

BMJ Open Design, rationale and protocol for Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs): an observational cohort study

The GO MOMs Study Group

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ABSTRACT

Introduction Given the increasing prevalence of both obesity and pre-diabetes in pregnant adults, there is growing interest in identifying hyperglycaemia in early pregnancy to optimise maternal and perinatal outcomes. Multiple organisations recommend first-trimester diabetes screening for individuals with risk factors; however, the benefits and drawbacks of detecting glucose abnormalities more mild than overt diabetes in early gestation and the best screening method to detect such abnormalities remain unclear.

Methods and analysis The goal of the Glycemic Observation and Metabolic Outcomes in Mothers and Offspring study (GO MOMs) is to evaluate how early pregnancy glycaemia, measured using continuous glucose monitoring and oral glucose tolerance testing, relates to the diagnosis of gestational diabetes (GDM) at 24–28 weeks' gestation (maternal primary outcome) and large-for-gestational-age birth weight (newborn primary outcome). Secondary objectives include relating early pregnancy glycaemia to other adverse pregnancy outcomes and comprehensively detailing longitudinal changes in glucose over the course of pregnancy. GO MOMs enrolment began in April 2021 and will continue for 3.5 years with a target sample size of 2150 participants.

Ethics and dissemination GO MOMs is centrally overseen by Vanderbilt University's Institutional Review Board and an Observational Study Monitoring Board appointed by National Institute of Diabetes and Digestive and Kidney Diseases. GO MOMs has potential to yield data that will improve understanding of hyperglycaemia in pregnancy, elucidate better approaches for early pregnancy GDM screening, and inform future clinical trials of early GDM treatment.

Trial registration number NCT04860336.

INTRODUCTION

Gestational diabetes mellitus (GDM) affects 7.8% of pregnant individuals in the USA^{1–4} and is associated with an increased risk of adverse pregnancy outcomes.^{5–8} Further, it is a harbinger of long-term metabolic disease in affected parents and children

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) is a multicentre study that is designed to reflect the demography of the pregnant population in the USA.
- ⇒ GO MOMs participants wear blinded continuous glucose monitoring devices at four timepoints over the course of pregnancy and complete oral glucose tolerance tests at both 10–14 weeks' and 24–28 weeks' gestation, generating a uniquely valuable data resource for characterising the longitudinal glycaemic profile of pregnancy.
- ⇒ The study design and sample size for GO MOMs will support development and validation of predictive criteria for gestational diabetes in pregnant individuals at 24–28 weeks' gestation and large-for-gestational-age birth weight in newborns using early pregnancy data.
- ⇒ Multiple laboratory measures and chart abstraction data will complement glycaemic measurements.
- ⇒ As in any observational, longitudinal study, confounders and missing data may be limitations of the GO MOMs study.

exposed in utero.^{5–8} Randomised trials have demonstrated that treatment of GDM in the third trimester results in a reduction in the frequency of large-for-gestational-age birth weight (LGA) and other adverse perinatal outcomes.^{9–14} Therefore, in the USA, all pregnant individuals accessing prenatal care are typically screened for GDM between 24 and 28 weeks' gestation.^{15 16}

Due to the increasing prevalence of both obesity and pre-diabetes, along with the recognition that individuals who meet traditional GDM criteria early in pregnancy have a greater risk of adverse outcomes than those diagnosed later, there is growing interest in first trimester identification of hyperglycaemia.¹⁷ Although treatment for GDM in the

third trimester does not seem to result in improvements in long-term sequelae for exposed neonates, whether treatment of hyperglycaemia in early pregnancy would be associated with decreased metabolic risk in children exposed in utero is not well understood.^{18–20} Available evidence suggests that the mechanism by which in utero exposure to hyperglycaemia might lead to obesity and metabolic disease later in life is through fetal hyperinsulinaemia and the resultant accrual of excess adipose tissue.²¹ Studies of amniotic fluid insulin levels demonstrate that fetal hyperinsulinaemia occurs as early as 15 weeks' gestation, preceding the gestational age at which GDM is usually diagnosed^{22–24} and suggesting that intervention at earlier gestational ages than the current standard might prevent long-term sequelae. However, available trials of screening and treatment at less than 20 weeks' gestation based on conventional GDM diagnostic criteria have not consistently demonstrated a beneficial effect on birth weight or other adverse perinatal outcomes.^{25–28}

Although the International Association of Diabetes and Pregnancy Study Groups (IADPSG),²⁹ the American Diabetes Association (ADA)¹⁶ and the American College of Obstetricians and Gynecologists (ACOG)¹⁵ recommend early pregnancy diabetes screening for individuals at increased risk, a 2021 United States Preventive Services Task Force guideline concluded that evidence was insufficient to assess the balance of benefits and drawbacks of screening for hyperglycaemia before 24 weeks' gestation.³⁰ In addition, the optimal method and criteria for diagnosing hyperglycaemia in early pregnancy have not been established.^{31–39} As a result, various testing modalities including haemoglobin A1c (A1c), fasting glucose and oral glucose tolerance tests (OGTTs) are used with variable criteria applied.

In 2017, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a workshop to identify research gaps in GDM and highlighted three areas related to early diagnosis of GDM as priorities for further investigation: (1) diagnostic criteria and definitions, (2) alternative markers for diagnosis and (3)

effects of early diagnosis and treatment on outcomes.²⁰ The NIDDK-supported Glycemic Observation and Metabolic Outcomes in Mothers and Offspring study (GO MOMs) was designed to address these gaps. The goal of GO MOMs is to use early pregnancy glycaemia to predict late pregnancy GDM (diagnosed with traditional criteria) and LGA. A secondary objective is to provide a comprehensive, longitudinal description of changes in glucose throughout pregnancy leveraging continuous glucose monitoring (CGM). A substudy, the GO MOMs Nutrition Study, is collecting dietary information on a subset of participants and will link dietary components to maternal glycaemia and offspring outcomes. It is hoped that these data will elucidate improved approaches for GDM screening in early pregnancy and inform future clinical trials of early GDM treatment.

METHODS AND ANALYSIS

GO MOMs is being conducted at seven clinical centres (table 1), the Biostatistics Research Center (BRC) at Northwestern University Data Analysis and Coordinating Center (Chicago, IL) and the Central Laboratory at the Advanced Research and Diagnostic Laboratory at University of Minnesota (Minneapolis, MN). The protocol and study design were developed by the GO MOMs steering committee, which consists of investigators from each clinical site, the BRC, the Central Laboratory and the NIDDK.

Eligibility, recruitment process and consent

Inclusion and exclusion criteria are described in table 2. Prior to initial study procedures at 10–14 weeks' gestation, participants must have an ultrasound confirming dating and a viable, singleton gestation. During the first study visit, participants undergo a 75-gram, 2-hour OGTT and haemoglobin A1c measurement. Both the OGTT and the haemoglobin A1c are performed because the OGTT is the most sensitive method for detection of diabetes and the haemoglobin A1c is currently the most commonly used method to diagnose diabetes. If haemoglobin A1c

Table 1 Glycemic Observation and Metabolic Outcomes in Mothers and Offspring study centres

Clinical centres	
Columbia University Irving Medical Center	New York, NY
Kaiser Permanente Northwest and Kaiser Permanente Hawaii	Portland, OR/Honolulu, HI
Massachusetts General Hospital and Tufts University Medical Center	Boston, MA
Northwestern Memorial Hospital	Chicago, IL
University of Pittsburgh Medical Center Magee-Women's Hospital	Pittsburgh, PA
Women & Infants Hospital of Rhode Island	Providence, RI
Yale University	New Haven, CT
Biostatistics research centre	
Northwestern University Data Analysis and Coordinating Center	Chicago, IL
Central laboratory	
Advanced Research and Diagnostic Laboratory at University of Minnesota	Minneapolis, MN

Table 2 Glycemic Observation and Metabolic Outcomes in Mothers and Offspring inclusion and exclusion criteria

Inclusion	Exclusion
Age ≥ 18 at consent	Pre-existing diabetes at enrolment
Single gestation	Current self-monitoring of blood glucose
Gestational age between 10 weeks 0 days and 14 weeks 0 days confirmed by ultrasound and study dating criteria*	Current use of a medication with glycaemic effects
Conceived using own oocyte	Fetal malformation evident at or before enrolment that is likely lethal
Willing and able to wear continuous glucose monitor as directed and adhere to instructions	Known fetal aneuploidy or high-risk cell-free fetal DNA result for aneuploidy
Planning to deliver at a study-affiliated hospital	Participation in another research study that may modify glycaemic profile or study outcomes
	History of bariatric surgery
	Significant allergy to adhesive or extensive skin changes or diseases making continuous glucose monitoring sensor use problematic
	Previous participation in the study
	Current bulimia or anorexia nervosa
	Overnight shift work that alters the sleep/wake periods
	Current psychiatric illness/social situation that would limit compliance with study requirements
	Haemoglobin A1c $\geq 6.5\%$, or fasting glucose ≥ 126 mg/dL, or 2-hour glucose ≥ 200 mg/dL during the visit 1 oral glucose tolerance test

*Participants are required to have a first trimester ultrasound to confirm or establish pregnancy dating and confirm a viable, singleton gestation. The estimated due date established by ultrasound measure of the crown-rump length is used for participants without a sure last menstrual period (LMP) and/or for whom ultrasound dating is discordant with LMP dating according to American College of Obstetricians and Gynecologists criteria. For participants with pregnancies resulting from assisted reproductive technologies (ART), ART-dating is used.⁷³

$\geq 6.5\%$, fasting glucose ≥ 126 mg/dL or 2-hour glucose ≥ 200 mg/dL, the participant is excluded, having met criteria for overt diabetes.¹⁶ Participants who do not meet these criteria are eligible to continue in the study, and results below these thresholds remain masked to participants, their providers and research staff.

Recruitment strategies leverage each site's unique clinical and electronic medical record (EMR) infrastructure. Once identified, potential participants are approached to gauge interest and provide details on study participation. Written informed consent is obtained prior to study procedures.

Study cohort

The study opened to enrolment in April 2021. Recruitment is projected to continue until January 2025. We expect the GO MOMs cohort to represent the demography of the population of US pregnant individuals, including race and ethnicity, body weight distribution and the adult reproductive age spectrum.⁴⁰

Outcomes

Table 3 summarises the primary, secondary and exploratory outcomes.

Primary outcome in pregnant individuals: GDM

GDM is ascertained between 24 and 28 weeks' gestation according to Carpenter-Coustan criteria applied to a 3-hour, 100-gram OGTT.^{15 16} We chose the Carpenter-Coustan criteria because they are the most commonly used criteria for GDM diagnosis in the USA. Given that the 1-hour non-fasting glucose challenge test (GCT) has imperfect sensitivity,⁴¹ GO MOMs participants forego the 1-hour GCT and all complete the 3-hour diagnostic OGTT for GDM ascertainment.

Primary outcome in newborns LGA

LGA, defined as birth weight greater than the 90th percentile for gestational age and sex according to a 2017 USA based reference,⁴² is the primary newborn outcome. Fetal overgrowth is the most common clinically relevant consequence of maternal hyperglycaemia, increases morbidity in the perinatal period, and confers long-term metabolic risk in childhood.⁴³ The LGA coprimary outcome will facilitate development of new early pregnancy hyperglycaemia screening criteria for prediction of fetal overgrowth.

Predictors

GO MOMs will develop a prediction model, incorporating glycaemic and clinical measures, which can be

Table 3 GO MOMs primary, secondary and exploratory outcomes

Primary outcomes	Definition
Gestational diabetes mellitus	100-gram 3-hour OGTT meeting Carpenter-Coustan criteria at 24w0d-28w0d gestation
Large for gestational age	Birth weight >90th percentile for gestational age according to Aris <i>et al</i> ⁴²
Secondary outcomes	
Hypertensive disorders of pregnancy	Includes pre-eclampsia with and without severe features, gestational hypertension, eclampsia, and haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome
Caesarean delivery	
Flank skinfold	Evaluated as a continuous measure and dichotomised as >90th percentile
Small for gestational age	Birth weight <10th percentile for gestational age according to Aris <i>et al</i> ⁴²
Preterm birth	Delivery prior to estimated gestational age 37w0d
Shoulder dystocia	Defined clinically, requiring documentation that providers applied manoeuvres to reduce the shoulder at delivery
Neonatal birth injury	Brachial plexus palsy or clavicular, humeral or skull fracture
Neonatal hypoglycaemia	Neonatal hypoglycaemia requiring treatment
Neonatal respiratory morbidity	Need for respiratory support within 72 hours after birth and consisting of one or more of the following: the use of continuous positive airway pressure (CPAP) or high-flow nasal cannula for at least two consecutive hours, supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least four continuous hours, extracorporeal membrane oxygenation (ECMO) or mechanical ventilation. A high flow of air or blended air and oxygen is defined as more than 1 L/min
Neonatal hyperbilirubinaemia	Treatment of hyperbilirubinaemia in the first week of life with phototherapy or exchange transfusion or a diagnosis of kernicterus
Exploratory outcomes	
NICU admission	Admission to the NICU prior to hospital discharge
Neonatal length of admission/length of stay	Includes NICU or entire delivery hospitalisation
Spontaneous abortion	Pregnancy loss at <20w0d of gestation
Stillbirth	Intrauterine fetal demise ≥20w0d of gestation
Neonatal death	Death within the first 28 days of life
Major congenital malformation	Birth defects that have significant medical, social or cosmetic consequences for the affected individual, and typically require medical intervention
Antepartum admissions or maternal readmissions	Admissions that occur after GO MOMs enrolment and up to 30 days following delivery
Low Apgar score	Apgar score <7 at 5 min

d, days; GO MOMs, Glycemic Observation and Metabolic Outcomes in Mothers and Offspring; NICU, neonatal intensive care unit; OGTT, oral glucose tolerance test; w, weeks.

used in early pregnancy to identify individuals who will have GDM and/or deliver LGA infants (figure 1).

Glycaemic predictors

Models will incorporate summary measures of CGM or OGTT data obtained at visit 1 (V1). ‘Excess time above range’ will be the primary summary measure of CGM data to best reflect hyperglycaemia. The primary predictor will be nocturnal percentage of time above range, calculated from midnight to 06:00.⁴⁴ Overnight hyperglycaemia has previously been linked to LGA in GDM.⁴⁵ A range

of cut-off values for both the glucose threshold defining ‘above range’ and the percentage of time spent above a given threshold to define ‘excess’ will be evaluated. Other CGM metrics including 24-hour time above range and mean glucose will also be evaluated. Additionally, timed OGTT glucose measurements obtained at V1 will be evaluated as predictors of outcomes, starting with the IADPSG criteria for GDM⁴⁶ (fasting ≥92 mg/dL, 1 hour ≥180 mg/dL, 2 hours ≥153 mg/dL) and exploring various cut-offs for each timepoint to develop a dichotomous predictor

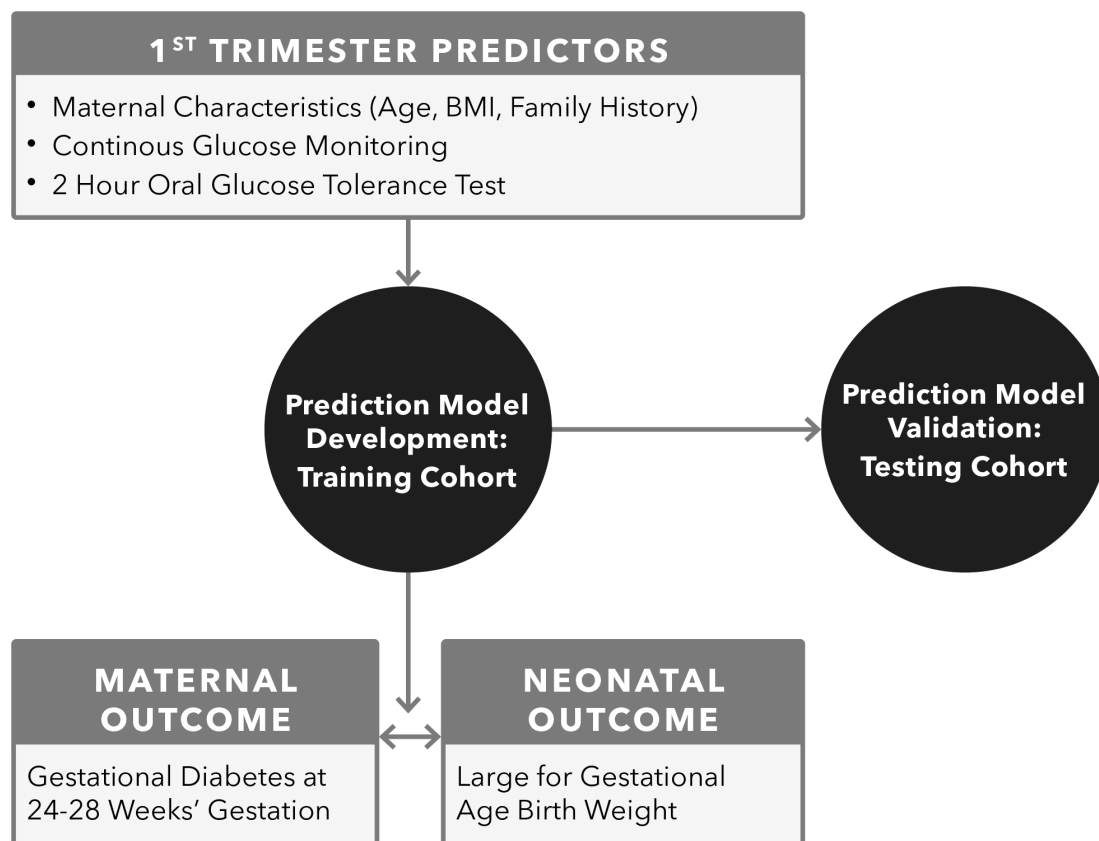


Figure 1 GO MOMs Primary Analyses Statistical analyses for the primary objectives will evaluate predictive models for the gestational diabetes and large for gestational age birth weight co-primary outcomes. Training and validation data sets will be identified a priori with all observations from a subset of sites used for training, and observations from the remaining sites use for validation.

using the V1 OGTT values. Secondary and exploratory analyses will incorporate continuous versions of CGM and OGTT data, CGM predictors from other gestational time points, and additional glycaemic and metabolic laboratory measures including maternal triglycerides, free fatty acids, haemoglobin A1c, C-peptide, insulin and calculated insulin physiology indices, complete blood count, and alternative glyated markers (glycated CD59, glycated albumin, 1,5-anhydroglucitol).

Clinical predictors

Predictive models that incorporate clinical factors and CGM or OGTT data will be compared with models including only clinical factors, specifically maternal age, body mass index (BMI) and family history of diabetes. These were selected based on clinical factors that have been commonly used in previous reports of clinical predictive models for GDM.^{47–53} While previously published predictors for GDM and LGA have sometimes included race and ethnicity, GO MOMs will develop a model that does not incorporate race and ethnicity variables. Race and ethnicity are social constructs which, when included in prediction models, could perpetuate healthcare disparities.^{54 55} Additional clinical factors may also be evaluated for their contributions to predictive accuracy.

Study procedures

Overview

Table 4 summarises the study procedures following enrolment. To capture glycaemic changes across pregnancy, we conduct visits and place CGM devices at four timepoints: 10–14 (V1), 16–20 (visit 2: V2), 24–28 (visit 3: V3) and 32–36 (visit 4: V4) weeks' gestation. We administer a 2-hour 75-gram OGTT at V1 and a 3-hour 100-gram OGTT at V3. Within 72 hours of delivery, neonatal anthropometric measures are obtained. A postpartum follow-up survey occurs remotely between 4 and 13 weeks after delivery. Medical record abstraction occurs 30–90 days after delivery and captures relevant diagnoses and hospital readmissions. The timing of the gestational windows for the V1 and V3 in-person study visits was chosen to facilitate data collection for the primary analyses. The gestational windows for V2 and V4 were chosen to capture an additional early pregnancy time point (V2) and to facilitate assessment of the impact of GDM treatment (V4) prior to term.

Continuous glucose monitoring

CGM provides a nuanced, detailed determination of dynamic glycaemic patterns by measuring interstitial glucose every 5 min, providing up to 288 glucose readings per day. We chose the Dexcom G6 Pro CGM (Dexcom,

Table 4 GO MOMs visits and procedures

	Screening visit	V1: 10w0d–14w0d gestation	V2: 16w0d–20w0d gestation	V3: 24w0d–28w0d gestation	V4: 32w0d–36w0d gestation	Delivery	Chart abstraction: 30d–90d after delivery	Remote follow-up: 4w0d–12w6d after delivery
Ultrasound, estimated delivery date (can occur at screening or V1)								
10-day CGM								
2-hour 75-gram OGTT, with fasting and hourly timed samples								
3-hour 100-gram OGTT, with fasting and hourly timed samples								
Non-fasting blood sample								
Maternal urine								
Maternal height								
Maternal weight								
Maternal interview								
Newborn birth weight, length, flank skinfold, abdominal circumference								
Medical chart abstraction								

CGM, continuous glucose monitor; d, days; GO MOMs, Glycemic Observation and Metabolic Outcomes in Mothers and Offspring; OGTT, oral glucose tolerance test; V1, visit 1; V2, visit 2; V3, visit 3; V4, visit 4; w, weeks.

San Diego, CA) because of its demonstrated accuracy in pregnancy,⁵⁶ ability to blind glucose values and lack of need for fingerstick calibration. Based on a participant's preference, the CGM is placed on the abdomen, upper arm, buttock or lower back/hip. CGM devices are used in 'blinded' mode so that participants, providers and the GO MOMs research team do not observe participants' CGM data. For 10 days after each visit, the participant wears the device and subsequently returns it to the clinical centre. CGM data are downloaded for quality assessment and summary by the BRC. If there are less than 5 days of data, participants are asked to repeat the CGM for a full 10-day wear if this can be accomplished during the study visit window.

Oral glucose tolerance tests

Both the 2-hour 75 g (V1) and 3-hour 100-gram (V3) OGTTs are conducted after an overnight fast (≥ 8 hours duration). After fasting samples are drawn (table 4), participants consume the oral glucose load within 10 min. Timing of hourly sample collection is based on when OGTT beverage consumption begins. To minimise in-vitro glycolysis,⁵⁷ blood samples from the OGTT are immediately placed on ice, centrifuged within 15 min of collection and promptly frozen at -80°C . Samples are shipped to the study's central laboratory where they are assayed within 80 hours of collection. A backup plasma sample from each draw time is stored at each local site at -80°C to allow for re-evaluation of glucose levels in case of primary sample loss or error. Glucose

is measured in EDTA plasma by a hexokinase method on the Roche Cobas c502 chemistry analyzer (Roche Diagnostics, Indianapolis, IN); the inter-assay CV is 2.4% at a mean concentration of 98.5 mg/dL and 3.1% at a mean concentration of 229.8 mg/dL. Additional periodic monitoring of the central laboratory glucose assay is assessed via measurement of value-assigned standard reference material from the National Institute of Standards and Technology and accuracy-based proficiency testing programmes that compare results to those obtained by a reference method procedure. Average glucose values for the study population are reviewed periodically by the study's laboratory committee to evaluate for sample drift over time. Masked OGTT results are reviewed by the same committee to evaluate for potential within-OGTT sample swaps. Both participants and study personnel are masked to the results from the V1 OGTT and A1c, unless the results are consistent with overt type 2 diabetes by ADA criteria.¹⁶ Results of the 3-hour OGTT similarly remain masked unless the glucose levels are consistent with GDM by Carpenter-Coustan criteria.¹⁶ If overt diabetes (V1) or GDM criteria are met (V3), the BRC shares results with the clinical centre, who notifies the participant's obstetric provider. Additional safety criteria for unblinding the 3-hour OGTT results include a fasting glucose of ≥ 126 mg/dL or a 2-hour or 3-hour glucose value of ≥ 250 mg/dL. If GDM is diagnosed at V3, it is treated according to standard practice by local obstetric providers.

Table 5 Glycemic Observation and Metabolic Outcomes in Mothers and Offspring (GO MOMs) laboratory measures and biospecimens

Laboratory measure or biospecimen	Visit 1		Visit 2	Visit 3		Visit 4
	Fasting	Post-load	Non-fasting	Fasting	Post-load	Non-fasting
Plasma glucose						
C-peptide						
Insulin						
Complete blood count						
Haemoglobin A1c						
Triglycerides						
Free fatty acids						
Glycated CD59						
1,5-anhydroglucitol						
Glycated albumin						
Packed cells (stored)						
Plasma and serum (stored)						
Urine (stored)						

Post load indicates hourly specimens after 75-gram (visit 1) or 100-gram (visit 3) glucose load. Biospecimens are shipped to the GO MOMs central laboratory. Glucose, insulin, C-peptide, haemoglobin A1c and complete blood counts are assayed within 80 hours of collection.

Additional biospecimen collection

Maternal blood and urine are obtained at each visit for additional laboratory measurements and future use (table 5).

Anthropometrics

Participant height is measured at V1 using a Seca Stadiometer 217 (portable) or Detecto Adult Stadiometer (non-portable). Weight is measured using a calibrated Seca Scale 869 at V1 through V4. These measurements are obtained two times; if the first two measurements differ by ≥ 0.5 cm for height or ≥ 0.5 kg for weight, a third measurement is taken. Measurements of newborns are obtained within 72 hours of delivery and include length using an Ellard length board, weight using a calibrated Seca 334 scale, flank skinfold using a calibrated Harpenden calliper, and abdominal circumference using the Gulick II tape measure. Newborn measurements are obtained two times; if the first two measurements differ by ≥ 0.5 cm for length, ≥ 10 g for weight, ≥ 0.5 mm for flank skinfold or ≥ 0.5 cm for abdominal circumference, a third measurement is taken.

Biospecimens are shipped to the GO MOMs Central Laboratory. Glucose, insulin, C-peptide, haemoglobin A1c and complete blood counts are assayed within 80 hours of collection.

Questionnaires

At V1, staff interview participants about obstetrical history, family history of diabetes, alcohol and tobacco use, medical conditions, medication use, food insecurity and other social and demographic information. Information about medical conditions, medication use, alcohol and tobacco use are updated at V2, V3 and V4. To gather

data on sleep, which may be associated with glycaemia during pregnancy,⁵⁸ participants complete the Pittsburgh Sleep Quality Index survey at V1 and V3. At V4, participants complete questionnaires on their perceptions of CGM and OGTT; those diagnosed with GDM also answer questions about nutritional management. The remote postpartum survey includes questions about breast feeding and maternal and newborn hospital admissions. Questionnaires are available in both English and Spanish.

Chart abstraction and adjudication

Data abstracted from each site's EMR are used to identify the newborn primary outcome and the predefined secondary and exploratory outcomes. Adjudication committees review outcomes requiring decision making beyond what is noted in the EMR and GDM cases diagnosed outside the study.

Nutrition substudy

A subset of participants who enrolled in GO MOMs between February 2023 and February 2024 are participating in the GO MOMs Nutrition Study. Substudy participants complete six 24-hour dietary recalls using the Automated Self-Administered 24-Hour Dietary Assessment Tool.⁵⁹ Two recalls occur during the V1 and V3 study visits and four unannounced recalls occur after each of the four study visits on a random day during the CGM wear period.

Risk to participants

The study is considered minimal risk to participants; risks are described to participants during the informed consent process. These include risks associated with blood drawing (eg, local pain, irritation, bruising, anxiety, syncope), oral

glucose tolerance testing (eg, headache, vomiting, symptoms of hypoglycaemia), collection of health information (eg, loss of confidentiality) and CGM placement/wear (eg, local pain, skin irritation, bleeding). At each visit, participants are asked about their experience with CGM wear and whether any problems occurred, such as skin irritation. If skin irritation from CGM occurs, the study team works with the participant to determine if future CGM placements should occur, with the option of using a barrier film spray to protect skin. Adverse events are reviewed by site investigators, recorded in the study database and reported to the IRB and Observational Study Monitoring Board (OSMB) when appropriate.

Statistical considerations

Statistical analyses for the primary objectives will evaluate predictive models based on logistic regression for GDM and LGA primary outcomes (figure 1). Training and validation data sets will be identified a priori with all observations from a subset of sites used for training, and observations from the remaining sites used for validation. First, predictive models using clinical variables at V1 will be developed for GDM and LGA. Model parameters will be estimated using 10-fold cross-validation in the training data set, maintaining equal GDM and LGA outcome frequencies across rounds of cross-validation.

After finalising predictive models using clinical variables, models that incorporate summary measures of V1 CGM or OGTT data will be developed. Predictive model parameters using CGM or OGTT data summaries will be estimated using 10-fold cross-validation in the training data set, maintaining equal GDM and LGA outcome frequencies across rounds of cross-validation. Improvements in predictive accuracy for models that add CGM or OGTT data to clinical factors will be examined. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) using assumed values of 5.6% GDM (the most recent published prevalence estimate at the time of study design³) and 10% LGA population prevalence will be used for primary reporting. PPV and NPV will also be estimated using the outcome prevalence in GO MOMs. Values of PPV and NPV will be evaluated across the full range of potential cut-offs in logistic regression models, and cut-offs meeting desired NPV and maximising PPV under cross-validation will be selected to define optimal predictive models based on clinical factors alone, CGM and clinical factors, and OGTT and clinical factors. Formal statistical hypothesis testing to compare the optimal predictive model with CGM and clinical factors vs clinical factors alone, and the optimal predictive model with OGTT and clinical factors versus clinical factors alone, will be conducted using methods that account for the paired nature of PPV values under different tests in the same population.⁶⁰ Predictive accuracy metrics for models optimised in the training data will be independently estimated along with 95% CIs in the validation data set.

Predictive modelling for GDM and LGA will be expanded in secondary analyses to discern whether models including clinical variables and CGM-based or OGTT-based criteria in the V1 time frame demonstrate comparable predictive performance across subgroups according to self-identified race and ethnicity and socio-economic variables. This will be examined by evaluating statistical interaction terms between the subgroup and the CGM-based and OGTT-based and other clinical variables in logistic regression models, and by examining PPV, NPV, sensitivity and specificity point estimates and 95% CIs within subgroups. In addition to V1 CGM and OGTT metrics and clinical risk factors, the added predictive contribution of continuous summaries of CGM and OGTT data and additional laboratory measures for primary outcomes will be explored.

While outcome prediction is a priority for GO MOMs, statistical analyses will also be performed to explore associations of clinical, CGM and laboratory data obtained at V1–V4 with secondary maternal and newborn outcomes. Statistical methods will include regression modelling and generalised longitudinal linear mixed models. Exploratory dynamic risk prediction models using CGM data over the course of pregnancy will also be examined. Mediation analyses using structural equation models will be conducted to estimate the effects of GDM management, if diagnosed, on the association between maternal glycaemia and newborn outcomes.

Sample size and power

Target enrolment for GO MOMs is 2150 participants. Sample size calculations were based on the primary aims to assess the predictive capacity of CGM and OGTT summary measures at V1 for the primary outcomes. Evaluation of GDM and LGA outcomes will be viewed as separate analyses and 5% two-sided type I error will be used for evaluation of each outcome. Since two formal hypothesis tests will be conducted for each outcome (ie, the evaluation of each outcome with predictive models comparing clinical factors alone to models also including V1 CGM or OGTT data), results will be considered statistically significant at two-sided $p < 0.025$ according to Bonferroni correction to maintain overall 5% type I error.

Sample size was determined based on evaluation of PPV for GDM and LGA at a set NPV for each. Published literature suggests that PPV for GDM using clinical factors that are identifiable early in pregnancy is approximately 0.20.^{47–53} Less information is available for LGA, but some reports indicate that a PPV of 0.15 is possible using maternal clinical risk factors that are identifiable early in pregnancy.⁶¹ Clinical factors in these predictive models uniformly included age and BMI and several also included family history of diabetes. GO MOMs was designed to detect a clinically meaningful increase in PPV from 0.20 to 0.40 for GDM and from 0.15 to 0.30 for LGA. Calculations were performed assuming 5.6% population prevalence for GDM based on the most recent published estimate at the time of study design³ and 10% population

prevalence for LGA. NPV was held constant for GDM at 0.97 and for LGA at 0.95. Sample size calculations were based on simulation studies using hypothesis testing methodology that accounts for the paired nature of PPV values under different tests in the same population.⁶⁰ Dependence was induced between observations of PPV under the null and alternative hypotheses using normally distributed random effects with mean 0 and between-subject variance ranging 0.1–1 (intraclass correlation coefficient 0–0.5). To detect the proposed improvements in PPV for GDM at 90% power, 860 GO MOMs participants with observed data for the primary GDM outcome are required. A sample size of 860 with complete data provides approximately 99% power to detect an increase in PPV from 0.15 to 0.30 at a constant NPV of 0.95 for the LGA primary outcome.

Existing literature does not support hypotheses about the exact CGM-based or OGTT-based criteria at V1 to be evaluated as predictors of GDM and LGA. Thus, a range of statistical summaries for CGM data and cut-off values for OGTT data will be explored. Given this, independent training and validation GO MOMs data sets are paramount. As noted above, 860 GO MOMs dyads will be required for hypothesis testing for improvements in PPV. Two times this number of GO MOMs participants will be enrolled, and training and validation data sets of equal sizes will be identified prior to predictive model development. Training and validation data sets will be designated after completion of data collection, but prior to formal statistical analyses. The full data from each site will be placed either into the training or validation data sets, maintaining comparable demographic and clinical characteristics and outcome frequencies across the two data sets. A sample size of 860 in the validation data set will provide 95% CIs with half-width of 0.10 surrounding the PPV estimate. Precision at this level is thought to be necessary to motivate potential changes in clinical practice for early screening.

In summary, 1720 participants (860 each in training and validation data sets) are required to accomplish the GO MOMs primary objectives. Assuming 80% of participants complete the study with observed outcomes, a total enrolment of 2150 participants is required.

Analyses of associations for secondary outcomes will collectively use observations from all 2150 participants. For analyses investigating associations of predictors with dichotomous secondary outcomes, assuming R^2 of the primary predictor with other model covariates of up to 0.4, this sample size affords 90% power at nominal two-sided $p < 0.05$ to detect ORs in the range of 1.25–1.60 for a continuous predictor higher by one SD for outcome frequencies ranging 0.05–0.30. ORs in the range of 1.59–4.31 are detectable for dichotomous predictors with frequencies ranging 0.05–0.30 for both the outcome and predictor. For continuous secondary outcomes, again assuming R^2 of the primary predictor with other model covariates of up to 0.4, adjusted mean differences ranging 0.22–0.46 SD are detectable at 90% power at nominal

two-sided $p < 0.05$ for dichotomous predictors with frequencies ranging 0.05–0.30. Partial correlation of 0.10 is detectable for a continuous predictor with a continuous outcome. All calculations assume 80% of participants complete the study and have observed outcomes. Analyses of exploratory outcomes are not formally powered.

PATIENT AND PUBLIC INVOLVEMENT

During study development, participants who had previously enrolled in a similar pregnancy study at the Massachusetts General Hospital site⁶² were invited to provide feedback and input into study design, recruitment plan and research protocol via focus groups. At the Yale site, investigators convened a stakeholder meeting with community members and leaders from organisations in the local black and Latino communities for feedback on the study plans. The participants in the focus groups and stakeholder meeting strongly supported the scientific rationale and the importance of the study to relevant communities. Input from the focus groups and stakeholder meetings informed the timing of study visits to minimise participant burden, the participant remuneration plan, the strategy for participant engagement and retention, the sharing of individual-level data and the methods for dissemination of study results, among other study details. GO MOMs participants who have consented to future contact will be sent a letter about the results of the study after study completion and publication of results will be made available to the relevant wider patient communities.

ETHICS AND DISSEMINATION

The GO MOMs OSMB, an independent review group appointed by NIDDK, reviewed the study protocol and granted approval in October 2020. Vanderbilt University's Institutional Review Board (Nashville, TN) granted protocol approval in January 2021 under IRB #202214. The BRC oversees certification of study personnel training to ensure standardisation of study conduct and data collection across sites.

After the study is completed and manuscripts addressing the primary and secondary hypotheses have been developed, a limited dataset will be transmitted to the NIDDK Central Repository, under the supervision of the NIDDK, for use by other researchers. De-identified biological samples will also be stored at the NIDDK Biorepository.

DISCUSSION

Despite clinical guidelines suggesting that at-risk pregnant patients should be screened for hyperglycaemia in the first trimester, there are knowledge gaps that hinder this approach. By gathering extensive data on glycaemia and other related biomarkers starting in the first trimester, GO MOMs may be able to identify better early pregnancy criteria for predicting GDM and

hyperglycaemia-associated adverse outcomes. By identifying individuals at risk for GDM and LGA in the first trimester, novel screening strategies, and ultimately, treatments can be developed to improve pregnancy health.

GO MOMs will leverage CGM technology in order to identify glycaemic patterns that may predict GDM, LGA, and other pregnancy complications better than currently employed diagnostic tools. Indeed, CGM is now being leveraged in prediction models for development of type 1 diabetes.^{63–66} CGM has also been used to describe glycaemic patterns in cohorts of people without diabetes, leading to improved understanding of physiological glycaemic variation.⁶⁷ Similarly, GO MOMs will describe physiological glycaemic patterns across pregnancy in a large cohort.

GO MOMs will extensively characterise the metabolic profile of pregnant participants. We will use insulin and C-peptide to assess insulin resistance and determine its relationship to the glycaemic patterns identified by CGM and GDM as diagnosed by traditional OGTT. We will also examine alternative GDM biomarkers, including plasma glycated CD59, glycated albumin and 1,5-anhydroglucitol.²⁰ Lipids, which are associated with fetal growth,⁶⁸ will also be examined. Such novel biomarkers, either alone or combined with CGM, could be a more reliable and efficient way to conduct GDM screening compared with OGTT and improve problems with reproducibility, adherence, patient burden and healthcare resources associated with currently recommended screening protocols.^{69–72}

The GO MOMs cohort will be comprised diverse individuals representing the US birthing population, allowing for generalisability and facilitating translation of findings to US clinical practice. The results will inform future clinical trials designed to prevent GDM and its sequelae. The GO MOMs cohort can also serve as a vehicle for ancillary studies. Such studies could focus on understanding the relationship between in-utero exposure to hyperglycaemia and long-term outcomes in offspring, which would have the potential to help break the intergenerational cycle of obesity and diabetes. Follow-up of the cohort could examine long-term cardiometabolic outcomes in GO MOMs parents which could lead to more effective preventive strategies for type 2 diabetes and cardiovascular disease. The stored samples from the NIDDK Biorepository will be a new resource for research on diabetes, metabolic disease and pregnancy.

Strengths of the GO MOMs study include the large sample size of pregnant participants which will facilitate a training and validation framework for any new criteria developed, the anticipated representativeness of the cohort, the detailed longitudinal glycaemic profiling using multiple assessment methods, and the use of a central laboratory and standardised processing protocol for laboratory analyses. Limitations of the study include its observational nature, which will preclude the ability to make conclusions about causality for the observed associations, limited duration of CGM monitoring in each

participant, lack of physical activity data collection, and nutrition data which is limited to a subset of the study population. The decisions about CGM monitoring duration and physical activity and nutrition data collection were made in an effort to minimise participant burden and increase adherence to the study protocol.

GO MOMs has the potential to advance our understanding of the effects of hyperglycaemia throughout gestation on outcomes for birthing persons and their children. Given the association between GDM and both short-term and long-term health consequences^{5–8} and the large number of people affected by GDM, data generated in GO MOMs could ultimately have a large impact on population health.

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and DS were responsible for primary drafting of all sections the manuscript and critical review of all content and suggested edits from the writing group. EL, JS, NZ, MF, EW and UR were all critical contributors to manuscript content review, writing and editing. All authors contributed to study design through cooperative activities of the GO MOMs Study Group. All members of the Writing Group and all members of the GO MOMs Steering Committee approve of this manuscript submission.

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