorse the criteria initially proposed by the International Association of Diabetes and Pregnancy Study Groups but disagreement persists.[4 6 54] There is also the acknowledgement that the optimal diagnostic strategy may vary depending on the characteristics of the local population. [1 8 9] The ideal prognostic prediction model would perform adequately across populations defined by a range of diagnostic criteria. Addressing this challenge will require developed models to be externally validated across these different populations.

Addressing treatment paradox regarding insulin use

Addressing the treatment paradox (in this case with insulin) is a challenge in prediction modelling studies. The traditional approach has been to accept predictions in the context of current care. However, this does not remove the possibility that a potentially useful model may appear to perform poorly due to the confounding effect of the judicious application of effective interventions to individual's whom clinicians subjectively assess to be at high risk of the outcome of interest.

Two solutions to address the problem of treatment paradox in prediction modelling studies have been advocated.[55] Firstly, the use of treatments suspected to confound the predictor-outcome relationship can be set as a predictor in the final model. Secondly, the use of such effective treatments can be included within a composite outcome to be predicted. For this study, both approaches were considered but deemed inappropriate. For the former, the inclusion of the requirement for insulin therapy as a predictor is not possible as this information is not available at the intended moment of prediction—the time of GDM diagnosis, usually around 24-28 weeks gestation. For the later, inclusion of the requirement for insulin therapy within the composite outcome would impair its interpretability as this outcome occurs at a significantly higher frequency than the other component outcomes (31% vs approximately 10% based on our prior work).[50] This is likely to lead to a less meaningful composite that is primarily driven by the need for insulin therapy and no longer predicts what we want (adverse pregnancy outcomes). While many promising novel approaches have been proposed in the statistical literature, such as multi-state modelling or marginal structural models for"treatment drop-ins,[56 57] at time of writing all are primarily based on empirical data and are yet to be applied to clinical prediction problems.

The three possible results from the sensitivity analysis to evaluate the effect of including the decision to treat with insulin will be informative and may be interpreted as follows. If the sensitivity analyses find that the inclusion of the decision to treat with insulin within the outcome:

1) Positively affects model performance, then this suggests the presence of treatment paradox. i.e. pregnancy complications are more likely to occur in the absence of insulin therapy;
2) Has no significant effect on model performance then this suggests that the model is robust with predictive performance not affected by the decision to treat. i.e. the

absolute risk of adverse pregnancy outcomes for an individual woman with GDM is not affected by insulin therapy;

3) Negatively affects model performance, then this would suggest that adverse pregnancy outcomes are more likely to occur in women treated with insulin, and thus imply more 'severe' GDM or a harmful effect for this treatment. (unlikely)

The effect of treatment with insulin will be further evaluated using an IPTW algorithm to weight women according to their propensity of having been treated and transformation of the logistic model into a multinomial model. This multinomial model will have four categories depending on the occurrence of the composite pregnancy outcome and whether the women have received treatment with insulin or not.

Ethics and dissemination

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). This study will be conducted in accordance with the principles of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research (2018).[58 59] All analyses will be conducted using non-identifiable data extracted from a pre-existing dataset. The data is collected as part of routine clinical care for the primary purpose of improving the quality of pregnancy care. Consent was not obtained for the secondary use of this data because it is not practical to do so, and this research is consistent with the primary purpose for which it was collected. This study protocol will be registered on the Australian and New Zealand Clinical Trials Registry. Results will be disseminated via presentation at scientific meetings and publication in peer-reviewed journals.

Conclusion

This study will utilise best practice prediction modelling methodology to develop a prediction model for adverse pregnancy outcomes in women affected by GDM that may be used at the time of diagnosis to aid shared decision-making. This model will be internally validated to calculate the apparent performance and examine and correct for optimism and externally validated to assess geographic and temporal transportability. Finally, the validated model will be evaluated using decision curve analysis to determine its suitability as a basis for a risk-stratified model-of-care.

Further external validation studies will be required to evaluate the settings in which the prediction model performs well and is clinically useful. Further work will be required to support the pragmatic implementation and evaluation of the prediction model into clinical care.

DECLARATIONS

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Formal analysis: Not applicable.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: SDC reports grants from the National Health and Medical Research Council (NHMRC), Diabetes Australia, the Australian Academy of Science and the Australian Government Department of Education and Training during the conduct of the study; JAB reports grants from the NHMRC during the conduct of the study; BMFF reports grants from CIBER (Biomedical Research Network in Epidemiology and Public Health, Madrid, Spain) during the conduct of the study and HJT reports grants from

the NHMRC and the Medical Research Future Fund during the conduct of the study; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication

Not required.

Ethical approval

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L).

Data availability

Not applicable.

Patient and Public Involvement

Patient and public perspectives will be essential to the formative research required to implement findings of this model development and validation study into clinical practice. As such patients and public will be invited to participate in this phase of our research.

Transparency

SDC and HJT affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as initially planned (and, if relevant, registered) have been explained.

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FIGURE LEGENDS

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

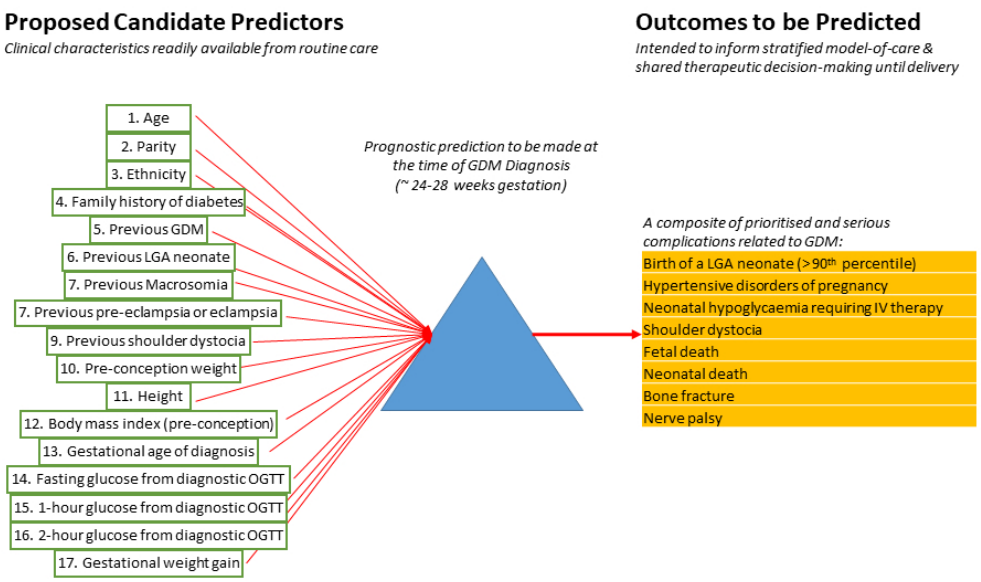

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

239x142mm (96 x 96 DPI)

Table S1. Potential outcomes to be predicted identified in a systematic review and review of other relevant literature.

Outcomes	**Models for pregnancy complications in women with GDM**					**Core outcome set for studies of GDM Treatment[1]**	**Hyperglycaemia and Adverse Pregnancy Outcomes study[2]**	**Model for insulin therapy initiation[3]**
	McIntyre *et al.*[4]	Park *et al.*[5]	Phaloprakarn and Tangjitgamol[6]	Pintaudi *et al.*[7]	Tomlinson *et al* [8]			
Outcomes to be predicted								
Birth of LGA neonate (> 90th percentile)	x	x		x	x	x	1º	x
HDP		x (GH, PE)	x (PE)			x	2º (PE)	
Shoulder dystocia	x%			x			2º (shoulder dystocia or birth injury)	x
Nerve palsy							2º (shoulder dystocia or birth injury)	
Bone fracture							2º (shoulder dystocia or birth injury)	
Perinatal (fetal and neonatal) death				x		x (neonatal death, stillbirth)		
Neonatal hypoglycaemia	x	x		x		x	1º (clinical)	x
Requirement for insulin therapy		x				x (Requirement & type of pharmacological therapy for hyperglycaemia)		

Outcomes excluded from prediction								
Birth weight						x		
Preterm birth						x	2º (delivery before 27 weeks gestation)	x (Early delivery, < 37 weeks)
Adherence to the intervention						x		
GWG						x		
Caesarean delivery	x[#]					x (Mode of birth)	1º (primary caesarean delivery)	x
SGA (<10th percentile)				x		x		x
GA at birth						x		
Neonatal jaundice		x		x			2º (hyperbilirubinaemia)	x
Neonatal adiposity	x							
Neonatal hyperinsulinaemia	x	x					1º	
Admission to the NICU		x		x			2º	
Malformations				x				
Neonatal hypocalcaemia				x				
Neonatal respiratory distress syndrome				x				
Cord-blood serum C-peptide level							x	

above the 90th percentile								

GDM, gestational diabetes, COS, core outcome set; LGA, large-for-gestational age; HDP, hypertensive disorders of pregnancy; PE, preeclampsia, GH, gestational hypertension; 2º, primary outcome; 2º, secondary outcome; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit.

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Table S2. Predictors selected for final related models.

Candidate predictors for modelling	**Models for pregnancy complications in women with GDM included in systematic review**					**Model for GDM Diagnosis[1]**	**Model for insulin therapy initiation[2]**
	McIntyre *et al.*[3]	Park *et al.*[4]	Phaloprakarn and Tangjitgamol[5]	Pintaudi *et al.*[6]	Tomlinson *et al* [7]		
Age	x				x		x
Parity	x						
Gestational age of diagnosis			x				x
Fasting glucose from diagnostic OGTT	x	x			x	NA	x
1-hour glucose from diagnostic OGTT	x					NA	
2-hour glucose from diagnostic OGTT	x					NA	
Ethnicity							
Family history of diabetes				x			x
Gestational weight gain					x		
Previous GDM							x
History of macrosomia					x		
BMI	x (at time of OGTT)	x (at time of diagnosis)	x (first trimester)	x (pre-pregnancy)			x
Height	x						
Poor glycaemic control		x	x				
Enlarged fetal abdominal circumference on ultrasound					x		
HbA1c at diagnosis							x

GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index.

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2. Barnes RA, Wong T, Ross GP, et al. A novel validated model for the prediction of insulin therapy initiation and adverse perinatal outcomes in women with gestational diabetes mellitus. *Diabetologia* 2016;59(11):2331-38. doi: 10.1007/s00125-016-4047-8 [published Online First: 2016/07/10]

3. McIntyre HD, Gibbons KS, Lowe J, et al. Development of a risk engine relating maternal glycemia and body mass index to pregnancy outcomes. *Diabetes Res Clin Pract* 2018;139:331-38. doi: 10.1016/j.diabres.2018.02.036 [published Online First: 2018/03/20]

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7
	5c	D;V	Give details of treatments received, if relevant.	7
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	9
Sample size	8	D;V	Explain how the study size was arrived at.	10
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	10
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	11
	10c	V	For validation, describe how the predictions were calculated.	11
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	11
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	11
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	NA
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	NA
	15b	D	Explain how to the use the prediction model.	NA
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	NA
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	NA
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	20

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Model design and protocol for development and validation of the PeRSonal GDM pregnancy risk model

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TITLE PAGE

Title

Model design and protocol for development and validation of the PeRSonal GDM pregnancy risk model

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ABSTRACT

Introduction

Gestational diabetes (GDM) is a common yet highly heterogeneous condition. The ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman with GDM would allow preventative and therapeutic interventions to be delivered to women at high-risk, sparing women at low-risk from unnecessary care. The PrEdiction for Risk-Stratified care for women with GDM (PeRSonal GDM) Study will develop, validate and evaluate the clinical utility of a prediction model for adverse pregnancy outcomes in women with GDM.

Methods and analysis

We undertook formative research to conceptualise and design the prediction model. Informed by these findings, we will conduct a model development and validation study using a retrospective cohort design with participant data collected as part of routine clinical care across three hospitals. The study will include all pregnancies resulting in births from 1 July 2017 to 31 December 2018 coded for a diagnosis of GDM (estimated sample size 2,430 pregnancies). We will use a temporal split-sample development and validation strategy. A multivariable logistic regression model will be fitted. The performance of this model will be assessed, and the validated model will also be evaluated using decision curve analysis. Finally, we will explore modes of model presentation suited to clinical use, including electronic risk calculators.

Results

There is a need to estimate the absolute risk of a composite of prioritised, objective and serious adverse pregnancy outcomes using clinical characteristics routinely available at the time of GDM diagnosis. We will report the results of model development and validation at study completion.

Ethics and dissemination

This study was approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). We will disseminate results via presentations at scientific meetings and publication in peer-reviewed journals.

Registration

Systematic review proceeding this work was registered on PROSPERO (CRD42019115223).

ARTICLE SUMMARY

Strengths and limitations of this study

- We have designed a prediction model to meet an established clinical need by integrating learnings from a systematic review and critical appraisal of existing models, consensus from a clinical study steering committee and consideration of consumer perspectives.
- This study will build upon relevant literature, including a systematic review of existing prediction modelling studies to formulate a composite of prioritised, objective and serious adverse pregnancy outcomes and identify a broad series of relevant candidate predictors.

- We will adopt best practice methods for model development and validation framed by learnings from a critical appraisal of existing models.
- We will develop and validate the model using routinely-collected healthcare data in an ethnically and socioeconomically diverse population from multiple hospitals. This data was collected contemporaneously and prospectively, albeit not specifically for the purposes of this study hence missing data is likely.
- We will use decision curve analysis to formally evaluate the clinical utility of the model. This will inform the suitability of the validated model as a basis for risk-stratified model-of-care.

KEYWORDS

gestational diabetes, prediction model, prognosis, pregnancy complications, adverse pregnancy outcomes, large-for-gestational-age (LGA), pre-eclampsia, neonatal hypoglycaemia

MAIN TEXT

INTRODUCTION

Gestational diabetes (GDM) is diabetes that is first diagnosed during pregnancy, typically the second or third trimester of pregnancy and not consistent with pre-existing type 1 or type 2 diabetes.[1] It is a prominent health concern as it is common, affecting 7.5% to 27.0% of pregnancies,[2] and confers an increased risk of complications with health consequences for mother and baby.[3] However, current approaches to care are based on the false premise that the diagnostic criteria used define a group of women who are all at high-risk of adverse pregnancy outcomes.[4] In reality, the identified group is highly heterogeneous with a broad and continuous range of risk related to inter-related factors, which are inadequately integrated into the current glucocentric treatment paradigm. Therefore, the ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman with GDM would support shared decision-making and a personalised approach to care. Here, the intensity of intervention could be stratified by risk of pregnancy complications such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from unnecessary intervention.

The International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria sought to translate the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study into clinical practice.[4 5] This large multi-national prospective cohort study demonstrated that the risk of two adverse pregnancy outcomes (birth of a large-for-gestational-age neonate, clinical neonatal hypoglycaemia), an obstetric intervention (primary caesarean section) and a surrogate marker for fetal hyperglycaemia (cord-blood serum C-peptide > 90th percentile) was positively associated with maternal glycaemia at 24 to 28 weeks gestation as measured by an oral glucose tolerance test (OGTT). The IADPSG diagnostic criteria dichotomise the risks related to GDM on serum glucose levels using an odds ratio of 1.75 for the above outcomes. The use of an arbitrary threshold has led to disagreement amongst experts and professional societies.[6 7] Indeed the optimal diagnostic strategy may vary depending on the characteristics of the local population.[1 8 9] Ultimately, these diagnostic criteria have had the unintended consequence of fostering a glucocentric approach to the treatment of GDM. This study will address this need for a more refined method of risk prediction and the targeting of intervention.

The need for refined and targeted approaches is strengthened by the heterogeneous population defined by current diagnostic criteria for GDM.[10] Pregnancy risk is clearly related to elevated glucose in GDM, but the relationship is complex, and an individual's risks are modified by interrelated factors including maternal weight,[11 12] gestational weight gain,[13] ethnicity,[14] and genotype.[15] For example, it has recently been shown that within the two largest maternity services in Australia, ethnic Chinese women with GDM had a lower risk of large-for-gestational-age (LGA) babies and neonatal hypoglycaemia compared to Caucasian women, even adjusting for confounders.[16] A prediction model could integrate these risk factors to estimate risk of adverse pregnancy outcome.

The feasibility of estimating an individual's absolute risk of adverse pregnancy outcomes by integrating oral glucose tolerance test results, maternal weight and pregnancy history was established in our systematic review.[17] However, critical appraisal established that existing prediction models were not yet suitable for application to clinical practice due to high risks of bias due to methodologic limitations. The Prediction for Risk-Stratified care for women with

GDM (PeRSonal GDM) study will leverage the rapidly evolving methodologic advances in prediction modelling to achieve the evolution required to transform promising statistical models into useful clinical tools. In this project, we integrate the findings of this systematic review and critical appraisal of existing models, pertinent findings from landmarks trials, clinical expertise and best practice methods from contemporary guidelines to inform the methodological design of the PeRSonal GDM study.

Objectives

The aims of the PeRSonal GDM study are to:

1. Develop and internally validate a prediction model for adverse pregnancy outcomes in GDM to aid shared decision-making and stratify care;
2. Externally validate the model to demonstrate temporal transportability;
3. Evaluate the clinical utility of the model as a basis for a risk-stratified model-of-care.

METHODS AND ANALYSIS

This work was undertaken in two sequential phases to maximise the clinical acceptability and robustness of the proposed model. Phase I focussed on establishing the requirements of the model (prediction model design). Phase II focuses on the development and validation of a model to address these requirements. Here we report the methods and results from Phase I and the methods for Phase II, the study protocol for the PeRSonal GDM study, the results of which will be reported at completion.

Phase I: Prediction model design

We conducted formative research to conceptualise and design a robust and clinically acceptable prediction model. First, a systematic review and critical appraisal of existing prediction models for adverse pregnancy outcomes in women with GDM was conducted following a peer-reviewed protocol.[18] Second, the study steering committee comprising two obstetricians, three endocrinologists and a neonatologist formulated key clinical requirements of the prediction model. Finally, a multidisciplinary clinical working group was formed to provide feedback on the proposed requirements, gauge its clinical acceptability and consider its clinical application. The working group included endocrinologists (n = 9), diabetes nurse educators (n = 3), dieticians (n = 2), midwives (n = 2), administration staff (n = 2) and an obstetrician (n = 1) actively involved in the provision of GDM care at several maternity hospitals. We considered consumer perspectives throughout this process, from parallel qualitative research on GDM diagnosis and risk.[19]

Having established the fundamental clinical requirements of the prediction model the study steering committee considered (a) which outcomes should be the subject of prediction and (b) which predictors should be evaluated in model development (candidate predictors). This work was informed by relevant literature and clinical experience.

Phase II: Model development and validation

Study design

We will conduct a prediction model development and validation study using a retrospective cohort design. It will be conducted following expert guidance for model development and validation,[20-25] and reported per the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[26]

Data sources and validation strategy

This study will use routinely collected health data for pregnancies resulting in a birth from 1 July 2017 to 31 December 2018 from an existing pregnancy outcomes database from a maternity service. Maternal, obstetric and neonatal data are collected prospectively for all women booked to deliver their baby at the service. This data is collected with consent as part of routine clinical care. This data is of high-quality and completeness as it is collected under statute with the primary aim to facilitate improvements in quality of care. We will link these data deterministically to pathology data and clinical data extracted from the medical record of the parent health service. Linked pathology data is available for approximately 70% of pregnancies, and linked clinical data is available for approximately 90% of pregnancies. All collected data will be rendered non-identifiable for all research purposes, including analysis.

The data will be split by time into two groups (analysis type 2b in TRIPOD).[27] We will develop the prediction model using pregnancies resulting in births from the first 12 months of the study period (1 July 2017 to 30 June 2018). Pregnancies resulting in births from the last six months of the study period (1 July 2018 to 31 December 2018) will be used to evaluate the predictive performance of the developed model (external validation). This strategy will evaluate the temporal transportability of the model.

Participants

Study setting

This maternity service is one of the largest in Australia, provides universal access to healthcare comprising multiple large maternity hospitals and serves an ethnically and socioeconomically diverse population within a catchment of 1.6 million in South-East Melbourne. All levels of maternity care are available across the three hospitals with shared staff and institutional protocols and practices. Maternity care is provided to more than 9,000 women each year.

Eligibility criteria

Pregnancies coded for GDM during the study period stated above will be included. There will be no exclusion criteria.

Treatment received

GDM is diagnosed and treated following institutional protocol and practices. At our service GDM is diagnosed using the International Association of Diabetes and Pregnancy Study Groups 2010 criteria,[4] as endorsed by the Australian Diabetes in Pregnancy Society with universal screening at 24-28 weeks with a one-step procedure using the 75g OGTT.[6] Early screening is based on the presence of risk factors as soon as practicable using the same testing procedure with a repeat at 24-28 weeks if negative. The treatment package for GDM consists of an initial 2-hour group education session with diabetes nurse educator and dietician. Lifestyle management involves dietary modification, physical activity and weight management. Follow up reviews occur with an endocrinologist or endocrinology specialist trainee every one to three weeks. Insulin is commenced where glucose targets (fasting < 5.5 mmol/L and 2-hour post-prandial < 7.0 mmol/L) are not met and are not amenable to further dietary modification. Metformin is used where there is evidence of significant insulin resistance, where targets are not achieved with insulin alone or when insulin use is relatively contraindicated due to the risk of significant psychological harm.

Outcome

The outcome to be predicted will be a composite consisting of a combination of eight prioritised, objective and serious adverse pregnancy outcomes defined in Table 1.

Table 1. The adverse pregnancy outcomes to be predicted: Definition, variable type and categories.

Outcome	Definition
Maternal	
Hypertensive disorders of pregnancy	Pregnancy-induced hypertension, pre-eclampsia or eclampsia
Fetal/ Neonatal	
LGA	Birth weight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[28]
Neonatal hypoglycaemia requiring intravenous treatment	A neonate with a low blood glucose level fulfilling institutional criteria for intravenous treatment consisting of either a dextrose bolus or dextrose infusion
Shoulder dystocia	When, after delivery of the head, the baby's anterior shoulder gets caught above the mother's pubic bone
Fetal death	Death of fetus after 20 weeks gestation
Neonatal death	Death of live-born neonate
Bone fracture	Neonatal fracture (femur, humerus, clavicle or skull) suffered at birth
Nerve palsy	Neonatal nerve palsy (brachial plexus injury or facial nerve injury) suffered at birth

LGA, large-for-gestational-age

Outcome assessment

LGA assessment will be based on a population-based growth chart rather than customised centiles to avoid incorporation of predictor information such as ethnicity into outcome assessment. Blinding to predictors in the assessment of the outcome will not be feasible.

Predictors

Definition of predictors and measurement

Candidate predictors to be evaluated for inclusion in the model are defined in Table 2. There will be no blinding between the assessment of a predictor and the outcome nor to other predictors.

Table 2. Candidate predictors to be evaluated in model development: Definition, variable type and units/ categories.

Candidate predictor	Definition	Variable type	Units/ categories
Demographics			
Age	Mother's age	continuous	years
Clinical history			
Nulliparity	The condition in a woman of never having given birth	binary	0 "No" 1 "Yes"
Gestational age at diagnosis	Gestational age at diagnosis of GDM in the index pregnancy	continuous	weeks' gestation

Ethnicity	Self-reported ethnicity with classification aligned to the Australian Standard Classification of Cultural and Ethnic Groups[29]	categorical	ethnicity classified into approximately 5-6 categories
Previous GDM	Previous diagnosis of GDM	binary	0 "No" 1 "Yes"
Previous LGA	Previous child with birthweight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[28]	binary	0 "No" 1 "Yes"
Previous pre-eclampsia or eclampsia	Pre-eclampsia or eclampsia in a previous pregnancy	binary	0 "No" 1 "Yes"
Previous shoulder dystocia	Shoulder dystocia in a previous pregnancy	binary	0 "No" 1 "Yes"
Family history of diabetes	Any family history of diabetes	binary	0 "No" 1 "Yes"
Height	The mother's self-reported height at about the time of conception.	continuous	centimetres (cm)
Body mass index	Body mass divided by the square of the body height	continuous	kg/m2
Weight	Mother's self-reported weight (body mass) about the time of conception	continuous	kilograms (kg)
Physical examination			
Incremental gestational weight gain	Weight at first GDM clinic appointment (at around 30 weeks gestation) minus preconception weight divided by gestational weeks completed at the time of the first GDM clinic appointment	continuous	kilograms (kg)
Laboratory investigations			
Fasting glucose from diagnostic OGTT	Glucose level from baseline or time zero of diagnostic oral glucose tolerance test	continuous	mmol/L
1h glucose from diagnostic OGTT	Glucose level 1 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L
2h glucose from diagnostic OGTT	Glucose level 2 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L

GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index

Data extraction

We will extract records for eligible participants to create a research dataset with each observation representing a pregnancy. Participants may be included more than once due to multiple pregnancy or repeat pregnancies within the study period. We will manually review

eligible participant's medical record to ensure the accuracy of the diagnosis of GDM. Linked pathology and additional clinical data will be extracted and merged with the research dataset. The research dataset will be rendered non-identifiable for all subsequent analyses.

Sample size

In this study, the adequacy of the sample size of our developmental dataset will be determined by the total number of events of the composite binary outcome. Approximately 9,000 women are delivered annually at the institution from which the development dataset will be derived. The prevalence of GDM at this institution is 18% (unpublished data). Therefore, over the 12-month period used for model development, we conservatively estimate that the development dataset will include 1,620 cases of women with GDM. We anticipate that at least 10% of these women will deliver neonates that have a birth weight that is LGA defined as greater than the 90th percentile for the population (approximately 162 events). Furthermore, using unpublished data from our institution, the prevalence of hypertensive disorders of pregnancy is 7% (approximately 113 events) and neonatal hypoglycaemia requiring IV treatment is 11% (approximately 178 events). Therefore the expected event count is greater than 453 once the additional contribution of the less common component outcomes are also considered (shoulder dystocia, fetal death, neonatal death, bone fracture, nerve palsy). Given we envisage including up to 20 candidate predictors, our study should be adequately powered as the dataset will have in excess of ten events per predictor as is commonly recommended to avoiding overfitting.[30]

Over the 6-month period used for external validation, the expected event count is 50% of that for the 12-month period used for development, hence approximately 225. This is greater than the recommended minimum of 100 events for validation.[31]

Missing data

We do not expect considerable missing data, but some will inevitably occur, with not all cases providing all variables of interest. Handling of missing data will be determined individually on a per predictor basis. The missing indicator method will be used for predictors where data is missing not at random. Multiple imputation by chained equations will be used to impute missing data as long as the data is missing at random. If necessary, we will include a supplementary table comparing predictor distributions between patients with missing data and patients with complete data.

Statistical analysis methods

To make individualized predictions for the binary composite of an adverse pregnancy outcome, we will apply a logistic regression model with the composite outcome as the dependent variable.

Handling of predictors

Continuous variables will be kept as continuous in the model (rather than dichotomising), to avoid a loss of prognostic information. Those predictors that are highly correlated with others contribute little information and will be excluded from the statistical analysis.

The functional form of the relationship of continuous predictors with the outcome will be assessed. If non-linear they will be modelled with fractional polynomials (FP). If this is the case, as several continuous variables were included in the model, we will use the multivariable fractional polynomial algorithm. Multiple imputation and FPs will be combined using the procedure described by Morris and colleagues.[32]

Model-building procedures (including predictor selection)

Candidate predictor variables will be selected *a priori* based on existing literature and clinical expertise as described above. During modelling, predictors will be selected by using a LASSO (Least Absolute Shrinkage and Selection Operator) method, which simultaneously selects the variables and penalises the model coefficients for over-optimism.[33]

Examination of predictor interactions will be undertaken for the following groups of predictors: weight, gestational weight gain (GWG) and body mass index (BMI), and fasting, 1h and 2h glucose levels from OGTT.

Internal validation and assessment of model performance

The model performance will be assessed in terms of discrimination and calibration. We will use a bootstrap re-sampling technique to adjust for over-optimism in the estimation of model performance due to validation in the same dataset that is used to develop the model itself. We will use the area under the curve (AUC) of the receiver operating characteristic (ROC) curve with 95% confidence interval to assess the overall discriminatory ability of the developed model. We will report the apparent and adjusted for over-optimism model performance. A calibration plot will be created. This plot will facilitate the graphical assessment of calibration by putting affected women into groups ordered by predicted risk and considering the agreement between the mean predicted risk and the observed events in each risk group, usually deciles. The calibration will be summarized using the intercept and slope of the calibration plot. Internal validation, where the model's predictions are compared to the observed data, should return perfect calibration to the development data (calibration slope = 1).

External validation

External validation of the developed model will be undertaken to assess temporal transportability. It will be undertaken using the model coefficients from the developed model to calculate the risk for each woman. We will report the predictive performance in a more recently treated cohort at the same maternity service using the same measures of discrimination and calibration as used in internal validation. Development and validation data are identical in terms of eligibility criteria, outcome and predictors.

Presentation of a simplified model for clinical use

Once a final model is identified, we will simplify and adapt the presentation of the model to facilitate its application to clinical practice. Alternative modes of presentation will be explored with a focus on maximising end-user usability and promoting translation into clinical care. Various presentation formats will be considered, including a simplified scoring system, nomogram and web or app-based electronic risk calculators.

Assessment of clinical utility

To supplement traditional measures of predictive model performance, discrimination and calibration, clinical utility will be formally evaluated. We will use decision curve analysis to explore the net benefit of developed models over the entire range of probability thresholds.[23 27 34] We will represent the net benefit as a function of the decision threshold in a decision curve plot. This will explore whether there is an overall net-benefit for using the models to stratify the population into two risk groups as a basis for a risk-stratified model of care:

1. Low-risk where the risk of adverse pregnancy outcomes is less than a pre-specified value—this group may be considered for a less intensive model-of-care;
2. High-risk where the risk is greater than a pre-specified value—this group should receive specialist-led hospital-based care.

Further formative research is planned to ascertain optimal risk thresholds. This will include engagement with stakeholders, including women affected by GDM and clinicians. A combination of focus groups and an electronic survey will be used.

Sensitivity analyses

We will conduct additional analysis to address the confounding effect of insulin treatment on predictor-outcome associations and hence the performance of the prediction model. This will consider four possible approaches with sensitivity analysis used to evaluate the robustness of each:

1. Derivation of a propensity score of being treated with insulin based on women pre-treatment characteristics. We will then weight observations by using the inverse probability of treatment weighting (IPTW). In this way, women with lower propensity to be treated will have more weight in the development of the prognostic model than those who had a higher probability of being treated.
2. Inclusion of insulin treatment as a component of the composite outcome.
3. Exclusion of cases where insulin treatment was used.
4. Exploration of the multinomial regression model framework for combinations of the composite outcome of adverse pregnancy outcome and insulin treatment.

The primary analysis will develop and validate a model based on clinical characteristics. Prognosis may also be influenced by an affected woman's capacity to implement lifestyle measures such a dietary modification and increased exercise. Therefore, we will undertake a sensitivity analysis to evaluate whether measures of socioeconomic disadvantage can improve the prediction of adverse pregnancy outcomes.

All statistical analysis will be performed using Stata version 16.1 (College Station, TX: StataCorp LLC.).

Patient and Public Involvement

No patient and public involvement in the development of this protocol. Patient and public perspectives will be essential to the formative research required to implement findings of this model development and validation study into clinical practice. As such patients and public will be invited to participate in this phase of our research.

RESULTS

Phase I: Prediction model design

The fundamental clinical requirements of the prediction model were established (Table 3), and a model addressing these requirements was designed (Figure 1).

Table 3. The fundamental requirements of a prediction model for adverse pregnancy outcomes in women with gestational diabetes.[35] Framework adapted from that originally

proposed by Moons and colleagues to consider in framing a systematic review of prediction modelling studies.[35]

Criteria	Specifications
1. Prognostic versus diagnostic prediction model	The aim is to predict future events (prognostic prediction model)
2. Intended scope	To inform clinicians' therapeutic decision-making and serve as a rational basis for the stratification of GDM care
3. The target population to whom the prediction model applies	Pregnant women with GDM, per diagnostic criteria in clinical practice
4. The outcome to be predicted	Pregnancy complications related to GDM affecting the mother (obstetric or maternal) or the baby (fetal or neonatal)
5. Timespan of prediction	Complications occurring during pregnancy or soon after birth
6. Intended moment of using the model	At diagnosis of GDM, typically at 24 to 28 weeks gestation but may be earlier

GDM, gestational diabetes.

Formulation of outcome(s) to be predicted

The study steering committee considered a large number of adverse pregnancy outcomes for inclusion in the composite (Online Supplementary Table S1). Outcomes predicted by existing models identified in our systematic review and predicted by a related model for insulin therapy initiation[36] were considered. The working group also considered outcomes in the final core outcome set (COS) for GDM treatment research.[37] Reference to the COS for future GDM treatment research provided objective prioritisation of outcomes from a large international multidisciplinary group of relevant stakeholders. Finally, the group considered all outcomes studied in the HAPO study,[5] the landmark international multi-centre observational study that demonstrated associations between increasing levels of glucose levels on oral glucose tolerance testing and adverse pregnancy outcomes.

From this, a composite outcome was constructed to reflect the multiple adverse pregnancy outcomes related to GDM. Construction of the composite outcome considered recommendations that components are (1) of similar importance, (2) occur with similar frequency and (3) are likely to have similar relative risk reductions (or predictive effects moving in the same direction) with similar underlying biology.[38] The rationale for inclusion or exclusion from the composite outcome to be predicted is presented in Table 4.

Table 4. The rationale for outcomes to be predicted.

Outcomes	Clinical rationale for inclusion/ exclusion
Outcomes to be predicted	
LGA (> 90th percentile)	Excess fetal growth is the central adverse pregnancy outcome in pregnancies affected by GDM with many mechanisms implicated including but not limited to the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[39] This adverse outcome is also upstream on the causal pathway to other clinically relevant complications, including those related to difficulties at delivery. LGA will be used rather than macrosomia as it is a measure of birth weight corrected for gestational age and is also less variably defined.[40]
HDP	Significant association with GDM and if at high-risk, then closer monitoring during pregnancy may be required.
Shoulder dystocia	Associated with GDM and clinically significant.
Nerve palsy	May be associated with GDM and clinically significant.
Bone fracture	May be associated with GDM and clinically significant.
Perinatal (fetal and neonatal) death	Rare but of utmost clinical significance.
Neonatal hypoglycaemia	This is the central marker of the maladaptive metabolic response of the neonate exposed to hyperglycaemia in utero as per the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[41] Severe cases requiring intravenous treatment are likely to be most clinically relevant.
The requirement for insulin therapy	A treatment for GDM that reduces the risk of some adverse outcomes.
Outcomes excluded from prediction	
Preterm birth	Not directly related to GDM and may be more related to IUGR; strongly clinician-driven.
Adherence to the intervention	Possible predictor.
GWG	Possible predictor.
Caesarean delivery	Highly clinician-driven and institution dependent.
SGA (<10th percentile)	Not directly related to GDM, more related to IUGR.
GA at birth	May be clinician-driven.
Neonatal jaundice	Only severe cases are clinically relevant and may be more closely related to prematurity rather than the maternal hyperglycaemia of GDM.
Neonatal adiposity	Not routinely assessed in clinical practice.

Neonatal hyperinsulinaemia	Neonatal hypoglycaemia is a more meaningful clinical outcome.
Admission to the NICU	Highly clinician-driven and institution dependent.
Malformations	Associated with pre-gestational diabetes and less relevant in gestational diabetes.
Neonatal hypocalcaemia	As its severity is related to the level of hyperglycaemia unlike in pre-gestational diabetes, it is rarely seen in GDM and if present is usually asymptomatic and resolves spontaneously.[42]
Neonatal respiratory distress syndrome	Only severe cases are clinically relevant and may be more closely related to prematurity rather than hyperglycaemia.[43]
Cord-blood serum C-peptide level above the 90th percentile	Not routinely assessed in clinical practice and clinical relevance unclear.

GDM, gestational diabetes; LGA, large-for-gestational-age; HDP, hypertensive disorders of pregnancy; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational-age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit

Identification of candidate predictors

Candidate predictors were identified from those selected for the final models included in the systematic review of models for pregnancy complications in women with GDM, selected in a model for GDM diagnosis previously developed by our group,[44] and selected in a related model for insulin therapy initiation.[36] (Online Supplementary Table S2) Thirteen of the 16 predictors from these existing related models will be evaluated for inclusion in this prediction modelling study (Table 2). Three predictors selected for related models (poor glycaemic control, enlarged abdominal circumference and HbA1c at diagnosis) could not be evaluated in this study as the data are not routinely collected at our service.

One previous study selected history of macrosomia as a predictor for LGA. [45] Indeed, in clinical practice, past history is often seen as a major risk factor for future occurrence. Therefore, this study will evaluate previous histories of components of the composite outcome for inclusion in the model. Such data is available for macrosomia, LGA, pre-eclampsia and eclampsia, and shoulder dystocia, and therefore, these four predictors will be evaluated as candidate predictors.

In addition to the candidate predictors identified from their use in existing related models, ethnicity and GWG were identified as potential predictors requiring formal evaluation due to the emergence of evidence supporting their role as significant prognostic factors. Chinese women affected by GDM were at a lower risk of a range of adverse pregnancy outcomes including LGA and neonatal hypoglycaemia compared to affected Caucasian women in an Australian cohort,[16] and South Asian babies exposed to GDM were smaller across gestation than babies of White European in an English cohort.[46] Emerging physiologic data suggests highly variable degrees of beta-cell function and insulin resistance amongst women diagnosed with GDM,[47] and that classifying women with GDM by these physiologic defects may stratify women by their risk of adverse pregnancy outcomes.[48] Ethnicity may serve as a surrogate marker for these physiologic defects avoiding the need for additional investigations. Hence, ethnicity is an appealing candidate predictor for models to predict the development of adverse pregnancy outcomes.

GWG has also been shown to be a risk factor for adverse pregnancy outcomes, independent of BMI.[13] Specifically, GWG is associated with an increased proportion of LGA over and above that which is associated with GDM and overweight or obesity, in a general obstetric population.[49] BMI, parity and GWG together, better predict adverse pregnancy outcomes than BMI alone in a cohort attending a general antenatal clinic (women with GDM and normoglycaemia).[50] The effect of GWG is likely to be modified by other predictors, including ethnicity, supporting its integration within a multivariable model rather than a single prognostic factor-based approach.

Phase II: Model development and validation

The results from Phase II will be reported at the completion of this proposed study.

DISCUSSION

Strengths

The formative research undertaken established the clinical need for a robust prediction model for adverse pregnancy outcomes in GDM to support therapeutic decision-making and stratification of care. Engagement with stakeholders in the model design stage should

improve the clinical acceptability of the model and support future implementation efforts. The composite outcome of prioritised, objective and serious adverse events was formulated with reference to a systematic review and critical appraisal of existing models (manuscript submitted for publication, 2020), the relevant core outcome set,[51] and clinical expertise of endocrinologists, obstetricians and a neonatologist. This composite will be composed of LGA, neonatal hypoglycaemia, hypertensive disorders of pregnancy, shoulder dystocia, severe birth trauma (nerve palsy and bone fracture) and perinatal death. The transportability of the developed model will also be enhanced by the selection of candidate predictors using existing literature and clinical expertise, independent of the predictor-outcome association in the development dataset.

Prediction of a composite outcome will more accurately quantify the multiple adverse pregnancy outcomes related to GDM and therefore, will be more translatable into clinical practice. This composite will be valid and clinically useful because the component outcomes are of similar importance, the three main components (LGA, neonatal hypoglycaemia and hypertensive disorders of pregnancy) occur with a similar frequency (approximately 10%), [52] and the predictive effects are likely to move in the same direction due to similar underlying biology.[38]

A method to estimate the absolute risk of adverse pregnancy outcomes for an individual woman affected by GDM would be of great benefit to affected woman, their clinicians and the health system. It would allow affected woman to better understand the implication of GDM on their pregnancy and facilitate shared-decision making with clinicians regarding the relative risks and benefits of interventions. At a system-level these individualised risk estimates would support a risk-stratified model-of-care which recognises the breadth and continuum of pregnancy risk attributable to GDM such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from low-value care. Ultimately, a robust prediction model would facilitate the transition from a glucocentric model-of-care to an individualised and holistic approach to this widespread public health problem.

Translating prediction models into clinical care is challenging.[53-55] Previous efforts of addressing this clinical prediction problem have been hampered by the use of methods, which increase the risk of biased predictions limiting the transportability of developed models to new but related populations (manuscript submitted for publication, 2020). Thus, rigorous and robust methods have been adopted for model development and validation in this study. Methods have been framed by the learnings from our critical appraisal of existing models and will be guided by Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement.[26]

Limitations

Use of routine-collected healthcare data

The development dataset was created using routinely-collected healthcare data. This data was collected contemporaneously, and in a prospective fashion, however, they were not collected specifically for the purposes of this study. In prediction modelling studies, the use of routinely collected data enables the accruement of a greater number of events, which increases power to consider a greater number of candidate predictors without risking overfitting. However, the retrospective direction of enquiry creates the possibility of poor-quality data for both predictors and outcome, potential unmeasured predictors and as such

careful evaluation of missing data and application of appropriate methods to address it are essential to minimise the effect on performance and applicability of developed models. [35]

Maternal death during pregnancy or any other complications that preclude delivery at the hospital will not be captured within the source perinatal outcomes database.

Varying diagnostic criteria

Diagnostic criteria used for GDM are controversial. Some professional societies endorse the criteria initially proposed by the International Association of Diabetes and Pregnancy Study Groups but disagreement persists.[4 6 56] There is also the acknowledgement that the optimal diagnostic strategy may vary depending on the characteristics of the local population.[1 8 9] The ideal prognostic prediction model would perform adequately across populations defined by a range of diagnostic criteria. Addressing this challenge will require developed models to be externally validated across these different populations.

Addressing treatment paradox regarding insulin use

Addressing the treatment paradox (in this case with insulin) is a challenge in prediction modelling studies. The traditional approach has been to accept predictions in the context of current care. However, this does not remove the possibility that a potentially useful model may appear to perform poorly due to the confounding effect of the judicious application of effective interventions to individual's whom clinicians subjectively assess to be at high risk of the outcome of interest.

Two solutions to address the problem of treatment paradox in prediction modelling studies have been advocated.[57] Firstly, the use of treatments suspected to confound the predictor-outcome relationship can be set as a predictor in the final model. Secondly, the use of such effective treatments can be included within a composite outcome to be predicted. For this study, both approaches were considered but deemed inappropriate. For the former, the inclusion of the requirement for insulin therapy as a predictor is not possible as this information is not available at the intended moment of prediction—the time of GDM diagnosis, usually around 24-28 weeks gestation. For the later, inclusion of the requirement for insulin therapy within the composite outcome would impair its interpretability as this outcome occurs at a significantly higher frequency than the other component outcomes (31% vs approximately 10% based on our prior work).[52] This is likely to lead to a less meaningful composite that is primarily driven by the need for insulin therapy and no longer predicts what we want (adverse pregnancy outcomes). While many promising novel approaches have been proposed in the statistical literature, such as multi-state modelling or marginal structural models for"treatment drop-ins,[58 59] at time of writing all are primarily based on empirical data and are yet to be applied to clinical prediction problems.

The three possible results from the sensitivity analysis to evaluate the effect of including the decision to treat with insulin will be informative and may be interpreted as follows. If the sensitivity analyses find that the inclusion of the decision to treat with insulin within the outcome:

1) Positively affects model performance, then this suggests the presence of treatment paradox. i.e. pregnancy complications are more likely to occur in the absence of insulin therapy;
2) Has no significant effect on model performance then this suggests that the model is robust with predictive performance not affected by the decision to treat. i.e. the

absolute risk of adverse pregnancy outcomes for an individual woman with GDM is not affected by insulin therapy;

3) Negatively affects model performance, then this would suggest that adverse pregnancy outcomes are more likely to occur in women treated with insulin, and thus imply more 'severe' GDM or a harmful effect for this treatment. (unlikely)

The effect of treatment with insulin will be further evaluated using an IPTW algorithm to weight women according to their propensity of having been treated and transformation of the logistic model into a multinomial model. This multinomial model will have four categories depending on the occurrence of the composite pregnancy outcome and whether the women have received treatment with insulin or not.

Ethics and dissemination

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). This study will be conducted in accordance with the principles of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research (2018).[60 61] All analyses will be conducted using non-identifiable data extracted from a pre-existing dataset. The data is collected as part of routine clinical care for the primary purpose of improving the quality of pregnancy care. Consent was not obtained for the secondary use of this data because it is not practical to do so, and this research is consistent with the primary purpose for which it was collected. This study protocol will be registered on the Australian and New Zealand Clinical Trials Registry. Results will be disseminated via presentation at scientific meetings and publication in peer-reviewed journals.

DECLARATIONS

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Competing interests

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Patient consent for publication

Not required.

Ethical approval

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L).

Data availability

Not applicable.

Transparency

SDC and HJT affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as initially planned (and, if relevant, registered) have been explained.

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FIGURE LEGENDS

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

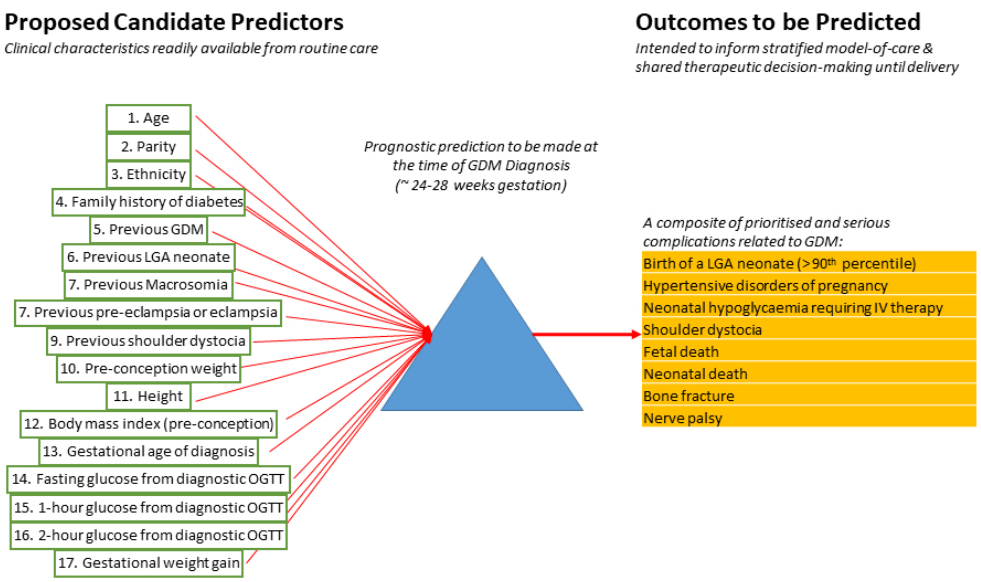

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

239x142mm (96 x 96 DPI)

Table S1. Potential outcomes to be predicted identified in a systematic review and review of other relevant literature.

Outcomes	**Models for pregnancy complications in women with GDM**					**Core outcome set for studies of GDM Treatment[1]**	**Hyperglycaemia and Adverse Pregnancy Outcomes study[2]**	**Model for insulin therapy initiation[3]**
	McIntyre *et al.*[4]	Park *et al.*[5]	Phaloprakarn and Tangjitgamol[6]	Pintaudi *et al.*[7]	Tomlinson *et al* [8]			
Outcomes to be predicted								
Birth of LGA neonate (> 90th percentile)	x	x		x	x	x	1º	x
HDP		x (GH, PE)	x (PE)			x	2º (PE)	
Shoulder dystocia	x%			x			2º (shoulder dystocia or birth injury)	x
Nerve palsy							2º (shoulder dystocia or birth injury)	
Bone fracture							2º (shoulder dystocia or birth injury)	
Perinatal (fetal and neonatal) death				x		x (neonatal death, stillbirth)		
Neonatal hypoglycaemia	x	x		x		x	1º (clinical)	x
Requirement for insulin therapy		x				x (Requirement & type of pharmacological therapy for hyperglycaemia)		

Outcomes excluded from prediction								
Birth weight						x		
Preterm birth						x	2º (delivery before 27 weeks gestation)	x (Early delivery, < 37 weeks)
Adherence to the intervention						x		
GWG						x		
Caesarean delivery	x[#]					x (Mode of birth)	1º (primary caesarean delivery)	x
SGA (<10th percentile)				x		x		x
GA at birth						x		
Neonatal jaundice		x		x			2º (hyperbilirubinaemia)	x
Neonatal adiposity	x							
Neonatal hyperinsulinaemia	x	x					1º	
Admission to the NICU		x		x			2º	
Malformations				x				
Neonatal hypocalcaemia				x				
Neonatal respiratory distress syndrome				x				
Cord-blood serum C-peptide level							x	

above the 90th percentile								

GDM, gestational diabetes, COS, core outcome set; LGA, large-for-gestational age; HDP, hypertensive disorders of pregnancy; PE, preeclampsia, GH, gestational hypertension; 2º, primary outcome; 2º, secondary outcome; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit.

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Table S2. Predictors selected for final related models.

Candidate predictors for modelling	**Models for pregnancy complications in women with GDM included in systematic review**					**Model for GDM Diagnosis[1]**	**Model for insulin therapy initiation[2]**
	McIntyre *et al.*[3]	Park *et al.*[4]	Phaloprakarn and Tangjitgamol[5]	Pintaudi *et al.*[6]	Tomlinson *et al* [7]		
Age	x				x		x
Parity	x						
Gestational age of diagnosis			x				x
Fasting glucose from diagnostic OGTT	x	x			x	NA	x
1-hour glucose from diagnostic OGTT	x					NA	
2-hour glucose from diagnostic OGTT	x					NA	
Ethnicity							
Family history of diabetes				x			x
Gestational weight gain					x		
Previous GDM							x
History of macrosomia					x		
BMI	x (at time of OGTT)	x (at time of diagnosis)	x (first trimester)	x (pre-pregnancy)			x
Height	x						
Poor glycaemic control		x	x				
Enlarged fetal abdominal circumference on ultrasound					x		
HbA1c at diagnosis							x

GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index.

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7
	5c	D;V	Give details of treatments received, if relevant.	7
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	9
Sample size	8	D;V	Explain how the study size was arrived at.	10
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	10
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	11
	10c	V	For validation, describe how the predictions were calculated.	11
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	11
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	11
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	NA
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	NA
	15b	D	Explain how to the use the prediction model.	NA
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	NA
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	NA
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	20

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

BMJ Open

Protocol for development and validation of a clinical prediction model for adverse pregnancy outcomes in women with gestational diabetes

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Date Submitted by the Author:	25-Sep-2020
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Obstetrics and gynaecology, Health services research, Patient-centred medicine, Public health
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, OBSTETRICS, PUBLIC HEALTH

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TITLE PAGE

Title

Protocol for development and validation of a clinical prediction model for adverse pregnancy outcomes in women with gestational diabetes

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ABSTRACT

Introduction

Gestational diabetes (GDM) is a common yet highly heterogeneous condition. The ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman with GDM would allow preventative and therapeutic interventions to be delivered to women at high-risk, sparing women at low-risk from unnecessary care. The Prediction for Risk-Stratified care for women with GDM (PeRSonal GDM) Study will develop, validate and evaluate the clinical utility of a prediction model for adverse pregnancy outcomes in women with GDM.

Methods and analysis

We undertook formative research to conceptualise and design the prediction model. Informed by these findings, we will conduct a model development and validation study using a retrospective cohort design with participant data collected as part of routine clinical care across three hospitals. The study will include all pregnancies resulting in births from 1 July 2017 to 31 December 2018 coded for a diagnosis of GDM (estimated sample size 2,430 pregnancies). We will use a temporal split-sample development and validation strategy. A multivariable logistic regression model will be fitted. The performance of this model will be assessed, and the validated model will also be evaluated using decision curve analysis. Finally, we will explore modes of model presentation suited to clinical use, including electronic risk calculators.

Ethics and dissemination

This study was approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). We will disseminate results via presentations at scientific meetings and publication in peer-reviewed journals.

Registration

Systematic review proceeding this work was registered on PROSPERO (CRD42019115223) and the study was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12620000915954).

ARTICLE SUMMARY

Strengths and limitations of this study

- We have designed a prediction model to meet an established clinical need by integrating learnings from a systematic review and critical appraisal of existing models, consensus from a clinical study steering committee and consideration of consumer perspectives.
- This study will build upon relevant literature, including a systematic review of existing prediction modelling studies to formulate a composite of prioritised, objective and serious adverse pregnancy outcomes and identify a broad series of relevant candidate predictors.
- We will adopt best practice methods for model development and validation framed by learnings from a critical appraisal of existing models.

- We will develop and validate the model using routinely-collected healthcare data in an ethnically and socioeconomically diverse population from multiple hospitals. This data was collected contemporaneously and prospectively, albeit not specifically for the purposes of this study hence missing data is likely.
- We will use decision curve analysis to formally evaluate the clinical utility of the model. This will inform the suitability of the validated model as a basis for risk-stratified model-of-care.

KEYWORDS

gestational diabetes, prediction model, prognosis, pregnancy complications, adverse pregnancy outcomes, large-for-gestational-age (LGA), pre-eclampsia, neonatal hypoglycaemia

MAIN TEXT

INTRODUCTION

Gestational diabetes (GDM) is diabetes that is first diagnosed during pregnancy, typically the second or third trimester of pregnancy and not consistent with pre-existing type 1 or type 2 diabetes.[1] It is a prominent health concern as it is common, affecting 7.5% to 27.0% of pregnancies,[2] and confers an increased risk of complications with health consequences for mother and baby.[3] However, current approaches to care are based on the false premise that the diagnostic criteria used define a group of women who are all at high-risk of adverse pregnancy outcomes.[4] In reality, the identified group is highly heterogeneous with a broad and continuous range of risk related to inter-related factors, which are inadequately integrated into the current glucocentric treatment paradigm. Therefore, the ability to calculate the absolute risk of adverse pregnancy outcomes for an individual woman with GDM would support shared decision-making and a personalised approach to care. Here, the intensity of intervention could be stratified by risk of pregnancy complications such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from unnecessary intervention.

The International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria sought to translate the results of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study into clinical practice.[4 5] This large multi-national prospective cohort study demonstrated that the risk of two adverse pregnancy outcomes (birth of a large-for-gestational-age neonate, clinical neonatal hypoglycaemia), an obstetric intervention (primary caesarean section) and a surrogate marker for fetal hyperglycaemia (cord-blood serum C-peptide > 90th percentile) was positively associated with maternal glycaemia at 24 to 28 weeks gestation as measured by an oral glucose tolerance test (OGTT). The IADPSG diagnostic criteria dichotomise the risks related to GDM on serum glucose levels using an odds ratio of 1.75 for the above outcomes. The use of an arbitrary threshold has led to disagreement amongst experts and professional societies.[6 7] Indeed the optimal diagnostic strategy may vary depending on the characteristics of the local population.[1 8 9] Ultimately, these diagnostic criteria have had the unintended consequence of fostering a glucocentric approach to the treatment of GDM. This study will address this need for a more refined method of risk prediction and the targeting of intervention.

The need for refined and targeted approaches is strengthened by the heterogeneous population defined by current diagnostic criteria for GDM.[10] Pregnancy risk is clearly related to elevated glucose in GDM, but the relationship is complex, and an individual's risks are modified by interrelated factors including maternal weight,[11 12] gestational weight gain,[13] ethnicity,[14] and genotype.[15] For example, it has recently been shown that within the two largest maternity services in Australia, ethnic Chinese women with GDM had a lower risk of large-for-gestational-age (LGA) babies and neonatal hypoglycaemia compared to Caucasian women, even adjusting for confounders.[16] A prediction model could integrate these risk factors to estimate risk of adverse pregnancy outcome.

The feasibility of estimating an individual's absolute risk of adverse pregnancy outcomes by integrating oral glucose tolerance test results, maternal weight and pregnancy history was established in our systematic review.[17] However, critical appraisal established that existing prediction models were not yet suitable for application to clinical practice due to high risks of bias due to methodologic limitations.

The Prediction for Risk-Stratified care for women with GDM (PeRSonal GDM) study will leverage the rapidly evolving methodologic advances in prediction modelling to achieve the evolution required to transform promising statistical models into useful clinical tools. In this project, we integrate the findings of this systematic review and critical appraisal of existing models, pertinent findings from landmarks trials, clinical expertise and best practice methods from contemporary guidelines to inform the methodological design of the PeRSonal GDM study.

Objectives

The aims of the PeRSonal GDM study are to:

1. Develop and internally validate a prediction model for adverse pregnancy outcomes in GDM to aid shared decision-making and stratify care;
2. Externally validate the model to demonstrate temporal transportability;
3. Evaluate the clinical utility of the model as a basis for a risk-stratified model-of-care.

METHODS AND ANALYSIS

Prediction model design

We conducted formative research to conceptualise and design a robust and clinically acceptable prediction model. First, a systematic review and critical appraisal of existing prediction models for adverse pregnancy outcomes in women with GDM was conducted following a peer-reviewed protocol.[18] Second, the study steering committee comprising two obstetricians, three endocrinologists and a neonatologist formulated key clinical requirements of the prediction model (Table 1). A model addressing these requirements was designed (Figure 1). Finally, a multidisciplinary clinical working group was formed to provide feedback on the proposed requirements, gauge its clinical acceptability and consider its clinical application. The working group included endocrinologists (n = 9), diabetes nurse educators (n = 3), dieticians (n = 2), midwives (n = 2), administration staff (n = 2) and an obstetrician (n = 1) actively involved in the provision of GDM care at several maternity hospitals. We considered consumer perspectives throughout this process, from parallel qualitative research on GDM diagnosis and risk.[19]

Table 1. The fundamental requirements of a prediction model for adverse pregnancy outcomes in women with gestational diabetes. Framework adapted from that originally proposed by Moons and colleagues to consider in framing a systematic review of prediction modelling studies.[20]

Criteria	Specifications
1. Prognostic versus diagnostic prediction model	The aim is to predict future events (prognostic prediction model)
2. Intended scope	To inform clinicians' therapeutic decision-making and serve as a rational basis for the stratification of GDM care
3. The target population to whom the prediction model applies	Pregnant women with GDM, per diagnostic criteria in clinical practice

4. The outcome to be predicted	Pregnancy complications related to GDM affecting the mother (obstetric or maternal) or the baby (fetal or neonatal)
5. Timespan of prediction	Complications occurring during pregnancy or soon after birth
6. Intended moment of using the model	At diagnosis of GDM, typically at 24 to 28 weeks gestation but may be earlier

Abbreviations: GDM, gestational diabetes.

Study design

We will conduct a prediction model development and validation study using a retrospective cohort design. It will be conducted following expert guidance for model development and validation,[21-26] and reported per the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement.[27]

Data sources and validation strategy

This study will use routinely collected health data for pregnancies resulting in a birth from 1 July 2017 to 31 December 2018 from an existing pregnancy outcomes database from a maternity service. Maternal, obstetric and neonatal data are collected prospectively for all women booked to deliver their baby at the service. This data is collected with consent as part of routine clinical care. This data is of high-quality and completeness as it is collected under statute with the primary aim to facilitate improvements in quality of care. We will link these data deterministically to pathology data and clinical data extracted from the medical record of the parent health service. Linked pathology data is available for approximately 70% of pregnancies, and linked clinical data is available for approximately 90% of pregnancies. All collected data will be rendered non-identifiable for all research purposes, including analysis.

The data will be split by time into two groups (analysis type 2b in TRIPOD).[28] We will develop the prediction model using pregnancies resulting in births from the first 12 months of the study period (1 July 2017 to 30 June 2018). Pregnancies resulting in births from the last six months of the study period (1 July 2018 to 31 December 2018) will be used to evaluate the predictive performance of the developed model (external validation). This strategy will evaluate the temporal transportability of the model.

Participants

Study setting

This maternity service is one of the largest in Australia, provides universal access to healthcare comprising multiple large maternity hospitals and serves an ethnically and socioeconomically diverse population within a catchment of 1.6 million in South-East Melbourne. All levels of maternity care are available across the three hospitals with shared staff and institutional protocols and practices. Maternity care is provided to more than 9,000 women each year.

Eligibility criteria

Pregnancies coded for GDM during the study period stated above will be included. There will be no exclusion criteria.

Treatment received

GDM is diagnosed and treated following institutional protocol and practices. At our service GDM is diagnosed using the International Association of Diabetes and Pregnancy Study Groups 2010 criteria,[4] as endorsed by the Australian Diabetes in Pregnancy Society with universal screening at 24-28 weeks with a one-step procedure using the 75g OGTT.[6] Early screening is based on the presence of risk factors as soon as practicable using the same testing procedure with a repeat at 24-28 weeks if negative. The treatment package for GDM consists of an initial 2-hour group education session with diabetes nurse educator and dietician. Lifestyle management involves dietary modification, physical activity and weight management. Follow up reviews occur with an endocrinologist or endocrinology specialist trainee every one to three weeks. Insulin is commenced where glucose targets (fasting < 5.5 mmol/L and 2-hour post-prandial < 7.0 mmol/L) are not met and are not amenable to further dietary modification. Metformin is used where there is evidence of significant insulin resistance, where targets are not achieved with insulin alone or when insulin use is relatively contraindicated due to the risk of significant psychological harm.

Outcome

The outcome to be predicted will be a composite consisting of a combination of eight prioritised, objective and serious adverse pregnancy outcomes defined in Table 2.

Table 2. The adverse pregnancy outcomes to be predicted: Definition, variable type and categories.

Outcome	**Definition**
Maternal	
Hypertensive disorders of pregnancy	Pregnancy-induced hypertension, pre-eclampsia or eclampsia
Fetal/ Neonatal	
LGA	Birth weight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[29]
Neonatal hypoglycaemia requiring intravenous treatment	A neonate with a low blood glucose level fulfilling institutional criteria for intravenous treatment consisting of either a dextrose bolus or dextrose infusion
Shoulder dystocia	When, after delivery of the head, the baby's anterior shoulder gets caught above the mother's pubic bone
Fetal death	Death of fetus after 20 weeks gestation
Neonatal death	Death of live-born neonate
Bone fracture	Neonatal fracture (femur, humerus, clavicle or skull) suffered at birth
Nerve palsy	Neonatal nerve palsy (brachial plexus injury or facial nerve injury) suffered at birth

Abbreviations: LGA, large-for-gestational-age.

Formulation of outcome(s) to be predicted

The study steering committee considered a large number of adverse pregnancy outcomes for inclusion in the composite (Online Supplementary Table S1). Outcomes predicted by existing models identified in our systematic review and predicted by a related model for insulin therapy initiation[30] were considered. The committee also considered outcomes in the final core outcome set (COS) for GDM treatment research.[31] Reference to the COS for future GDM treatment research provided objective prioritisation of outcomes from a large international multidisciplinary group of relevant stakeholders. Finally, the committee considered all outcomes studied in the HAPO study,[5] the landmark international multi-centre

observational study that demonstrated associations between increasing levels of glucose levels on oral glucose tolerance testing and adverse pregnancy outcomes. From this, a composite outcome was constructed to reflect the multiple adverse pregnancy outcomes related to GDM. Construction of the composite outcome considered recommendations that components are 1) of similar importance, 2) occur with similar frequency and 3) are likely to have similar relative risk reductions (or predictive effects moving in the same direction) with similar underlying biology.[32] The rationale for inclusion or exclusion from the composite outcome to be predicted is presented in Online Supplementary Table S2.

Outcome assessment

LGA assessment will be based on a population-based growth chart rather than customised centiles to avoid incorporation of predictor information such as ethnicity into outcome assessment. Blinding to predictors in the assessment of the outcome will not be feasible.

Predictors

Definition of predictors and measurement

Candidate predictors to be evaluated for inclusion in the model are defined in Table 3. There will be no blinding between the assessment of a predictor and the outcome nor to other predictors.

Table 3. Candidate predictors to be evaluated in model development: Definition, variable type and units/ categories.

Candidate predictor	**Definition**	**Variable type**	**Units/ categories**
Demographics			
Age	Mother's age	continuous	years
Clinical history			
Nulliparity	The condition in a woman of never having given birth	binary	0 "No" 1 "Yes"
Gestational age at diagnosis	Gestational age at diagnosis of GDM in the index pregnancy	continuous	weeks' gestation
Ethnicity	Self-reported ethnicity with classification aligned to the Australian Standard Classification of Cultural and Ethnic Groups[33]	categorical	ethnicity classified into approximately 5-6 categories
Previous GDM	Previous diagnosis of GDM	binary	0 "No" 1 "Yes"
Previous LGA	Previous child with birthweight > 90th percentile corrected for gestation and fetal sex using Australian population growth chart[29]	binary	0 "No" 1 "Yes"
Previous pre-eclampsia or eclampsia	Pre-eclampsia or eclampsia in a previous pregnancy	binary	0 "No" 1 "Yes"
Previous shoulder dystocia	Shoulder dystocia in a previous pregnancy	binary	0 "No" 1 "Yes"
Family history of diabetes	Any family history of diabetes	binary	0 "No" 1 "Yes"

Height	The mother's self-reported height at about the time of conception.	continuous	centimetres (cm)
Body mass index	Body mass divided by the square of the body height	continuous	kg/m2
Weight	Mother's self-reported weight (body mass) about the time of conception	continuous	kilograms (kg)
Physical examination			
Incremental gestational weight gain	Weight at first GDM clinic appointment (at around 30 weeks gestation) minus preconception weight divided by gestational weeks completed at the time of the first GDM clinic appointment	continuous	kilograms (kg)
Laboratory investigations			
Fasting glucose from diagnostic OGTT	Glucose level from baseline or time zero of diagnostic oral glucose tolerance test	continuous	mmol/L
1h glucose from diagnostic OGTT	Glucose level 1 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L
2h glucose from diagnostic OGTT	Glucose level 2 hour following a 75g oral glucose load of diagnostic oral glucose tolerance test	continuous	mmol/L

Abbreviations: GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index.

Identification of candidate predictors

Candidate predictors were identified from those selected for the final models included in the systematic review of models for pregnancy complications in women with GDM, selected in a model for GDM diagnosis previously developed by our group,[34] and selected in a related model for insulin therapy initiation.[30] (Online Supplementary Table S3) Thirteen of the 16 predictors from these existing related models will be evaluated for inclusion in this prediction modelling study (Table 3). Three predictors selected for related models (poor glycaemic control, enlarged abdominal circumference and HbA1c at diagnosis) could not be evaluated in this study as the data are not routinely collected at our service.

One previous study selected history of macrosomia as a predictor for LGA.[35] Indeed, in clinical practice, past history is often seen as a major risk factor for future occurrence. Therefore, this study will evaluate previous histories of components of the composite outcome for inclusion in the model. Such data is available for macrosomia, LGA, pre-eclampsia and eclampsia, and shoulder dystocia, and therefore, these four predictors will be evaluated as candidate predictors.

In addition to the candidate predictors identified from their use in existing related models, ethnicity and GWG were identified as potential predictors requiring formal evaluation due to the emergence of evidence supporting their role as significant prognostic factors. Chinese women affected by GDM were at a lower risk of a range of adverse pregnancy outcomes

including LGA and neonatal hypoglycaemia compared to affected Caucasian women in an Australian cohort,[16] and South Asian babies exposed to GDM were smaller across gestation than babies of White European in an English cohort.[36] Emerging physiologic data suggests highly variable degrees of beta-cell function and insulin resistance amongst women diagnosed with GDM,[37] and that classifying women with GDM by these physiologic defects may stratify women by their risk of adverse pregnancy outcomes.[38] Ethnicity may serve as a surrogate marker for these physiologic defects avoiding the need for additional investigations. Hence, ethnicity is an appealing candidate predictor for models to predict the development of adverse pregnancy outcomes.

GWG has also been shown to be a risk factor for adverse pregnancy outcomes, independent of BMI.[13] Specifically, GWG is associated with an increased proportion of LGA over and above that which is associated with GDM and overweight or obesity, in a general obstetric population.[39] BMI, parity and GWG together, better predict adverse pregnancy outcomes than BMI alone in a cohort attending a general antenatal clinic (women with GDM and normoglycaemia).[40] The effect of GWG is likely to be modified by other predictors, including ethnicity, supporting its integration within a multivariable model rather than a single prognostic factor-based approach.

Data extraction

We will extract records for eligible participants to create a research dataset with each observation representing a pregnancy. Participants may be included more than once due to multiple pregnancy or repeat pregnancies within the study period. We will manually review eligible participant's medical record to ensure the accuracy of the diagnosis of GDM. Linked pathology and additional clinical data will be extracted and merged with the research dataset. The research dataset will be rendered non-identifiable for all subsequent analyses.

Sample size

In this study, the adequacy of the sample size of our developmental dataset will be determined by the total number of events of the composite binary outcome. Approximately 9,000 women are delivered annually at the institution from which the development dataset will be derived. The prevalence of GDM at this institution is 18% (unpublished data). Therefore, over the 12-month period used for model development, we conservatively estimate that the development dataset will include 1,620 cases of women with GDM. We anticipate that at least 10% of these women will deliver neonates that have a birth weight that is LGA defined as greater than the 90th percentile for the population (approximately 162 events). Furthermore, using unpublished data from our institution, the prevalence of hypertensive disorders of pregnancy is 7% (approximately 113 events) and neonatal hypoglycaemia requiring IV treatment is 11% (approximately 178 events). Therefore the expected event count is greater than 453 once the additional contribution of the less common component outcomes are also considered (shoulder dystocia, fetal death, neonatal death, bone fracture, nerve palsy). Given we envisage including up to 20 candidate predictors, our study should be adequately powered as the dataset will have in excess of ten events per predictor as is commonly recommended to avoiding overfitting.[41]

Over the 6-month period used for external validation, the expected event count is 50% of that for the 12-month period used for development, hence approximately 225. This is greater than the recommended minimum of 100 events for validation.[42]

Missing data

We do not expect considerable missing data, but some will inevitably occur, with not all cases providing all variables of interest. Handling of missing data will be determined individually on a per predictor basis. The missing indicator method will be used for predictors where data is missing not at random. Multiple imputation by chained equations will be used to impute missing data as long as the data is missing at random. If necessary, we will include a supplementary table comparing predictor distributions between patients with missing data and patients with complete data.

Statistical analysis methods

To make individualized predictions for the binary composite of an adverse pregnancy outcome, we will apply a logistic regression model with the composite outcome as the dependent variable.

Handling of predictors

Continuous variables will be kept as continuous in the model (rather than dichotomising), to avoid a loss of prognostic information. Those predictors that are highly correlated with others contribute little information and will be excluded from the statistical analysis.

The functional form of the relationship of continuous predictors with the outcome will be assessed. If non-linear they will be modelled with fractional polynomials (FP). If this is the case, as several continuous variables were included in the model, we will use the multivariable fractional polynomial algorithm. Multiple imputation and FPs will be combined using the procedure described by Morris and colleagues.[43]

Model-building procedures (including predictor selection)

Candidate predictor variables will be selected *a priori* based on existing literature and clinical expertise as described above. During modelling, predictors will be selected by using a LASSO (Least Absolute Shrinkage and Selection Operator) method, which simultaneously selects the variables and penalises the model coefficients for over-optimism.[44]

Examination of predictor interactions will be undertaken for the following groups of predictors: weight, gestational weight gain (GWG) and body mass index (BMI), and fasting, 1h and 2h glucose levels from OGTT.

Internal validation and assessment of model performance

The model performance will be assessed in terms of discrimination and calibration. We will use a bootstrap re-sampling technique to adjust for over-optimism in the estimation of model performance due to validation in the same dataset that is used to develop the model itself. We will use the area under the curve (AUC) of the receiver operating characteristic (ROC) curve with 95% confidence interval to assess the overall discriminatory ability of the developed model. We will report the apparent and adjusted for over-optimism model performance. A calibration plot will be created. This plot will facilitate the graphical assessment of calibration by putting affected women into groups ordered by predicted risk and considering the agreement between the mean predicted risk and the observed events in each risk group, usually deciles. The calibration will be summarized using the intercept and slope of the calibration plot. Internal validation, where the model's predictions are compared to the observed data, should return perfect calibration to the development data (calibration slope = 1).

External validation

External validation of the developed model will be undertaken to assess temporal transportability. It will be undertaken using the model coefficients from the developed model to calculate the risk for each woman. We will report the predictive performance in a more recently treated cohort at the same maternity service using the same measures of discrimination and calibration as used in internal validation. Development and validation data are identical in terms of eligibility criteria, outcome and predictors.

Presentation of a simplified model for clinical use

Once a final model is identified, we will simplify and adapt the presentation of the model to facilitate its application to clinical practice. Alternative modes of presentation will be explored with a focus on maximising end-user usability and promoting translation into clinical care. Various presentation formats will be considered, including a simplified scoring system, nomogram and web or app-based electronic risk calculators.

Assessment of clinical utility

To supplement traditional measures of predictive model performance, discrimination and calibration, clinical utility will be formally evaluated. We will use decision curve analysis to explore the net benefit of developed models over the entire range of probability thresholds.[24 28 45] We will represent the net benefit as a function of the decision threshold in a decision curve plot. This will explore whether there is an overall net-benefit for using the models to stratify the population into two risk groups as a basis for a risk-stratified model of care:

1. Low-risk where the risk of adverse pregnancy outcomes is less than a pre-specified value—this group may be considered for a less intensive model-of-care;
2. High-risk where the risk is greater than a pre-specified value—this group should receive specialist-led hospital-based care.

Further formative research is planned to ascertain optimal risk thresholds. This will include engagement with stakeholders, including women affected by GDM and clinicians. A combination of focus groups and an electronic survey will be used.

Sensitivity analyses

We will conduct additional analysis to address the confounding effect of insulin treatment on predictor-outcome associations and hence the performance of the prediction model. This will consider four possible approaches with sensitivity analysis used to evaluate the robustness of each:

1. Derivation of a propensity score of being treated with insulin based on women pre-treatment characteristics. We will then weight observations by using the inverse probability of treatment weighting (IPTW). In this way, women with lower propensity to be treated will have more weight in the development of the prognostic model than those who had a higher probability of being treated.
2. Inclusion of insulin treatment as a component of the composite outcome.
3. Exclusion of cases where insulin treatment was used.
4. Exploration of the multinomial regression model framework for combinations of the composite outcome of adverse pregnancy outcome and insulin treatment.

The primary analysis will develop and validate a model based on clinical characteristics. Prognosis may also be influenced by an affected woman's capacity to implement lifestyle measures such a dietary modification and increased exercise. Therefore, we will undertake a sensitivity analysis to evaluate whether measures of socioeconomic disadvantage can improve the prediction of adverse pregnancy outcomes.

All statistical analysis will be performed using Stata version 16.1 (College Station, TX: StataCorp LLC.).

Patient and Public Involvement

No patient and public involvement in the development of this protocol. Patient and public perspectives will be essential to the formative research required to implement findings of this model development and validation study into clinical practice. As such patients and public will be invited to participate in this phase of our research.

DISCUSSION

Strengths

The formative research undertaken established the clinical need for a robust prediction model for adverse pregnancy outcomes in GDM to support therapeutic decision-making and stratification of care. Engagement with stakeholders in the model design stage should improve the clinical acceptability of the model and support future implementation efforts. The composite outcome of prioritised, objective and serious adverse events was formulated with reference to a systematic review and critical appraisal of existing models (manuscript submitted for publication, 2020), the relevant core outcome set,[46] and clinical expertise of endocrinologists, obstetricians and a neonatologist. This composite will be composed of LGA, neonatal hypoglycaemia, hypertensive disorders of pregnancy, shoulder dystocia, severe birth trauma (nerve palsy and bone fracture) and perinatal death. The transportability of the developed model will also be enhanced by the selection of candidate predictors using existing literature and clinical expertise, independent of the predictor-outcome association in the development dataset.

Prediction of a composite outcome will more accurately quantify the multiple adverse pregnancy outcomes related to GDM and therefore, will be more translatable into clinical practice. This composite will be valid and clinically useful because the component outcomes are of similar importance, the three main components (LGA, neonatal hypoglycaemia and hypertensive disorders of pregnancy) occur with a similar frequency (approximately 10%),[47] and the predictive effects are likely to move in the same direction due to similar underlying biology.[32]

A method to estimate the absolute risk of adverse pregnancy outcomes for an individual woman affected by GDM would be of great benefit to affected woman, their clinicians and the health system. It would allow affected woman to better understand the implication of GDM on their pregnancy and facilitate shared-decision making with clinicians regarding the relative risks and benefits of interventions. At a system-level these individualised risk estimates would support a risk-stratified model-of-care which recognises the breadth and continuum of pregnancy risk attributable to GDM such that preventative and therapeutic interventions could be delivered to women at high-risk, sparing women at low-risk from low-value care. Ultimately, a robust prediction model would facilitate the transition from a

glucocentric model-of-care to an individualised and holistic approach to this widespread public health problem.

Translating prediction models into clinical care is challenging.[48-50] Previous efforts of addressing this clinical prediction problem have been hampered by the use of methods, which increase the risk of biased predictions limiting the transportability of developed models to new but related populations (manuscript submitted for publication, 2020). Thus, rigorous and robust methods have been adopted for model development and validation in this study. Methods have been framed by the learnings from our critical appraisal of existing models and will be guided by Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Statement.[27]

Limitations

Use of routine-collected healthcare data

The development dataset was created using routinely-collected healthcare data. This data was collected contemporaneously, and in a prospective fashion, however, they were not collected specifically for the purposes of this study. In prediction modelling studies, the use of routinely collected data enables the accruement of a greater number of events, which increases power to consider a greater number of candidate predictors without risking overfitting. However, the retrospective direction of enquiry creates the possibility of poor-quality data for both predictors and outcome, potential unmeasured predictors and as such careful evaluation of missing data and application of appropriate methods to address it are essential to minimise the effect on performance and applicability of developed models.[20]

Maternal death during pregnancy or any other complications that preclude delivery at the hospital will not be captured within the source perinatal outcomes database.

Varying diagnostic criteria

Diagnostic criteria used for GDM are controversial. Some professional societies endorse the criteria initially proposed by the International Association of Diabetes and Pregnancy Study Groups but disagreement persists.[4 6 51] There is also the acknowledgement that the optimal diagnostic strategy may vary depending on the characteristics of the local population.[1 8 9] The ideal prognostic prediction model would perform adequately across populations defined by a range of diagnostic criteria. Addressing this challenge will require developed models to be externally validated across these different populations.

Addressing treatment paradox regarding insulin use

Addressing the treatment paradox (in this case with insulin) is a challenge in prediction modelling studies. The traditional approach has been to accept predictions in the context of current care. However, this does not remove the possibility that a potentially useful model may appear to perform poorly due to the confounding effect of the judicious application of effective interventions to individual's whom clinicians subjectively assess to be at high risk of the outcome of interest.

Two solutions to address the problem of treatment paradox in prediction modelling studies have been advocated.[52] Firstly, the use of treatments suspected to confound the predictor-outcome relationship can be set as a predictor in the final model. Secondly, the use of such effective treatments can be included within a composite outcome to be predicted. For this study, both approaches were considered but deemed inappropriate. For the former, the

inclusion of the requirement for insulin therapy as a predictor is not possible as this information is not available at the intended moment of prediction—the time of GDM diagnosis, usually around 24-28 weeks gestation. For the later, inclusion of the requirement for insulin therapy within the composite outcome would impair its interpretability as this outcome occurs at a significantly higher frequency than the other component outcomes (31% vs approximately 10% based on our prior work).[47] This is likely to lead to a less meaningful composite that is primarily driven by the need for insulin therapy and no longer predicts what we want (adverse pregnancy outcomes). While many promising novel approaches have been proposed in the statistical literature, such as multi-state modelling or marginal structural models for"treatment drop-ins,[53 54] at time of writing all are primarily based on empirical data and are yet to be applied to clinical prediction problems.

The three possible results from the sensitivity analysis to evaluate the effect of including the decision to treat with insulin will be informative and may be interpreted as follows. If the sensitivity analyses find that the inclusion of the decision to treat with insulin within the outcome:

1) Positively affects model performance, then this suggests the presence of treatment paradox. i.e. pregnancy complications are more likely to occur in the absence of insulin therapy;
2) Has no significant effect on model performance then this suggests that the model is robust with predictive performance not affected by the decision to treat. i.e. the absolute risk of adverse pregnancy outcomes for an individual woman with GDM is not affected by insulin therapy;
3) Negatively affects model performance, then this would suggest that adverse pregnancy outcomes are more likely to occur in women treated with insulin, and thus imply more 'severe' GDM or a harmful effect for this treatment. (unlikely)

The effect of treatment with insulin will be further evaluated using an IPTW algorithm to weight women according to their propensity of having been treated and transformation of the logistic model into a multinomial model. This multinomial model will have four categories depending on the occurrence of the composite pregnancy outcome and whether the women have received treatment with insulin or not.

The target population to whom the prediction model applies

The focus of this model and eventual clinical risk calculator is on those women who develop GDM and has been developed to address the priorities of frontline health care workers and services on the potential for risk stratified care for the one in five women who are diagnosed with GDM. Future work, should consider whether learnings from this project can be applied to a broader population, including pregnant women without GDM in particular those with maternal overweight or obesity.

Ethics and dissemination

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L). This study will be conducted in accordance with the principles of the Declaration of Helsinki and the National Statement on Ethical Conduct in Human Research (2018).[55 56] All analyses will be conducted using non-identifiable data extracted from a pre-existing dataset. The data is collected as part of routine clinical care for the primary purpose of improving the quality of pregnancy care. Consent was not obtained for the secondary use of this data because it is not practical to do so, and this research is consistent with the primary

purpose for which it was collected. This study has been registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12620000915954).[57] Results will be disseminated via presentation at scientific meetings and publication in peer-reviewed journals.

DECLARATIONS

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: SDC reports grants from the National Health and Medical Research Council (NHMRC), Diabetes Australia, the Australian Academy of Science and the Australian Government Department of Education and Training during the conduct of the study; JAB reports grants from the NHMRC during the conduct of the study; BMFF reports grants from CIBER (Biomedical Research Network in Epidemiology and Public Health, Madrid, Spain) during the conduct of the study and HJT reports grants from the NHMRC and the Medical Research Future Fund during the conduct of the study; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent for publication

Not required.

Ethical approval

This study has been approved by the Human Research Ethics Committee of Monash Health (RES-19-0000713L).

Data availability

Not applicable.

Transparency

SDC and HJT affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as initially planned (and, if relevant, registered) have been explained.

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FIGURE LEGENDS

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

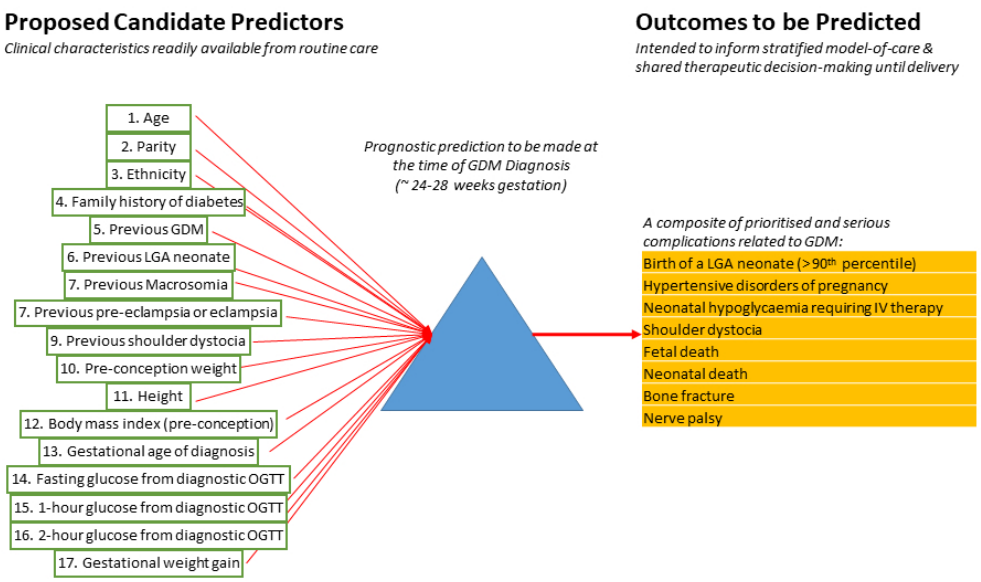

Figure 1: The design of the PeRSonal Pregnancy GDM Risk Model—Prediction for Risk-Stratified care for women with Gestational Diabetes (GDM). GDM, gestational diabetes; LGA, large-for-gestational-age; OGTT, oral glucose tolerance test.

239x142mm (96 x 96 DPI)

Table S1. Potential outcomes to be predicted identified in a systematic review and review of other relevant literature.

Outcomes	**Models for pregnancy complications in women with GDM**					**Core outcome set for studies of GDM Treatment[1]**	**Hyperglycaemia and Adverse Pregnancy Outcomes study[2]**	**Model for insulin therapy initiation[3]**
	McIntyre *et al.*[4]	Park *et al.*[5]	Phaloprakarn and Tangjitgamol[6]	Pintaudi *et al.*[7]	Tomlinson *et al* [8]			
Outcomes to be predicted								
Birth of LGA neonate (> 90th percentile)	x	x		x	x	x	1^{o}	x
HDP		x (GH, PE)	x (PE)			x	2^{o} (PE)	
Shoulder dystocia	x$^{\%}$			x			2^{o} (shoulder dystocia or birth injury)	x
Nerve palsy							2^{o} (shoulder dystocia or birth injury)	
Bone fracture							2^{o} (shoulder dystocia or birth injury)	
Perinatal (fetal and neonatal) death				x		x (neonatal death, stillbirth)		
Neonatal hypoglycaemia	x	x		x		x	1^{o} (clinical)	x
Requirement for insulin therapy		x				x (Requirement & type of pharmacological therapy for hyperglycaemia)		

Outcomes excluded from prediction								
Birth weight						x		
Preterm birth						x	2º (delivery before 27 weeks gestation)	x (Early delivery, < 37 weeks)
Adherence to the intervention						x		
GWG						x		
Caesarean delivery	x[#]					x (Mode of birth)	1º (primary caesarean delivery)	x
SGA (<10th percentile)				x		x		x
GA at birth						x		
Neonatal jaundice		x		x			2º (hyperbilirubinaemia)	x
Neonatal adiposity	x							
Neonatal hyperinsulinaemia	x	x					1º	
Admission to the NICU		x		x			2º	
Malformations				x				
Neonatal hypocalcaemia				x				
Neonatal respiratory distress syndrome				x				
Cord-blood serum C-peptide level							x	

above the 90th percentile								

Abbreviations: GDM, gestational diabetes, COS, core outcome set; LGA, large-for-gestational age; HDP, hypertensive disorders of pregnancy; PE, preeclampsia, GH, gestational hypertension; 2°, primary outcome; 2°, secondary outcome; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit.

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Table S2. The rationale for outcomes to be predicted.

Outcomes	**Clinical rationale for inclusion/ exclusion**
Outcomes to be predicted	
LGA (> 90th percentile)	Excess fetal growth is the central adverse pregnancy outcome in pregnancies affected by GDM with many mechanisms implicated including but not limited to the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[1] This adverse outcome is also upstream on the causal pathway to other clinically relevant complications, including those related to difficulties at delivery. LGA will be used rather than macrosomia as it is a measure of birth weight corrected for gestational age and is also less variably defined.[2]
HDP	Significant association with GDM and if at high-risk, then closer monitoring during pregnancy may be required.
Shoulder dystocia	Associated with GDM and clinically significant.
Nerve palsy	May be associated with GDM and clinically significant.
Bone fracture	May be associated with GDM and clinically significant.
Perinatal (fetal and neonatal) death	Rare but of utmost clinical significance.
Neonatal hypoglycaemia	This is the central marker of the maladaptive metabolic response of the neonate exposed to hyperglycaemia in utero as per the hyperglycaemia-fetal hyperinsulinaemia hypothesis.[3] Severe cases requiring intravenous treatment are likely to be most clinically relevant.
The requirement for insulin therapy	A treatment for GDM that reduces the risk of some adverse outcomes.
Outcomes excluded from prediction	
Preterm birth	Not directly related to GDM and may be more related to IUGR; strongly clinician-driven.
Adherence to the intervention	Possible predictor.
GWG	Possible predictor.
Caesarean delivery	Highly clinician-driven and institution dependent.
SGA (<10th percentile)	Not directly related to GDM, more related to IUGR.
GA at birth	May be clinician-driven.

Neonatal jaundice	Only severe cases are clinically relevant and may be more closely related to prematurity rather than the maternal hyperglycaemia of GDM.
Neonatal adiposity	Not routinely assessed in clinical practice.
Neonatal hyperinsulinaemia	Neonatal hypoglycaemia is a more meaningful clinical outcome.
Admission to the NICU	Highly clinician-driven and institution dependent.
Malformations	Associated with pre-gestational diabetes and less relevant in gestational diabetes.
Neonatal hypocalcaemia	As its severity is related to the level of hyperglycaemia unlike in pre-gestational diabetes, it is rarely seen in GDM and if present is usually asymptomatic and resolves spontaneously.[4]
Neonatal respiratory distress syndrome	Only severe cases are clinically relevant and may be more closely related to prematurity rather than hyperglycaemia.[5]
Cord-blood serum C-peptide level above the 90th percentile	Not routinely assessed in clinical practice and clinical relevance unclear.

Abbreviations: GDM, gestational diabetes; LGA, large-for-gestational-age; HDP, hypertensive disorders of pregnancy; GWG, gestational weight gain; GA, gestational age; SGA, small-for-gestational-age; OGTT, oral glucose tolerance test; NICU, neonatal intensive care unit.

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Table S3. Predictors selected for final related models.

Candidate predictors for modelling	**Models for pregnancy complications in women with GDM included in systematic review**					**Model for GDM Diagnosis[1]**	**Model for insulin therapy initiation[2]**
	McIntyre *et al.*[3]	Park *et al.*[4]	Phaloprakarn and Tangjitgamol[5]	Pintaudi *et al.*[6]	Tomlinson *et al* [7]		
Age	x				x		x
Parity	x						
Gestational age of diagnosis			x				x
Fasting glucose from diagnostic OGTT	x	x			x	NA	x
1-hour glucose from diagnostic OGTT	x					NA	
2-hour glucose from diagnostic OGTT	x					NA	
Ethnicity							
Family history of diabetes				x			x
Gestational weight gain					x		
Previous GDM							x
History of macrosomia					x		
BMI	x (at time of OGTT)	x (at time of diagnosis)	x (first trimester)	x (pre-pregnancy)			x
Height	x						
Poor glycaemic control		x	x				
Enlarged fetal abdominal circumference on ultrasound					x		
HbA1c at diagnosis							x

Abbreviations: GDM, gestational diabetes; OGTT, oral glucose tolerance test; BMI, body mass index.

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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	7
	5b	D;V	Describe eligibility criteria for participants.	7
	5c	D;V	Give details of treatments received, if relevant.	7
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	9
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	9
Sample size	8	D;V	Explain how the study size was arrived at.	10
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	10
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	10
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	11
	10c	V	For validation, describe how the predictions were calculated.	11
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	11
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	11
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	NA
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	NA
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	NA
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	NA
	15b	D	Explain how to the use the prediction model.	NA
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	NA
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	17
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	NA
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	17
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	NA
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	20

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.