Trials

STUDY PROTOCOL

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Metformin versus insulin in glycemic control in pregnancy (MevIP): a randomized clinical trial protocol

Carolina Freitas Alves Amaral-Moreira[1], Daiane Sofia Morais Paulino[1], Belmiro G. Pereira[1], Patricia Moretti Rehder[1] and Fernanda G. Surita[1*]

Abstract

Background Gestational diabetes is one of the most prevalent diseases in pregnancy, with an incidence of 5 to 18% in Brazil, and is associated with high morbidity rates. The first-line treatment is insulin, although some recent studies have indicated that metformin might also be effective. Metformin is safe in pregnancy and appears to produce better results than insulin, including reduced gestational weight gain (GWG) and smaller gestational-age newborns. Few studies have been conducted on this topic in low- and middle-income countries.

Methods We designed an open randomized controlled trial comparing two treatments for pregnant women with type II diabetes mellitus (DM) and gestational diabetes (DMG): the metformin group (intervention) and the insulin group (as a routine service). The primary outcome is glycemic control. The secondary outcomes are GWG, the occurrence of hypertensive syndromes, macrosomia, and neonatal hypoglycemia. The sample will comprise 92 pregnant women, 46 per group. The inclusion criteria will be GDM or type II DM requiring medication for glycemic control, singleton pregnancy, and gestational age under 34 weeks. The exclusion criteria will be current treatment with any medication for glycemic control, type I DM, and intolerance to the study medications (metformin or insulin). Women will be routinely followed during antenatal care, childbirth, and the postpartum period. Statistical analyses will include the intention-to-treat approach and a comparison between the two groups.

Discussion Considering the Brazilian socioeconomic reality and the safety of metformin demonstrated in previous trials, we expect that the MevIP study will demonstrate that metformin is an adequate and appropriate medication for GDM treatment in the Brazilian population, representing an alternative to insulin for GDM.

Trial registration This protocol has been registered prospectively in ReBEC under the ID RBR-3j3cktx in August 11, 2023.

Keywords Gestational diabetes, Metformin, Pregnancy, Diabetes

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Title {1}	METFORMIN VERSUS INSULIN IN GLYCEMIC CONTROL IN PREGNANCY (MevIP): A RANDOMIZED CLINICAL TRIAL PROTOCOL
Trial registration {2a and 2b}	RBR-3j3cktx, Registro Brasileira de Ensaio Clínico (ReBEC), https://ensaiosclinicos.gov.br/rg/RBR-3j3cktx
Protocol version {3}	December, 25th, 2024, version 2.0
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Author details {5a}	Carolina FA Amaral-Moreira[1], (CFAAM) Daiane S M Paulino[1] (DSMP), Belmiro G Pereira [1] (BGP), Patricia Moretti Rehder [1], Fernanda G Surita[1](FGS) [1] Department of Obstertrics &Gynecology, School of Medical Science, Universidade Estadual de Campinas
Name and contact information for the trial sponsor {5b}	FGS, Ph.D, MD, [+ 551935219304] [surita@unicamp.br].
Role of sponsor {5c}	This is a trial that follows the routines of hospital medical care for the patients included. The medications used are routinely provided free of charge by the government

Introduction

Background and rationale {6a}

Gestational diabetes (GDM) is one of the most prevalent diseases occurring during pregnancy, with an incidence of around 14% worldwide. GDM has serious consequences for both women and their fetuses, including macrosomia, increased requirement of cesarean sections, shoulder dystocia, preterm birth, premature rupture of the membrane, and respiratory distress; GDM also increases the offspring's diabetes risk in adulthood [1]. The incidence of GDM is increasing more rapidly in low and middle-income countries than in high-income countries due to the poor diet and excess weight gain observed in these populations [1].

Although GDM and type II diabetes are classified as two different conditions, they present similar pathophysiology of insulin resistance. The degree of pathophysiology differs, producing separate diagnostic cutoffs. GDM can be considered when patients present a fasting glucose level between 92 and 125 mg/dl, and type II diabetes when this value exceeds 125 mg/dL. Additionally, women with GDM typically demonstrate normal fasting glucose levels after pregnancy ends, since the levels of placental hormones that provoke insulin resistance reduce; however, they remain at a higher risk for developing type II diabetes in the future [2].

The first line of treatment for GDM is dietary improvement and physical activity, which can be effective. Nevertheless, 20% of patients will require drug intervention [3], with insulin being the standard medication. However, several oral medications have been suggested as alternatives, due to difficulties in administering and storing insulin and its potential adverse effects, such as hypoglycemia. Metformin is of particular interest because it addresses the pathophysiology of GDM [3].

The main concern when prescribing metformin in pregnancy is that it crosses the placenta and may therefore affect the fetus into childhood and adulthood [4]. However, no previous studies have demonstrated increased risks when using metformin in place of insulin [4, 5]. On this basis, the National Institute for Health and Care Excellence (NICE) in the UK and The American College of Obstetricians and Gynecologists (ACOG) have accepted metformin as a treatment option for GDM [5]. In Brazil, metformin is administered to pregnant women taking high-dose insulin, as described in the High-Risk Pregnancy Manual developed by the Brazilian Health Ministry (MS) [6].

The incidence of GDM in Brazil is approximately 18%, as reported by the Ministry of Health [7]. Brazil is considered one of the eight low-income countries (LMIC) responsible for 55% of the worldwide diabetes burden [7]. Appropriate treatment strategies for GDM must therefore be in place to reduce its consequences [7]. Medication adherence is one of the main challenges in treating such diseases. This is especially true of injectable medications, such as insulin, as patients often fear needles or lack confidence in administering injections themselves [8]. In Brazil, both metformin and insulin are provided by the government. Metformin is cheaper than insulin and is therefore more accessible, which improves adherence, especially in LMIC [9].

Objectives {7}

Since metformin is considered safe in pregnancy, we will perform an open randomized controlled trial in Brazil, an LMIC, to compare the maternal (glycemic control, weight gain, labor, and incidence of hypertensive syndromes) and neonatal (weight, height, birth weight adequacy for gestational age, and need for intensive care) outcomes between new intervention (metformin) and routine service (insulin) groups. This will be an equivalence trial comparing metformin and insulin.

Trial design {8}

The MevIP study is an open-label randomized controlled trial with parallel groups and two arms, with a 1:1 allocation rate. The study will evaluate equivalence between metformin and insulin in achieving glycemic control during pregnancy.

Methods: participants, interventions, and outcomes

Study setting {9}

The study setting is the Women's Hospital of the State University of Campinas, Southeast Brazil, a public referral center for high-risk pregnancy and maternal-infant care. Our hospital has high-risk antenatal care (ANC) and a specific weekday on which a specialized interdisciplinary team treats pregnant women with any type of diabetes.

Eligibility criteria {10}

Included study subjects will be women with singleton pregnancies < 34 weeks, who have been diagnosed with diabetes mellitus type II or GDM with inadequate glycemic control (over 30% of blood glucose measurements above the level stipulated by the MS [6]) and who have undergone dietary treatment and require medication. Exclusion criteria will be patients with other types of diabetes, those who are already treated with or cannot tolerate insulin or metformin, those with multiple pregnancy or fetuses with major malformations, or patients using corticosteroids.

Patients will be diagnosed with diabetes as established by the MS, through measurement of fasting glucose and blood glucose after main meals (breakfast, lunch, and dinner) [6].

Who will take informed consent? {26a}

Patients will be invited to participate in the trial by the researchers when dietary and lifestyle changes have proven insufficient for maintaining blood glucose levels properly and it is deemed necessary to start medication for glycemic control. Patients will be considered eligible when over 30% of glucose measurements are above the established threshold (over 95 mg/dL in fasting and over 140 mg/dL 1 h after breakfast, lunch, and dinner). Upon accepting to participate, patients will be randomized and medication initiated. Patients will have the opportunity to raise any doubts with the researchers before randomization. All patients will be asked to sign two copies of the informed consent form, one for the researchers and another for themselves. All participants will only be able to participate after voluntarily signing the informed consent form. The informed consent form includes the purpose, interventions, risks, potential benefits, and procedures associated with the study.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

We will request consent to review each participant's medical records. Biological specimens will not be collected by the researchers.

Interventions

Explanation for the choice of comparators {6b}

Metformin will be compared with insulin treatment; insulin is the standard treatment for diabetes during pregnancy as established by the MS and American Diabetes Association (ADA).

Intervention description {11a}

Patients will attend at least 10 medical appointments and one ultrasound per trimester and undergo two blood and urine analyses during pregnancy. This schedule follows the recommendations of the "High-Risk Pregnancy Manual" provided by the MS [6].

As explained above, the routine primary intervention is diet and exercise changes for all patients. If 30% of a patient's blood glucose measurements are unsatisfactory (fasting glucose over 95 mg/dL; glucose over 140 mg/dL 1 h after a meal), medication will be introduced for glycemic control [6, 10].

When medication is necessary, patients will be randomized into the insulin (control) or metformin (intervention) group. The initial dosage of metformin will be 500 mg/day. The initial dose of recombinant human insulin will be 6 to 10 U/day.

Dosages will be increased or decreased according to monitoring of the glycemic control (satisfactory or unsatisfactory). As with pre-intervention measurements, fasting glucose above 95 mg/dL and glucose 1 h after meals in excess of 140 mg/dL in over 30% of measurements will be considered unsatisfactory control, as established by the MS and ADA [6, 10].

If a patient in the metformin group requires over 2 g/day, insulin will be added to their treatment regimen; if a patient in the insulin group requires over 80 U of recombinant human insulin, metformin will be added.

Criteria for discontinuing or modifying allocated interventions {11b}

Patients will be discontinued from the study at their request or if they are lost to follow-up (defined as not attending medical appointments and not responding to two to three telephone calls to reschedule).

Strategies to improve adherence to interventions {11c}

At each appointment, patients will be asked by their doctor whether they are adhering to their treatment and congratulated if they are. In addition, our multidisciplinary team will reinforce the importance of treatment adherence and help resolve any social or emotional concerns that might affect adherence.

The patients will measure their fasting and postprandial glucose levels three times a week and bring the results to their appointments to allow adjustment of

their medication. An ultrasound scan will be performed monthly to evaluate the fetal weight, amniotic fluid index, growth, and Doppler pulsatility index. A cardiotocography will be performed weekly after 32 weeks, and a daily fetal movement count will be conducted by the patients to evaluate fetal well-being.

Relevant concomitant care permitted or prohibited during the trial {11d}

Participants will be given nutritional advice and guidance during the trial. They will also be invited to participate in a nutritional counseling group in which they can share their experiences and difficulties in following the prescribed diet.

Patients will also be provided exercises, such as walking, aerobics, and resistance training, to perform during pregnancy for at least 150 min per week spread across at least 3 days, as recommended by the MS and Canadian Guidelines [6, 11]. Our institution has an exercise guide for pregnant women to access online, which can also be provided as a paper copy.

Provisions for post-trial care {30}

Since the trial has been approved by the ethics committee of the hospital, if any harm arises during participation, the hospital will provide the necessary assistance to the patients.

Outcomes {12}

The primary outcome is adequate glycemic control in pregnancy, that is, fasting glucose under 95 mg/dL and glucose levels under 140 mg/dL 1 h after a meal, as established by the MS and ADA [6, 10]. Glycemic control will be evaluated in ANC appointments and by self-monitored glucose performed by patients when fasting and 1 h after meals.

The secondary outcomes are gestational weight gain (GWG), the incidence of hypertensive syndromes, fetal growth, fetal well-being, the occurrence of polyhydramnios, Doppler pulsatility index variations, the need for neonatal intensive care, the incidence of neonatal hypoglycemia, adverse pregnancy outcomes (postpartum hemorrhage, intensive care requirement, and maternal death), and adverse neonatal outcomes (congenital disabilities and death).

Participant timeline {13}

Our ANC follows pregnant women with gestational diabetes. They will be invited to participate if they do not achieve satisfactory control with diet and exercise. All patients requiring intervention with medication will be invited to give their consent to participate. Then, they will be randomized into one of the two groups. The informed consent documentation explains the study's risks, benefits, and timeline.

For randomization, the patient will choose one of two sequentially numbered opaque envelopes presented by the research team after providing written informed consent. The group assignment will be inside the envelope. If the patient no longer wishes to participate, they will be asked why, the reason will be registered, and they will be followed up per standard procedures.

After patients are randomized, they will be followed in the diabetes-specific ANC according to the routine service described above and in Fig. 1.

Sample size {14}

The sample size was calculated by comparing the mean of the two groups (insulin and metformin) using a

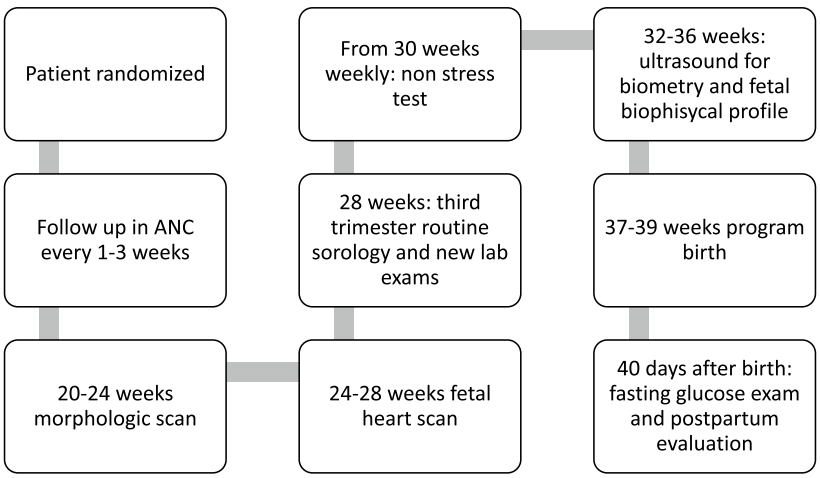

Fig. 1 Patient's timeline

quantitative variable, with a confidence interval of 95% (type I error of 5%) and a sample power of 80% (type II error of 20%). The standard deviation and mean values of maternal and neonatal characteristics of each group were used. The minimum sample size for the evaluation of the main objective (glycemic control) was 74. Estimating that 20% of the sample may be lost to follow-up, we will recruit 92 participants. Sample calculation was performed using the Statistical Analysis System (SAS) for Windows, version 9.2, based on methods described in the literature [12, 13].

The primary outcome—glycemic control—will be evaluated primarily through measurements of glucose levels after fasting and 1 h after meals, but also through indicators such as polyhydramnios and the incidence of a large-for-gestational-age-fetus, defined as an estimated fetal weight greater than the 90th percentile on ultrasound during treatment.

Recruitment {15}

The recruitment is shown in Fig. 2.

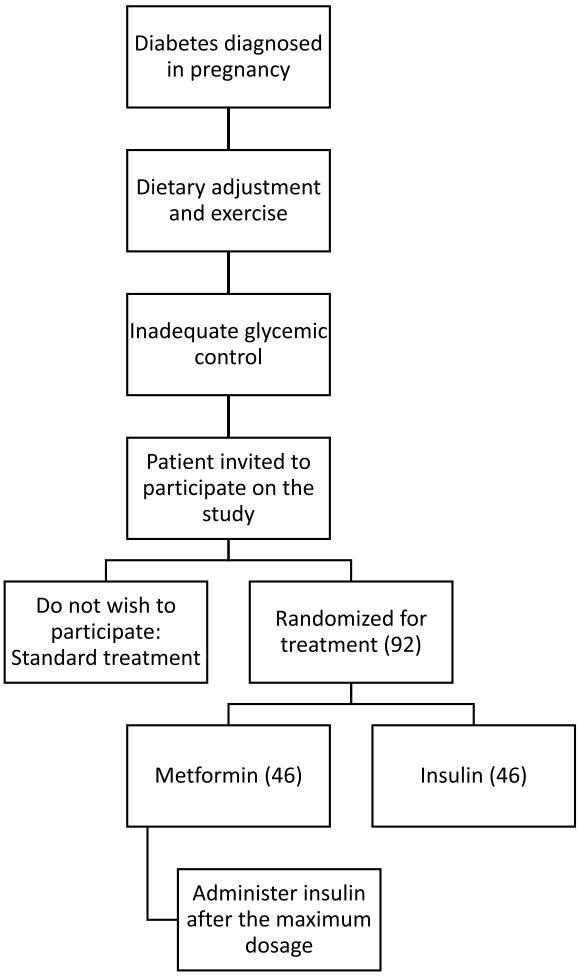

Fig. 2 Recruitment

Assignment of interventions: allocation

Sequence generation {16a}

The randomization sequence will be generated using the website https://www.random.org/lists. The researchers will not have access to the randomization list to avoid bias.

Concealment mechanism {16b}

The assigned treatment for each participant will be sealed in an opaque, sequentially numbered envelope. Patients will be offered the choice of two envelopes and allocated to the group according to their selection.

Implementation {16c}

The sequence generation will be generated the statistics department. The participants will be enrolled by other physicians, who will prescribe the assigned medication after randomization without having access to the sequence. All patients of the study will follow consultations under the researcher's supervision.

Assignment of interventions: blinding

Who will be blinded {17a}

The study will be an open RTC. All researchers and participants will know which intervention the patient is randomized to receive.

Procedure for unblinding if needed {17b}

Unblinding will not be necessary, as the study is an open-label trial.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data collection methods

All data will be collected using a structured form and entered into Excel spreadsheets. Data will be collected from the patients' institution charts. Since all patients will be followed at the same ANC, the quality of the information will be constantly evaluated to guarantee the reliability of the data. Only trained assessors will perform consultations.

Plans to promote participant retention and complete follow-up {18b}

To promote participant retention and follow-up, any patient missing a consultation will be contacted by telephone, and a new appointment scheduled. Our hospital relies on social service professionals who help patients attend the appointments and then return to their homes. Patients who are lost to follow-up will also be contacted

by phone and invited for a new consultation or asked about missing information by phone.

Data management {19}

The database will be stored in the University cloud, and only those with institutional email addresses and study participants will be allowed to access it. Only the researchers will be allowed to edit the database. Information will be coded according to a structured form to enable statistical analyses. Data will be added by the researchers and double-checked.

Confidentiality {27}

All patients will be identified only by their trial and hospital numbers, with no names associated with the data. All data will be collected from the patients' medical charts and transcribed into the trial database, which only the research team will have access to. The research team members are all health professionals and therefore are obliged to patient confidentiality. For statistical analysis, all identifying information such as hospital numbers and names will be excluded, with only the trial number retained. All data will be analyzed by group and will not include personal information. The database can only be accessed by institutional accounts, as it will be uploaded to and secured by the university mainframe.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

For this trial, the only examinations required are those of routine ANC. There will be two collections of blood and urine samples, which will not be stored by the laboratory. Glucose assessment will be performed and recorded by the patients themselves. The researchers will therefore not collect or keep any biological specimens, requiring only access patients' laboratory records.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Hypothesis

The hypothesis is to compare metformin and insulin treatments in pregnant women with diabetes.

Baseline patient characteristics

The first statistical analyses will include a sample description with frequency measurements, mean, and standard deviation. The variables described will be age, ethnicity, marital status, type of diabetes (type 2 or gestational diabetes), parity, pre-gestational weight and body mass index (BMI), and associated comorbidities for the overall sample and per group. These data will be presented as Table 1 in the resulting article.

Definition of outcomes

The primary outcome will be glycemic control. This will be defined as adequate or inadequate for each group and summarized as a percentage. Secondary outcomes will be fetal weight, described in kilograms; gestational age at birth, described in weeks; and maternal weight gain, described in kilograms. Each of these outcomes will be described by the mean and standard deviation, with the presence or absence of polyhydramnios, pre-eclampsia, gestational hypertension, and type of labor (cesarean, vaginal birth, or forceps birth). Incidence of birth complications and need for neonatal intensive care will be recorded as other maternal and fetal outcomes. The week at which the introduction of the medication is required will also be recorded as a secondary outcome.

Population analyses

As an intention-to-treat trial, the population will be analyzed in the group to which they were randomized. The adherence and percentage of each group completing the intervention will be reported.

Analysis methods

All data will be tabulated and described using the frequency, mean, and standard deviation. Continuous variables will be recorded in spreadsheets and analyzed using Student's *t*-test if normally distributed or the Mann–Whitney test if not. Categorical variables will be coded in a spreadsheet and later assessed using chi-squared or Fisher's exact tests if nonparametric, with a confidence interval of 95%.

Logistic regression analysis will be performed to determine which characteristics contribute to the need for insulin in the metformin group and which contribute

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
- Pregnant women diagnosed with GDM or diabetes mellitus type II -Inadequate glycemic control in over 30% of the measurements - Under 34 weeks pregnant - Singleton pregnancies	- Pregnant women diagnosed with diabetes type I or maturity-onset diabetes of the young - Multiple pregnancy - Patients already using medication for glycemic control -Major malformations - Patients using corticosteroids

to the need for medication in the first and second trimesters.

The primary analysis will compare glycemic control between groups.

Statistical software and analysis

The software used in our analysis will be the SAS, version 9.2.

Interim analyses {21b}

Groups will be analyzed twice (after every thirty patients) to compare treatment groups and evaluate whether metformin is causing any harm to the patients. The formal threshold for stopping the trial will be unsatisfactory glycemic control in the metformin group and increased incidence of large-for-gestational-age fetuses, fetal cardiopathy, and need for neonatal intensive care.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analysis will be performed according to gestational weight gain and initial maternal BMI, to assess the correlation with average fetal weight, incidence of preeclampsia, and maternal and fetal outcomes such as the need for cesarean section and labor complications.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Adherence and protocol deviations

Adherence to the protocol will be defined as a patient taking the prescribed medication as instructed and will be assessed at each visit. Major protocol deviation will be defined as the patient not taking the prescribed drug. As non-adherence is also a possible outcome of the study, the reason for not continuing the medication will be recorded and the percentage of non-adherence in each group reported. If necessary, non-adherent patients will be treated with medication that they were not allocated; however, they will be analyzed in their randomized group, as this is an intention-to-treat trial.

Minor protocol deviations include missed appointments, for which the patient will be recalled for a new appointment; not taking the prescribed dosage, for which a reason will recorded; and randomization of non-eligible participants. In the case of non-eligible participants randomized into the study groups, for example fetuses with major malformations or syndromes or initially unidentified twin pregnancies, only the maternal characteristics will be analyzed. The newborn data will be excluded to avoid bias, but will be detailed in the analyses.

Missing data

For missing data, we will attempt to contact the patient by telephone or message to fill any gaps. Analyses will be performed with the available data, and detailed in the sample if there are missing data.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The study protocol and results will be published in a peer-reviewed journal. The participant information and statistical code will not be published. The datasets analyzed and associated statistical code will be available from the corresponding author on reasonable request.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The coordinating center is composed of an interdisciplinary team involved in the outpatient clinic, which routinely provides for all patient groups and performs individual analyses. A nutritionist team provides a weekly dietary counseling group, follow-up, and guidance based on patients' economic situation. A social service assistance team assists patients in acquiring medication and transport, among other services, to facilitate their attendance at the clinic and treatment adherence. The interdisciplinary team also reinforces dietary guidance in outpatient care when a patient shares difficulties and doubts. All patients are also supported by nurses, who reinforce adequate medication use, providing another space for women to share their difficulties and doubts. All medical appointments are attended by senior Ob & Gyn residents, and a psychology team is available if required.

The trial steering committee is composed of researchers CFAAM, DSMP, and FGS. The committee meets monthly to analyze data and manage recruitment. CFAAM also attends the ANC weekly to evaluate all patients.

Composition of the data monitoring committee, its role and reporting structure {21a}

Our hospital is overseen by an ethics committee and adheres to established safety protocols. All adverse outcomes, such as neonatal death, are evaluated and documented. The hospital safety committee is composed of elected doctors of obstetrics, neonatology, and anesthetics; these members will not participate in this trial.

Adverse event reporting and harms {22}

Severe adverse events in our study will be defined as fetal or maternal death correlated with the intervention

in the experimental group. In this case, the event will be reported to National Committee of Ethics, the study terminated, and all patients switched to insulin.

Frequency and plans for auditing trial conduct {23}

CFAAM will audit the recruitment and data collection weekly. At least one form of statistical analysis will be performed before the end of the trial to ensure that the intervention is not causing any harm.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Protocol amendments will be submitted to the respective regulatory committees, such as the Registro Brasileiro de Ensaios Clínicos (ReBec) and the National Committee of Ethics in Research (CONEP).

Dissemination plans {31a}

We will publish our dataset on the university repository, REDU. The end of the trial will be reported on the relevant trial registry platforms. We intend to present the data in obstetrics and gynecology conferences and will produce a paper to be submitted to a peer-reviewed journal, preferably of Ob&Gyn and open access.

Discussion

The Brazilian population is heterogeneous, with different educational, economic, and health levels. These variations affect disease incidence, treatment adequacy, and the estimation of the impact of diseases and treatments [14]. In the country's southern region, the diabetes incidence is similar to that of Europe, at approximately 5% of pregnancies; overall, the country's estimated incidence is approximately 18% [7, 14].

When evaluating regional differences in treatment adherence across the country, it is necessary to consider access to medication and the ability to store and administer it. Insulin requires refrigeration for storage and trained personnel for administration, which represents a barrier for patients in certain regions; metformin is easier to take [8]. In terms of access, although the Brazilian Health System provides diabetes medication, insulin is more expensive than metformin. Given the financial challenges facing the healthcare system, metformin is therefore an interesting alternative for GDM treatment [14].

Metformin use in pregnancy is a more recent development than insulin, and there is a lack of long-term data on its use. However, the largest and longest follow-up study, MiG TOFU, compared the offspring of pregnant women with GDM treated with metformin or insulin over 9 years and reported no significant differences in body fat or metabolic measures between them; this suggests that metformin is safe [15].

Considering the Brazilian socioeconomic reality and the previously demonstrated safety of metformin, we expect that the MevIP study will provide evidence for metformin as an adequate and appropriate medication for GDM treatment in the Brazilian population, representing a viable alternative to insulin.

Trial status

This trial has been recruiting since August 12, after ReBEC approval RBR-3j3cktx was granted on August 11, 2023.

Abbreviations

ADA	American Diabetes Association
ANC	Antenatal care
CFAAM	Carolina FA Amaral- Moreira
CONEP	National Committee of Ethics
DSMPS	Daiane Sofia Morais Paulino
FGS	Fernanda Surita
GDM	Gestational diabetes
GWG	Gestational weight gain
ICU	Intensive care unit
LMIC	Low- and middle-income countries
MS	Brazilian Health Ministry
SAS	Statistical Analysis System
REBEC	Registro Brasileiro de Ensaios Clínicos (Brazilian Clinical Records Register)
REDU	Repositório de Dados de Pesquisa da Unicamp

Acknowledgements

Not applicable.

Authors' contributions {31b}

CFAAM, BGP, FGS, DSMP, and PMR conceived the idea and study design. FGS provided statistical expertise in clinical trial design. CFAAM wrote the draft version. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding {4}+

Medications and fasting glucose strips are provided by the state. The funding required for this research will cover the printing of consent terms and randomization cards, which will be obtained from state agencies supporting research or be self-funded.

Data availability {29}

All authors and statisticians will be given access to cleaned data sets. To ensure confidentiality, data will be presented with the patient study number only. Only CFAAM will have access to the identification list. The data will be uploaded to the university's closed cloud, and only the researchers will have access to the database. Data required to support the protocol can be supplied upon reasonable request.

Declarations

Ethics approval and consent to participate {24}

This research protocol has been approved by the National Ethical Committee of Research in Health, CONEP (CAAE: 32868920.9.0000.5404.) and registered in the government platform of clinical trials, ReBEC (RBR-3j3cktx).

Consent for publication {32}

This item is not applicable, as no personal information will be published or presented in the trial results.

Competing interests {28}
The authors declare that they have no competing interests.

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