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A study protocol for a randomized controlled trial evaluating the effect of antenatal dietary Myo-inositol supplementation in women during pregnancy on the incidence of gestational diabetes mellitus and fetal outcome (MiGDM) trial

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Title Page

Title of Study:

A study protocol for a randomized controlled trial evaluating the effect of antenatal dietary Myo-inositol supplementation in women during pregnancy on the incidence of gestational diabetes mellitus and fetal outcome

(MiGDM) trial

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) affects 23.6% of Qatari women and is associated with both maternal and perinatal morbidity as well as long term risk of the developing type 2 diabetes (T2DM). Multi modal evidence-based measures and interventions have been introduced in a bid to improve outcome of pregnancy in women with GDM. A number of challenges exist with current interventions including; non-compliance with dietary advice, reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Myo-inositol is readily available as an FDA approved food supplement with emerging but limited evidence suggesting it may be beneficial in reducing the incidence of GDM. Further studies, such as this one, from different ethnic contexts and with differing risk factors, are urgently needed to assess Myo-inositol effects on maternal and neonatal outcomes.

Methods and analysis: This study is a prospective, randomized, double-blinded, placebo controlled clinical trial, to either Myo-inositol supplementation or placebo.

We plan to enrol 640 pregnant women attending antenatal care at Sidra Medicine, 320 in each arm. This is sufficient to detect a clinically significant reduction of 40% in the incidence of GDM between groups using a two-tailed z-test of proportions between the two groups with 80% power and a 95% level of confidence, accounting for 20% drop out rate. This 40% reduction represents a 23.6 % incidence of newly detected diabetes in pregnancy in the placebo group and maximum of 14.2% in the Myo-insitol group.

Based on the trial findings, we aim to develop a predictive model of response to Myo-inositol supplementation in pregnancy that incorporates a composite of demographic, biophysical and biochemical (HOMA-IR) indices.

Ethics and dissemination: Ethical approval for the study was obtained from Sidra Medicine IRB. Results of the main trial outcome and secondary endpoints will be submitted for publication in a peer-reviewed journal.

Trial Registration: Registration number ISRCTN16448440 (ISRCTN registry).

Article Summary:

Strengths and limitations of this study

- This clinical trial is looking at the effect of Myo-inositol supplementation in women during pregnancy on the incidence of GDM; If hypothesis is proven true, these findings could change the way women with GDM are cared for.
- This is a well-designed prospective double-blinded randomized controlled trial with a high degree of reliability to test the effectiveness and safety of Myo-inositol supplement.
- There is limited data available on GDM interventions, mainly in Caucasian women in open label design studies; however this study will be the first RCT trial proposed in this ethnic population with high risk of GDM.
- The relative mobility of expatriate population in Qatar is a potential limitation of the study with regards to medium to long term follow up.
- The duration of Myo-inositol supplementation prior to OGTT is variable, between 12 and 20 weeks and this is a potential limitation of the study.

Keywords:

Gestational Diabetes

Pregnancy

Myo-inositol

Perinatal morbidity

Dietary supplementation

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). Identified risk factors for GDM include maternal age, maternal body mass index (BMI), ethnic background, family history and previous history of GDM (1). Globally, the International Diabetes Federation (IDF) estimates that 14% of all the deliveries are affected by GDM(2). Diabetes is a major public health issue in Qatar with increasing prevalence over the years. A recent study from Qatar showed that the prevalence of GDM among the Qatari women was 23.6% (3). GDM is a major pregnancy complication associated with both maternal and perinatal morbidity as well as long term risk of the development of type 2 diabetes (T2DM). The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multi-centric, observational study, evaluated the relationship between maternal hyperglycemia and adverse pregnancy outcomes, and identified elevated maternal serum glucose level during pregnancy as a major risk factor for adverse pregnancy outcomes, increasing rates of large-for-gestational-age infants, fetal hyperinsulinemia, neonatal hypoglycemia, and caesarean delivery (4).During pregnancy, GDM is associated with increased risk of pre-eclampsia, pre-term labor, Caesarean-section, macrosomia,

shoulder dystocia, as well as a substantial increase in medical cost(5),(6).A study in Denmark showed that, by the age of 18-27 years, 21% of the offspring who were exposed to GDM during pregnancy have developed T2DM, which was eight-fold higher than the background population(7). It had also been shown that exposure to hyperglycemia in pregnancy is independently associated with the offspring's risk of abnormal glucose tolerance, obesity, and higher blood pressure at 7 years of age(8).In the last decade, multi modal evidence-based measures and interventions have been introduced in a bid to improve outcome of pregnancy in women with GDM. It has also been shown that both life style modifications and Metformin therapy are effective in delaying or preventing diabetes in women with a history of GDM (9). Whilst significant progress has been made, a number of challenges remain with current interventions including; non-compliance with dietary advice, reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Inositol has been proposed as a food supplement that might reduce gestational diabetes incidence in high-risk pregnant women. Myo-inositol, an isomer of inositol, is a naturally occurring sugar commonly found in cereals, corn, legumes and meat. It is classed as a dietary supplement by the US Food and Drug Administration. It is one of the intracellular mediators of the insulin signaling pathway and correlated with insulin sensitivity in T2DM. It is an insulin-sensitizing mediator which is reported to reduce plasma glucose levels in polycystic ovary syndrome where it has gained increasing attention and used for its unique property of reducing insulin resistance. Inositol (in the MI or DCI isoforms) was reported to improve insulin sensitivity and ovulatory function in young women affected by polycystic ovary syndrome (10).Chiro- and Myo-inositols are major components of the two inositol phosphoglycan mediators of insulin action. It was found that, patients with Type 2 diabetes

compared to controls have less active chiro-inositol-containing mediator fractions form and a significantly reduced chiro-inositol to Myo-inositol ratio (11). In a prospective RCT including pregnant women with a parent with type 2 diabetes who were treated from the end of the first trimester with 2 g Myo-inositol plus 200 mcg folic acid twice a day (n = 110) and in the placebo group (n = 110), who were only treated with 200 mcg folic acid twice a day; Myo-Inositol supplementation reduced the incidence of GDM (6 %vs. 15.3%, P = 0.04) as well as the incidence of the delivery of a macrocosmic fetus (12).The potential beneficial effect on improving insulin sensitivity suggests that it may be useful for preventing GDM. Although Myo-inositol shows promise in preventing GDM, there is not enough evidence at this stage to support its routine use. A Cochrane Database Systematic Review in 2015 looked at the antenatal dietary supplementation with Myo-inositol in women during pregnancy for preventing gestational diabetes concluded that there is evidence from four trials of a potential benefit for reducing the incidence of gestational diabetes, although there was no consensus on neonatal outcomes. The authors recommended further studies to include pregnant women of different ethnicities and varying risk factors.(13). In a recent systematic review and meta-analysis including 5 RCTs, Myo-inositol supplementation is associated with significantly reduced incidence of gestational diabetes (risk ratio (RR) = 0.43; 95%CI = 0.21-0.89; p = .02), and preterm delivery (RR = 0.36; 95%CI = 0.17-0.73; p = .005), but has no substantial impact on 2-h glucose oral glucose tolerance test (OGTT) (mean difference (MD) = -6.90; 95%CI = -15.07 to 1.27; p = .10), gestational age at birth (MD = 0.74; 95%CI = -1.06 to 2.54; p = .42), birth weight (MD = -5.50; 95%CI = -116.99 to 105.99; p = .92), and macrosomia (RR = 0.65; 95%CI = 0.20-2.11; p = .47) (14). Another recent systematic review also supported these findings in addition to a lower incidence of 2h OGTT values (15).

In view of the ready availability of Myo-inositol as a dietary supplement and its relatively low cost compared to traditional interventions for preventing GDM, exploring its potential role in reduction of GDM is a much needed and timely study in a different socio-economic and population context, such as Qatar. In addition, such a study will contribute to the generalizable knowledge and direction of future research on GDM including comparison with other interventions (e.g. life style and Metformin).

Methods/Design

Aim and Hypothesis

This is a prospective, randomized, double-blind, placebo controlled clinical trial, to either Myo-inositol supplementation or placebo. The study plans to enroll 640 pregnant women attending antenatal care at Sidra Medicine with 320 pregnant women in each arm, the study overview is summarized in diagram A. The hypothesis for the study is that Myo-inositol in pregnancy reduces the risk of developing Gestational Diabetes.

Outcome Measures

The primary and secondary outcomes for the study are listed below.

Primary Outcome:

1. The occurrence of Gestational Diabetes in both groups

Secondary outcomes:

Maternal:

1. Gestational weight gain.
2. Need for metformin or insulin therapy.

3. Mode of delivery.
4. Hypertension in pregnancy

Fetal:

1. Large for Gestational Age at delivery (weight >95th centile for Gestation)
2. Small for Gestational Age at delivery (weight< 10th centile for Gestation)
3. Macrosomia (fetal weight ≥ 4000 g at delivery)
4. Shoulder dystocia and birth injury
5. Polyhydramnios.
6. NICU Admission for > 24 hours
7. Neonatal hypoglycaemia requiring intravenous Glucose
8. Preterm delivery (<37 weeks gestation)
9. Transient Tachypnea of the newborn
10. Respiratory distress syndrome

Inclusion and Exclusion criteria

All pregnant women booking for antenatal care at Sidra Medicine before 16 weeks of gestation will be approached to participate in the study and comprehensive written and oral information will be provided in both English and Arabic. This will ensure an early commencement of the study supplementation or placebo with sufficient time frame prior to undertaking the OGTT, thus optimizing any potential effect of the intervention. The following are the inclusion and exclusion criteria for the study:

Inclusion criteria:

1. Pregnant women booked for prenatal care at Sidra Medicine.
2. Gestational age less than 16 weeks.
3. Capacity to provide informed consent.
4. The absence of any of the exclusion criteria.

Exclusion criteria:

1. Pre-Gestational diabetes.
2. Booking fasting glucose of ≥5.1 mmol/l (92 mg/dl)
3. Women on steroids during pregnancy.
4. Women using Metformin for any other disorder e.g. PCOS.
5. Women taking Myo-inositol as part of any supplementation.
6. Cancer- Not in remission.
7. Women who lack the capacity to provide informed consent.
8. Women who had bariatric surgery.
9. Involvement in another interventional trial.
10. Polyhydramnios.

Study Plan

Women who agree to participate will be invited to attend the research clinic where they will be provided with detailed information about the study by the Principal investigator or delegated Co-investigators and, if agreeable, a written consent form will be obtained.

An acceptance rate of 50-60% is anticipated; hence, the target is to approach about 1000 women with a view to enrolling them in the study. The obstetric new antenatal booking

patient rate is between 8-14 per day and this translates into a projected average of 2860 patients annually, well above the recruitment target for this study. The study protocol is consistent with the principles of the Declaration of Helsinki and participants will be required to provide written informed consent prior to trial enrollment. The study overview is summaries in (supplementary Diagram 1)

Randomization and Study schedule

Randomization will be performed using computer-generated numbers, which would allocate participants into either Myo-inositol or Placebo arms. Both Myo-inositol and Placebo will have identical packaging prepared at source and supplied through Sidra pharmacy. All research team members and research participants will be blinded to the content of the research packs. The pharmacist shall seal, randomly number the sachets according to the computer-generated scheme and will be the sole healthcare provider to have access to this data until blinding is broken. Breaking blinding is possible after delivery and in cases of adverse reactions or if severe side effects are encountered.

The Myo-inositol pack will contain 2 g of Myo-inositol whereas the placebo pack will contain a pharmacologically inert substrate, and both arms will have twice daily dosing.Monthly (30 days) supply of the trial packs will be supplied and the research nurse will make scheduled contacts with all participants on a monthly basis, to arrange additional supply of trial packs and check on compliance. These scheduled contacts will be linked to the regular antenatal clinic schedules, so that participants do not have to make extra visits. All participants will have standard antenatal care as per Sidra prenatal care pathway.

The Oral Glucose Tolerance test (OGTT) will be performed at 24-28 weeks as per Sidra protocol for routine screening for GDM and additional blood sample for C-peptide and

Insulin will also be taken at the same time. All participants will complete at least 12 weeks of intervention or supplementation prior to undertaking the OGTT. Women will be advised to continue using the trial packs regardless of OGTT results. Those who are diagnosed as having GDM will have standard antenatal care as per Sidra prenatal care pathway.

Participants will be advised to stop study supplements only when admitted in spontaneous labour, for Induction of Labour or Lower Segment Caesarean Section, whichever comes earlier. The remaining and unused sachets will be collected on admission for delivery to evaluate patient compliance. The study schedule is summarised in (supplementary Table1)

Participants who withdraw from the study, or who fail to return for follow-up assessments, shall continue to have data collected from their routine diabetic or obstetrics clinic visits, unless they specifically withdraw consent for this. Data collected during the trial will be stored securely with appropriate data security governance in the hospital electronic System for Health records as source document.

Sample size and Statistical Analysis

The overall prevalence of newly detected diabetes in pregnancy in Qatar is 23.6%. A sample size of 640 pregnant women, with 320 in each arm, is sufficient to detect a clinically significant reduction of 40% in the incidence of GDM between groups using a two-tailed z-test of proportions between two groups with 80% power and a 95% level of confidence, accounting for 20% drop out rate. This 40% reduction represents a 23.6 % incidence of newly detected diabetes in pregnancy in the placebo group and maximum of 14.2% in the Myo-inositol group. All randomized subjects will be included in the analysis.

All statistical analyses will be applied using R and SAS v9.4 (SAS Institute). Statistical analyses will include both descriptive (numerical and graphical) and inferential statistics. Graphical analyses, where deemed appropriate, will be included in the analyses. Frequencies and proportions will be used to summarize qualitative variables, whereas means, median, standard deviation and quartiles will be used to summarize quantitative variables. The Student's t-test and chi-squared test will be used to evaluate the differences between continuous and categorical variables, respectively. Spearman's correlation coefficients will be estimated to determine associations between quantitative variables. Logistic regression analysis will be performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor. ORs and their 95% confidence intervals (95% CI) for associated factors will be estimated and all statistical assessments will be considered significant at P-value < 0.05. The statistical analyses are directed towards the assessment of the objectives of the study.

Data Monitoring Plan

The data-monitoring plan for this study includes the appointment of an independent expert with the role of performing and overseeing the interim analysis for the study. Interim analysis is planned at 12 months and/or at 50% of enrolment, whichever comes earlier. If the interim analysis shows that the difference between the two arms reaches statistical significance, the result of the analysis and recommendation for stopping the trial will be communicated to the IRB.

Discussion

The high prevalence of GDM among Qatari antenatal population with the associated maternal and perinatal morbidity, represents a significant burden on current and future healthcare resource utilization. More importantly, GDM remains an important surrogate marker for the future development of T2DM. Therefore, pregnancy is a unique and critical window of opportunity for interventions aimed at reducing the burden of Diabetes in Qatar in the long term.

Antenatal supplementation with Myo-inositol for the prevention of GDM is a relatively new and novel intervention. Myo-inositol is readily available as an FDA approved food supplement. Although the limited emerging evidence indicates that its use may be beneficial in reducing the incidence of GDM, further studies from different ethnic contexts and with differing risk factors, are urgently needed to assess its effects on maternal and neonatal outcomes. In view of its availability as a dietary supplement and its relatively low cost compared to traditional interventions for preventing GDM, exploring its potential role in reduction of GDM is a much needed and timely study for our population. In addition, such a study will contribute to the generalizable knowledge and direction of future research on GDM including comparison with other interventions (e.g. life style and Metformin).

List of Abbreviations

GDM- Gestational Diabetes

FDA-Food and drugs administration

IDF-International Diabetes Federation

T2DM-Type 2 Diabetes Mellitus

OGTT-Oral Glucose Tolerance Test

COVID-19-Coronavirus disease-19

NICU-Neonatal intensive care unit

Declarations

Ethics approval and consent to participate: This study was approved by the Sidra Medicine IRB on 12th April, 2021 with the approval reference number 1538656

Consent for publication: Written informed consent will be obtained for publication

Publication and dissemination plan: Planned publication in peer-reviewed journal.

All data generated or analyzed during this study will be included in the subsequent results publication.

Competing interests: The Authors declare that they have no competing interests.

Provenance and peer review: Not commissioned; externally peer reviewed.

Funding: The study is funded by Sidra Medicine, through the competitive Internal Research Grant fund, following external peer review of the study. The funding arm of Sidra Medicine is not involved in the design of the study, management, analysis, interpretation of data; writing of the report; the decision to submit the report for publication or writing of the protocol manuscript.

Patient and public involvement: No patient involved in the study.

Authors' contributions:

HA initiated the idea for the study, II , GO and HA produced the initial study design, GO prepared the draft manuscript. HA, II, OO, YF, AT, and GO contributed to the manuscript review. All authors read and approved the final manuscript.

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Diagram A, study overview.

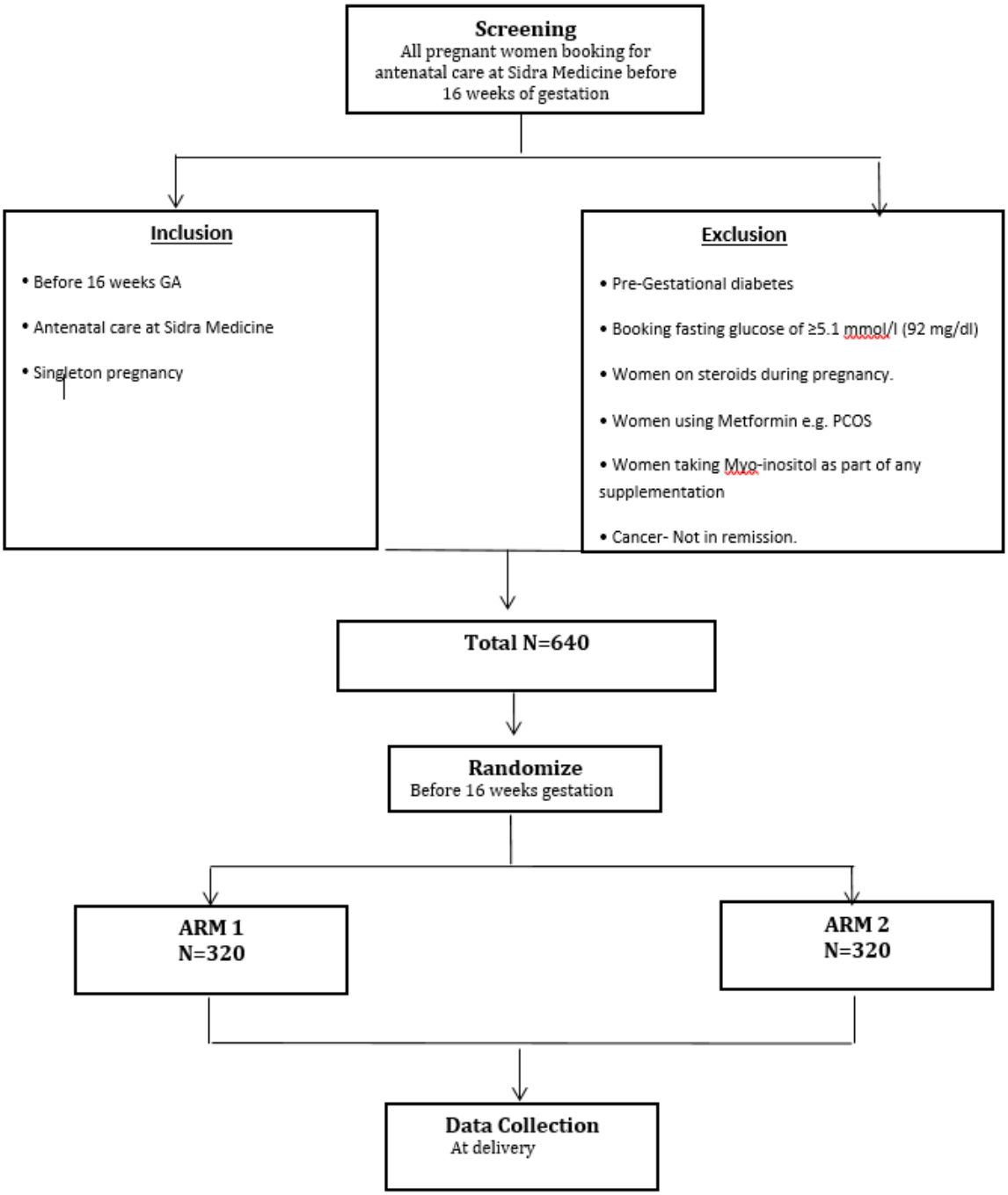

Table 1. MiGDM Study Overview

Time point	6-16 wks	20 wks	24 wks	28 wks	32 wks	36 wks	37 wks	38 wks	39 wks	40 wks	Delivery
Measurement											
Demographics	X										
Family history	X										
Pre-Pregnancy BMI	X										
BP and HR	X	X	XX	X	X	X	X	X	X	X	X
Physical activity	X										
Maternal outcomes											X
Neonatal outcomes											X
C-peptide Insulin, OGTT			X	X							
Routine clinic tests	X										
Ultrasound scan		X		X	X	X					

سدرة للطب Sidra Medicine	**SIDRA** **IRB RESEARCH PROPOSAL Template**

Section A

A. Research Proposal Title: Effect of antenatal dietary Myo-inositol supplementation in women during pregnancy on the incidence of gestational diabetes mellitus and fetal outcome : A randomized controlled trial (MiGDM TRIAL)

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Section B

A. Summary: Gestational Diabetes Mellitus (GDM) affects 23.6% of the Qatari women. GDM is a major pregnancy complication associated with both maternal and perinatal morbidity as well as long term risk of the development of type 2 diabetes (T2DM). In the last decade, multi modal evidence-based measures and interventions have been introduced in a bid to improve outcome of pregnancy in women with GDM. Whilst significant progress has been made, a number of challenges still remain with current interventions including; non-compliance with dietary advice, reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Myo-inositol is readily available as an FDA approved food supplement. Although the limited emerging evidence indicates that its use may be beneficial in reducing the incidence of GDM, further studies from different ethnic contexts and with differing risk factors, are urgently needed to assess its effects on maternal and neonatal outcomes. We plan to conduct a prospective, randomized, double-blind, placebo controlled clinical trial looking at the effect of antenatal dietary Myo-inositol supplementation in women during pregnancy on the Incidence of GDM. Pregnant women attending antenatal clinic at Sidra Medicine will be randomised, within the first 16 weeks gestation, to either receiving Myo-inositol or placebo. The primary objective is to reduce the incidence of GDM, and the secondary objectives to reduce gestational weight gain, need for metformin or insulin therapy, macrosomia, polyhydramnios and neonatal hypoglycaemia. We hypothesize that the intervention will reduce the incidence of GDM by 40%

B. Introduction Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Identified risk factors for GDM include maternal age, maternal body mass index (BMI), ethnic background, family history, previous history of GDM and previous/current adverse pregnancy outcome (1). Globally, the International Diabetes Federation (IDF) estimates that 14% of all the deliveries are affected by GDM(2). Diabetes is a major public health issue in Qatar with increasing prevalence over the years. A recent study from Qatar showed that the prevalence of GDM among the Qatari women was 23.5% (3). GDM is a major pregnancy complication associated with both maternal and perinatal morbidity as well as long term risk of the development of type 2 diabetes (T2DM). Recently, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multi-centric, observational study, evaluated the relationship between maternal hyperglycemia and adverse pregnancy outcomes, and identified elevated maternal serum glucose level during pregnancy as a major risk factor for adverse pregnancy outcomes, increasing rates of large-for-gestational-age infants, fetal hyperinsulinemia, neonatal hypoglycemia, and caesarean delivery (4).During pregnancy, GDM is associated with increased risk of pre-eclampsia, pre-term labor, Caesarean-section, macrosomia, shoulder dystocia, as well as a substantial increase in medical cost(5),(6).A study in Denmark showed that,

by the age of 18-27 years, 21% of the offspring who were exposed to GDM during pregnancy have developed T2DM, which was eight-fold higher than the background population(7). It had also been shown that exposure to hyperglycemia in pregnancy is independently associated with the offspring's risk of abnormal glucose tolerance, obesity, and higher blood pressure at 7 years of age(8).In the last decade, multi modal evidence-based measures and interventions have been introduced in a bid to improve outcome of pregnancy in women with GDM. It has also been shown that both life style modifications and Metformin therapy are effective in delaying or preventing diabetes in women with a history of GDM (9). Whilst significant progress has been made, a number of challenges still remain with current interventions including; non-compliance with dietary advice, reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Inositol has been proposed as a food supplement that might reduce gestational diabetes incidence in high-risk pregnant women. Myo-inositol, an isomer of inositol, is a naturally occurring sugar commonly found in cereals, corn, legumes and meat. It is classed as a dietary supplement by the US Food and Drug Administration. It is one of the intracellular mediators of the insulin signaling pathway and correlated with insulin sensitivity in T2DM. It is an insulin-sensitizing mediator which is reported to reduce plasma glucose levels in polycystic ovary syndrome where it has gained increasing attention and used for its unique property of reducing insulin resistance. Inositol (in the MI or DCI isoforms) was reported to improve insulin sensitivity and ovulatory function in young women affected by polycystic ovary syndrome (10).Chiro- and Myo-inositols are major components of the two inositol phosphoglycan mediators of insulin action. It was found that, patients with Type 2 diabetes compared to controls have less active chiro-inositol-containing mediator fractions form and a significantly reduced chiro-inositol to myo-inositol ratio (11). In a prospective RCT including pregnant women with a parent with type 2 diabetes who were treated from the end of the first trimester with 2 g Myo-inositol plus 200 mcg folic acid twice a day (n = 110) and in the placebo group (n = 110), who were only treated with 200 mcg folic acid twice a day; Myo-Inositol supplementation reduced the incidence of GDM (6 vs. 15.3%, P = 0.04) as well as the incidence of the delivery of a macrosomic fetus (12).The potential beneficial effect on improving insulin sensitivity suggests that it may be useful for preventing GDM. Although Myo-inositol shows promise in preventing GDM, there is not enough evidence at this stage to support its routine use. A Cochrane Database Systematic Review in 2015 looked at the antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes concluded that there is evidence from four trials of a potential benefit for reducing the incidence of gestational diabetes, although there was no consensus on neonatal outcomes. The authors recommended further studies to include pregnant women of different ethnicities and varying risk factors.(13).In a recent systematic review and meta-analysis including 5 RCTs, Myo-inositol supplementation is associated with significantly reduced incidence of gestational diabetes (risk ratio (RR) = 0.43; 95%CI = 0.21-0.89; p = .02), and preterm delivery (RR = 0.36; 95%CI = 0.17-0.73; p = .005), but has no substantial impact on 2-h glucose oral glucose tolerance test (OGTT) (mean difference (MD) = -6.90; 95%CI = -15.07 to 1.27; p = .10), gestational age at birth (MD = 0.74; 95%CI = -1.06 to 2.54; p = .42), birth weight (MD = -5.50; 95%CI = -116.99 to 105.99; p = .92), and macrosomia (RR = 0.65; 95%CI = 0.20-2.11; p = .47) (14). Another recent systematic review also supported these findings in addition to a lower incidence of 2h OGTT values (15).

C. Rationale The high prevalence of GDM among Qatari antenatal population with the associated maternal and perinatal morbidity, represents a significant burden on current and future healthcare resource utilization. More importantly, GDM remains an important surrogate marker for the future development of T2DM. Therefore, pregnancy is a unique and critical window of opportunity for interventions aimed at reducing the burden of Diabetes in Qatar in the long term. Any reduction in the incidence of GDM in Qatar will potentially translate into a reduction in the burden of T2DM (among women) in the long term. Antenatal supplementation with Myo-inositol for the prevention of GDM is a relatively new and novel intervention. Myo-inositol is readily available as an FDA

approved food supplement. Although the limited emerging evidence indicates that its use may be beneficial in reducing the incidence of GDM, further studies from different ethnic contexts and with differing risk factors, are urgently needed to assess its effects on maternal and neonatal outcomes. Our team at Sidra is well positioned to undertake this task in Qatar, the outcome of which could have significant impact on Diabetes care locally in Qatar and the region. Myo-inositol has been employed in previous clinical trials in pregnancy with no reported adverse effects. In view of its availability as a dietary supplement and its relatively low cost compared to traditional interventions for preventing GDM, exploring its potential role in reduction of GDM is a much needed and timely study for our population in Qatar. In addition, such a study will contribute to the generalizable knowledge and direction of future research on GDM including comparison with other interventions (e.g. life style and Metformin).

Section C

A. Research Objective: (State aims and objectives concisely defined, following on from hypothesis)
This study is a prospective, randomized, double-blind, placebo controlled clinical trial, to either Myo-inositol supplementation or placebo.
Hypothesis: Myo-inositol supplementation in pregnancy reduces the risk of developing GDM.

Primary Outcome:
The occurrence of GDM in both groups
Secondary outcomes:
Maternal:
Gestational weight gain.
Need for metformin or insulin therapy.
Mode of delivery
Hypertension in pregnancy
Fetal:
Large for Gestational Age at delivery (weight >95th centile for Gestation)
Small for Gestational Age at delivery (weight< 10th centile for Gestation)
Macrosomia (fetal weight ≥ 4000 g at delivery)
Shoulder dystocia and birth injury
Polyhydramnios.
NICU Admission for > 24 hours
Neonatal hypoglycaemia requiring intravenous Glucose
Preterm delivery (<37 weeks gestation)
Transient Tachypnea of the newborn
Respiratory distress syndrome
Some of the above maternal and fetal secondary outcomes are particularly relevant to pregnancies complicated by Diabetes. Although any differences between the two groups may not reach statistical significance because of the sample size, the trend is still of relevance in the context of similar studies.
B. Research Methods: (Study Design and methods including the research questions, setting, participant(s), inclusion and exclusion , data analysis, retention strategies and withdrawal criteria)
1. Data collection management and methods of assessment or measurement of data.
2. Outcome measures and end points

Study design and population
This study is a prospective, randomized, double-blind, placebo controlled clinical trial, to either Myo-inositol supplementation or placebo
We plan to enroll 640 pregnant women attending antenatal care at Sidra Medicine, 320 in each arm.
Inclusion criteria

All pregnant women booking for antenatal care at Sidra Medicine before 16 weeks of gestation will be approached to participate in the study and comprehensive written and oral information will be provided in both English and Arabic. This will ensure an early commencement of the study supplementation or placebo with sufficient time frame prior to undertaking the OGTT, thus optimizing any potential effect of the intervention.

SUBJECT SELECTION

Inclusion criteria

- All pregnant women booked for prenatal care at Sidra Medicine will be approached regardless of Age and regardless of language spoken and regardless of place for delivery
- Gestational age less than 16 weeks
- Capacity to provide informed consent
- The absence of any of the exclusion criteria

Exclusion criteria

- Pre-Gestational diabetes.
- Booking fasting glucose of ≥5.1 mmol/l (92 mg/dl)
- Women on steroids during pregnancy.
- Women using Metformin for any other disorder e.g. PCOS.
- Women taking Myo-inositol as part of any supplementation.
- Cancer- Not in remission.
- Women who lack the capacity to provide informed consent.
- Women who had bariatric surgery.
- Involvement in another interventional trial.
- Polyhydramnios (this is a very unlikely finding before 16 weeks)

Subject withdrawal criteria

- Participants who withdraw from the intervention protocol, or who fail to return for follow-up assessments, shall continue to have data collected from their routine diabetic or obstetrics clinic visits, unless they specifically withdraw consent for this.
- Data analysis shall use best available follow-up weights (closest within a window of ±3 months from routine attendances) and end of study diabetes status for participants who discontinue the formal weight management programmed. (Drug intolerance, diet intolerance or poor compliance shall be recorded: these patients shall be included in ITT analysis).

Basic Data collection

Patient's initials and ID, date of birth, nationality, ethnicity, general medical history, list of the medications currently taken, gestational age, parity, previous pregnancies, multiple pregnancy (index pregnancy), congenital fetal anomaly(index pregnancy) lifestyle exposures including smoking, physical activity and diet. All participants will have height and weight recorded.

All study participants will be given randomization numbers. These randomization numbers will be available on encrypted computers stored in the premises of Sidra with access available only to Lead PI and another delegated member of the team.

- Data collected during the trial will be recorded electronically in CERNER (Sidra electronic System for Heath records) as source document.
- CRF (Case Report Forms) will be electronically completed in an excel sheet using source data from CERNER.
- CRF has been developed, for all the data to be captured for each patient, please refer to CRF.

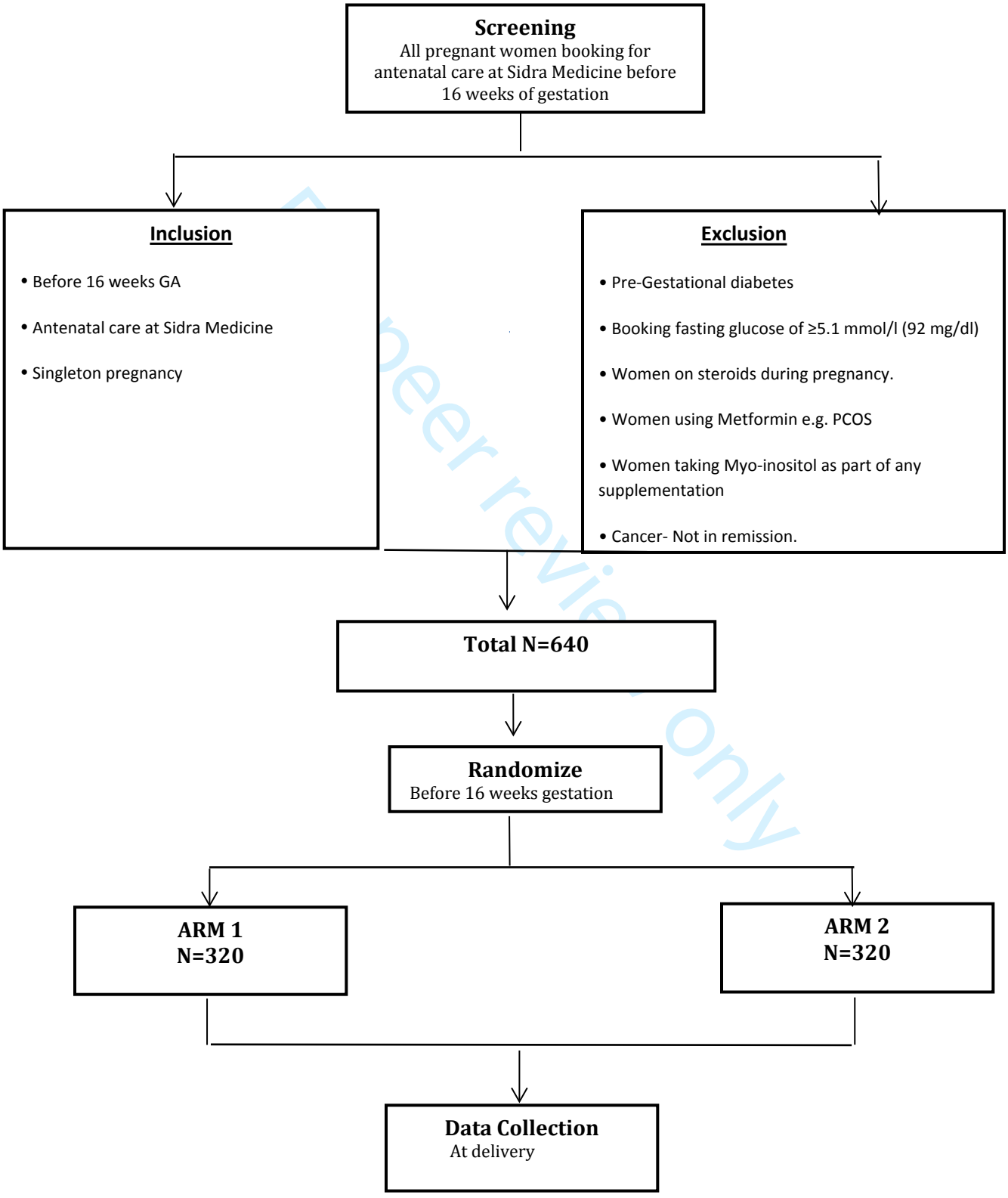
Study protocol

Women who agree to participate will be invited to attend the research clinic where they will be provided with detailed information about the study by the PI and delegated Co-investigators and, if agreeable, a written consent form will be obtained. In order to create a general awareness about the existence of this study, it will be mentioned on the Women's services page of Sidra Medicine website

as one of the planned/ongoing researches in women's services at Sidra. This is subject to approval and acceptance by Sidra communications and information unit

We anticipate an acceptance rate of 50-60%, hence we expect to approach about 1000 women. Currently we have an intake (new patients) rate of between 8 and 14 per clinic day. This translates into a projected average of 2860 patients annually, well above the recruitment target for this study.
The study protocol is consistent with the principles of the Declaration of Helsinki and participants will be required to provide written informed consent prior to trial enrollment.
Information regarding study protocol, risks, expected outcome and contact details will be given.
Standard complete history and anthropometric measurements will be documented.

Diagram A, study overview.



Description of the sequence and duration of all trial periods, including follow-up:

- Recruitment will continue for 18 months with a closing window of 6 months.
- The duration of study participation in this study will last between 24 weeks to 32 weeks (depending on the time of randomization, usually before 16 weeks of gestation)
- We also expect that this research study will last approximately two years to complete recruitment although each participant involvement will only be until the end of their pregnancy.
- These scheduled contacts will be linked to their regular antenatal clinic schedules, so that participants do not have to make extra visits.
- All participants will have standard antenatal care as per Sidra prenatal care pathway.
- The Oral Glucose Tolerance test (OGTT) will be performed at 24-28 weeks as usual per Sidra protocol for routine screening for GDM.
- All participants will complete at least 12 weeks of intervention or supplementation prior to undertaking the OGTT.
- Women will be advised to continue using the trial packs regardless of GTT results.
- Those who are diagnosed as having GDM will have standard antenatal care as per Sidra prenatal care pathway for women diagnosed with GDM.

Time point	6-16 wks	20 wks	24 wks	28 wks	32 wks	36 wks	37 wks	38 wks	39 wks	40 wks	Delivery
Measurement											
Demographics	X										
Family history	X										
Pre-Pregnancy BMI	X										
BP and HR	X	X	XX	X	X	X	X	X	X	X	X
Physical activity	X										
Maternal outcomes											X
Neonatal outcomes											X
C-peptide Insulin, OGTT			X	X							
Routine clinic tests	X										
Ultrasound scan		X		X	X	X					

Sample size:
The overall prevalence of newly detected diabetes in pregnancy in Qatar is 23.6%.
Population: Patients attending antenatal care at Sidra Medicine. A sample size of 640 pregnant women, 320 in each arm, is sufficient to detect a clinically significant reduction of 40% in the incidence of GDM between groups using a two-tailed z-test of proportions between two groups with 80% power and a 95% level of confidence, accounting for 20% drop out rate. This 40% reduction represents a 23.6 % incidence of newly detected diabetes in pregnancy in the placebo group and maximum of 14.2% in the Myo-inositol group.
Statistical analysis: All randomized subjects will be included in the analysis.
All statistical analyses will be applied using R and SAS v9.4 (SAS Institute). Statistical analyses will include both descriptive (numerical and graphical) and inferential statistics. Graphical analyses, where deemed appropriate, will be included in the analyses. Frequencies and proportions will be used to summarize qualitative variables, whereas means, median, standard deviation and quartiles will be

used to summarize quantitative variables. The Student's t-test and chi-squared test were used to evaluate the differences between continuous and categorical variables, respectively. Spearman's correlation coefficients were estimated to determine associations between quantitative variables. Logistic regression analysis will be performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor on infection risk. ORs and their 95% confidence intervals (95% CI) for associated factors were estimated. All statistical assessments were two-sided and considered significant at P-value < 0.05. The statistical analyses are directed towards the assessment of the objectives of the study. Based on the trial findings, we aim to develop a predictive model of response to Myo-inositol supplementation in pregnancy that incorporates a composite of demographic, biophysical and biochemical (HOMA-IR) indices.

Data Monitoring Plan

The data-monitoring plan for this study includes the appointment of Dr. Mamoun Elawad as an independent expert with the role of performing and overseeing the interim analysis for the study. Interim analysis is planned at 12 months and/or at 50% of enrollment, whichever comes earlier. If the interim analysis shows that the difference between the two arms reaches statistical significance, the result of the analysis and recommendation for stopping the trial will be communicated to the IRB. The appointment of Dr X as the independent expert is subject to approval by the IRB. A Short biography of Dr Elawad, the data safety-monitoring expert for this study is attached.

Summary of the known and potential risks and benefits to human subjects

- There is evidence from trials of a potential benefit of Myo-inositol supplement during pregnancy in reducing the incidence of gestational diabetes, preterm delivery and a lower incidence of 2h OGTT values (reference 13, 14, and 15).
- There are no known or reported risks associated with taking the research supplements, having been used widely around the world up to 4 grams of inositol daily, had been taken by pregnant women in many studies without adverse effects (reference 16, 17 and 18).
- Inositol supplements is well-tolerated by most people. However, mild side effects have been reported with doses of 12 grams per day or higher. These include nausea, gas, difficulty sleeping, headache, dizziness and tiredness.
- The procedure of blood drawing (venipuncture) to obtain blood samples may be associated with fainting, pain, bruising, bleeding at the site of the needle entry and rarely inflammation or infection of the vein site and this is documented and explained in the patient consent form.

Description, packaging and labelling of Investigational product

The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

- Myo-inositol/Placebo Sachets will be packaged within a white medication box and labelled as follows:

CLINICAL TRIAL MiGDM
'MYO-INOSITOL/PLACEBO Medication sachets'
Site name: Sidra Medicine
PI: Dr Ibrahim Ibrahim
Subject number: _____ (number inserted at time of dispensing)
Batch/Lot number: _____
Expiration date: _____
Please keep safe and store at 8□C-25□C.

Randomization, Drug preparation and Blinding:

The medicinal products Myo-Inositol and Placebo for the study will be manufactured, packaged and supplied by Nutrilinea S.r.l company based in Italy. Nutrilinea S.r.l will source the ingredients for the

manufacture of the medicinal products from two companies namely ZCHT-Zhucheng Haotian Pharm Co., Ltd and Vivatis Pharma. Nutrilinea company profile can be accessed at https://nutrilineasrl.it/nutrilinea/

Risks, Side Effects and/or Discomforts

The potential risks and side effects associated with procedures involved in the research are as follows:

- Blood samples: possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Taking the research supplements: There is no known risk we are aware of that is associated with taking the research supplement , having been used widely around the world.

Section D

A. Ethical Issues Informed Consent:

The participant must sign and date the latest approved version of the Informed Consent form before any study specific procedure is performed.

Written and verbal versions of the Informed consent will be presented to the participant detailing the exact nature of the study; the known side effects, what it will involve, the implications and constraints of the protocol, the known side effects and any risk involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice and with no obligation to give reasons for withdrawal. If a participant chooses to withdraw from the study after a period of participation, pregnancy care will continue to be provided according to the standard schedule of antenatal, intrapartum and postpartum care. The participant will be instructed to return the unused trial packs to the research nurse who will subsequently submit the unused packs to the trial Pharmacist.

The participants will be allowed time to consider the information given and the opportunity for questions to make the decision whether they will take part in the study.

Written Informed Consent will be obtained dated and signed by the participant and the person who obtained the Informed consent. The person who obtained the consent is suitably qualified and experienced and authorized by the Principal investigator. A copy of the Informed Consent will be given to the participant and the original signed form will be retained at the study site.

Safety reporting:

Any serious adverse event (SAE) will be reported to Sidra Medicine IRB and the Qatari Ministry of Public Health (MOPH). For MOPH reporting, Unanticipated Problem in terms of nature, frequency or severity. When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

(1) unexpected;
(2) related or possibly related to participation in the research; and
(3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
Only adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems.

Reporting of internal adverse events by investigators
Upon becoming aware of an adverse event, the investigator should assess whether the adverse event represents an unanticipated problem following the guidelines described above. If the investigator determines that the adverse event represents an unanticipated problem, the investigator must report it promptly to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.
If the investigator determines that an adverse event is not an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an unanticipated problem (for example, due to an unexpectedly higher frequency of the event), the monitoring entity should report this determination to the investigator, and such reports must be promptly submitted by the investigator to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.

Reporting of other unanticipated problems (not related to adverse events) by investigators
Upon becoming aware of any other incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem by applying the criteria described above. If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it promptly to the IRB, the institution head, the funding body, and Department of Research at Qatar Ministry of Public Health.

Subjects with confirmed adverse events will be followed up until the resolution of the event or up to the end of the trial period, whichever comes later.

Quality Assurance:
The sponsor will ensure that the trial is adequately monitored, at regular monitoring visits according to the developed monitoring plan., audited in accordance with the current approved protocol, relevant regulations and standard operating procedures
Ethical and regulatory procedures:
Will ensure that the study is conducted in accordance with the principles of Helsinki Declaration and in full conformity with relevant regulations.
All protocol, Informed consent, Information sheet and leaflet will be submitted to Sidra IRB for approval beforehand, including all substantial amendments to the original approved documents.
Reporting:

The Principal investigator shall submit once a year throughout the study or on request, an annual progress report to the IRB committee, Sidra Medicine. In addition, an end of study notification and final report will also be submitted.

B. Data – Security: (Confidentiality of patient data)

- Participants' personnel health information (such as name, MRN, age, etc.) will not be used in this trial.
- To protect the confidentiality of the participants, a randomization number will be assigned to each one.
- As this trial is randomized, the number assigned to each participant is called a "randomization number" and will determine in which of the experimental or control group the participant is assigned. All data will be stored on an encrypted computer(s) stored in the premises of Sidra. In order to be de-identified and the list that links the randomization number back to the subject identity will be only accessible to the physicians, research nurse and LPI. The subjects will not be identified in any publications or presentations about this study. Only investigators included in the trial will be enabled to access specimens and data. The study will comply with the data Protection Act, which requires data to be anonymized as soon as it is practically possible.

C. Confidentially of Patient Data: (Describe procedures for maintaining participant confidentiality and/or anonymity, especially if tape recording, photographs, movies or videotapes will be used.

1. Privacy: Address how the privacy of individuals or groups will be maintained (e.g. , how participants will be afforded privacy while participating in research activities).

2. Confidentiality: How will the confidentiality of data be ensured? Outline all of the precautions that will be used to maintain the confidentiality of identifiable information.

All participants will be anonymized and assigned a subject number on recruitment. There will be no patient identification details in the study and no tape-recording, photography, videos, movies taken at any time during the study.
All data will be stored in a password protected folder in a protected Sidra Medicine computer. This computer will be located in an office with swipe card access. Only de-identified data will be made publicly available.
Manually recorded forms sheets will be kept under lock and key in a filing cabinet in a secured office in the obstetrics department. Only the Principal investigator and other delegated PI(s) will have an access to the data. Forms and documents will be shredded in 3 years after manuscript completion and electronic data will also be destroyed at the same time.
Procedure for accounting for missing, unused, and spurious data
- Quality control (QC) would be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.
- QC will be reviewed on a daily basis and needs to be addressed and assessing all the data needed and source documents collected.

Section E

A. Timetable: (Realistic project schedule- Study plan showing flaw chart of orders, timing & site of procedures)

No	Expected Outcome/ Deliverable	Due date	Comments / more details
1	Obtain Ethical Approval for the Study.	Not yet applicable	Will be completed prior to the project start
2	First Planning Meeting of All Investigators.	Within 4 weeks of notification of Study Funding	
3	Recruitment of 1 full time Research Nurse	Within 12 weeks of Ethical Approval	
4	Recruitment of 1 part time Research coordinator	Within 12 weeks of Ethical Approval	
	Recruitment of 1 part time Clinical Pharmacist	Within 12 weeks of Ethical Approval	For allocation and randomization
5	Outpatient Clinic, WCMG and Pharmacy Staff-sensitization Meetings, and introduction of Research Nurses to all.	Within 2 weeks of recruitment of Research Nurses	
6	Commencement of patient Recruitment into Study	Within 3 months of Obtaining Ethical Approval.	
7.	First Investigators' Update Meeting	Within 3 months of commencing recruitment.	This will mainly address any feedback on recruitment so far, and if there are significant aspects of the study that require a re-visit.
8.	Quarterly Investigators' Update	4-months after First Investigator's Update and 4 monthly thereafter.	The Study Statistician will provide an interim analysis of incoming data.
9	Pre-conclusion Investigator's Meeting	24 months after first recruitment, or 4 weeks after Principal Investigator expresses decision to stop the study	
10.	Presentation of preliminary data, definitive data and preparation of First Report	27 months after patient recruitment	

B. References: List of all citation mentioned within the proposal)

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C. Budgeting: (Provide detail budget for each research and each core unit in their respective section of the application. Incorporate a detailed budget for all requested support for the first year)

Item	Unit cost (QAR)		Total cost (QAR)
Myo-inositol (4g per day) x 30 weeks(210 days, the cost of 4g is QR 2.39)	501.90	320 subjects	160,608.00
Placebo (4g per day) x 30 weeks(210 days the cost of 4g placebo material is QAR 1)	210.00	320 subjects	67,200.00
Packaging (Myo-inositol and Placebo)	210.00	640 subjects	67,200.00
Fasting Insulin at OGTT(Qatar)	161.00	640 subjects	103,040.00
Clinical Pharmacist cost	100.00	410 subjects	41,200.00
1 Research Nurses **(R9)** working full time	25,000.00	24 months	600,000.00

Patient information Leaflets	5.00	1000 leaflet	5,000.00
Telephone Bills for patient contact / month	150.00	18 months	2,700.00
Article Processing Fees for publication	-	-	5,400.00
Grand total (QAR)			**1,052,348.00**

[redacted]

Principal Investigator Statement of Compliance:
I understand and accept responsibility for ensuring the safety and welfare of all human subjects who participate in the proposed research project. I certify that all key personnel, including myself, sub/co-investigators, research coordinators, trainees, and students have completed the SIDRA required training on human subjects' protection. I agree to a continuing exchange of information with the SIDRA IRB including the requirements to (i) obtain IRB approval before making non-emergency changes/revisions to the project, except where necessary to eliminate apparent immediate hazards to subjects or others, (ii) provide progress reports to the SIDRA IRB at their request (and at least annually), and (iii) report promptly to the IRB all unanticipated problems and serious adverse events involving risk to human subjects (in accordance with required reporting timelines by the IRB (iv) Will accept responsibility to maintain original data and consent forms and submit them for review if requested.

SIGNATURE OF INVESTIGATOR **DATE OF SIGNATURE: 16/12/2020**

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry , Trial registration section
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable
Protocol version	3	Date and version identifier Not applicable
Funding	4	Sources and types of financial, material, and other supportFunding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors , Authors , Authors affiliation and Authors contributions
	5b	Name and contact information for the trial sponsor Funding
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Not applicable
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Background and introduction
	6b	Explanation for choice of comparators Background and Introduction
Objectives	7	Specific objectives or hypotheses Aim and Hypothesis

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Method/Design

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Method/Design
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Inclusin and exclusion criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Randomization and Study schedule
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) , Randomization and Study schedule
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) , Randomization and Study schedule
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Randomization and Study schedule
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Outcomes measures
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Attachment: Table 1. MiGDM Study Overview , and Diagram 1; study overview
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Sample size and Statistical Analysis
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Study plan

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions) Randomization and Study schedule
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Randomization and Study schedule
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Randomization and Study schedule
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Randomization and Study schedule
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Randomization and Study schedule

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Table 1. MiGDM Study Overview
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Page 11 second paragraph
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Informed consent ; Confidentially section 16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Sample size and Statistical Analysis

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Sample size and Statistical Analysis
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Randomization and Study schedule , Sample size and Statistical Analysis
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Data monitoring
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Data monitoring
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct IRB Research proposal under section Safety reporting:
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor IRB Research proposal under section Quality assurance and Reporting
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 13, Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) IRB Research proposal under section Reporting:
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 9, Study plan first paragraph
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Consent form section 23,24,25
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Consent form section 16

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 13 and 14 Declarations and Competing interests :
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Consent form section 16 confidentiality
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Consent form section 14, 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 14 Publication and dissemination plan
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 14 Authors' contributions
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates IRB 400 Informed consent form attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Relevant information are included in IRB 400 Informed consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of antenatal dietary Myo-inositol supplementation on the incidence of Gestational Diabetes Mellitus and fetal outcome: Protocol for a double blind randomized controlled trial.

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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Maternal medicine < OBSTETRICS, NUTRITION & DIETETICS

Title Page

Title of Study:

The effect of antenatal dietary Myo-inositol supplementation on the incidence of Gestational Diabetes Mellitus and fetal outcome: Protocol for a double blind randomized controlled trial.

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) affects 23.6% of Qatari women and is associated with maternal and perinatal morbidity and long-term risk of developing type 2 diabetes (T2DM). A number of challenges exist with current interventions, including non-compliance with dietary advice, the reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Myo-inositol is readily available as an FDA-approved food supplement with emerging but limited evidence suggesting it may be beneficial in reducing the incidence of GDM. Further studies, such as this one, from different ethnic contexts and with differing risk factors, are urgently needed to assess Myo-inositol effects on maternal and neonatal outcomes.

Methods and analysis: This study is a prospective, randomized, double-blinded, placebo controlled clinical trial to either Myo-inositol supplementation or placebo.

We plan to enrol 640 pregnant women attending antenatal care at Sidra Medicine, Doha, Qatar, 320 in each arm. All participants will complete at least 12 weeks of supplementation prior to undertaking the OGTT at 24-28 weeks. The daily use of the trial supplementation will continue until the end of pregnancy. All outcome measures will be collected from the electronic medical records.

Ethics and dissemination: Ethical approval for the study was obtained on 12/04/2021 from Sidra Medicine (IRB number 1538656). Results of the primary trial outcome and secondary endpoints will be submitted for publication in a peer-reviewed journal.

Trial Registration: Prospectively registered on 26/05/2021. Registration number ISRCTN16448440 (ISRCTN registry).

Article Summary:

Strengths and limitations of this study

- To our knowledge, this is the first large RCT in an ethnic population with a high prevalence of GDM to test the effectiveness of Myo-inositol supplementation.
- The early screening of diabetes in pregnancy used in Qatar ensures that women with pre-existing diabetes are excluded before enrolment.
- The duration of Myo-inositol supplementation prior to OGTT is variable, between 12 and 20 weeks and this is a potential limitation of the study.
- The study may not have enough power to address some of the secondary outcome measures.

Keywords:

Gestational Diabetes, Pregnancy, Myo-inositol, perinatal morbidity, Dietary supplementation

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). Identified risk factors for GDM include maternal age, maternal body mass index (BMI), ethnic background, family history, and previous history of GDM (1). Globally, the International Diabetes Federation (IDF) estimates that 14% of all deliveries are affected by GDM (2). Diabetes is a significant public health issue in Qatar with increasing prevalence over the years. A recent study from Qatar showed that the prevalence of GDM among Qatari women was 23.6% (3). GDM is a major pregnancy complication associated with both maternal and perinatal morbidity and long-term risk of the development of type 2 diabetes (T2DM). The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multi-centric, observational study, evaluated the relationship between maternal hyperglycemia and adverse pregnancy outcomes and identified elevated maternal serum glucose level during pregnancy as a major risk factor for adverse pregnancy outcomes, increasing rates of large-for-gestational-age infants, fetal hyperinsulinemia, neonatal hypoglycemia, and caesarean delivery (4). During pregnancy, GDM is associated with an increased risk of pre-eclampsia, preterm labor, Caesarean-section, macrosomia, shoulder dystocia, and a substantial increase in medical cost (5), (6). Exposure to hyperglycemia in pregnancy is shown to be associated with an increased risk to the offspring of abnormal glucose tolerance, Type 2 diabetes, obesity, and higher blood pressure (7), (8).

In the last decade, multi-modal evidence-based measures and interventions have been introduced to improve the outcome of pregnancy in women with GDM. It has also been shown that both lifestyle modifications and Metformin therapy effectively delay or prevent diabetes in women with a history of GDM (9). Whilst significant progress has been made,

several challenges remain with current interventions, including non-compliance with dietary advice and mothers' reluctance to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies.

Inositol has been proposed as a food supplement that might reduce GDM incidence in high-risk pregnant women. Myo-inositol, an isomer of inositol, is a naturally occurring sugar commonly found in cereals, corn, legumes, and meat. The US Food and Drug Administration class it as a dietary supplement. It is one of the intracellular mediators of the insulin signaling pathway and correlated with insulin sensitivity in T2DM. It is an insulin-sensitizing mediator, which is reported to reduce plasma glucose levels in polycystic ovary syndrome (PCOS), where it has gained increasing attention and is used for its unique property of reducing insulin resistance. Inositol isoforms were reported to improve insulin sensitivity and ovulatory function in young women affected by PCOS (10). Chiro- and Myo-inositol are major components of the two inositol phosphoglycan mediators of insulin action. Patients with T2DM, compared to controls, have less active chiro-inositol-containing mediator fractions form and a significantly reduced chiro-inositol to Myo-inositol ratio (11). Myo-inositol supplementation is shown in an RCT to reduce the incidence of GDM in pregnant women with a parent with type 2 diabetes (6 %vs. 15.3%, P = 0.04) as well as the incidence of the delivery of a macrocosmic fetus (12). The potential beneficial effect on improving insulin sensitivity suggests that it may be useful for preventing GDM. Although Myo-inositol shows promise in preventing GDM, there is not enough evidence at this stage to support its routine use. A more recent Cochrane Database Systematic Review looked at the antenatal dietary supplementation with Myo-inositol in women during pregnancy for preventing GDM, concluded that there is evidence from four trials of a potential benefit for reducing the incidence of GDM. However, there was no consensus on neonatal outcomes. The

authors recommended further studies to include pregnant women of different ethnicities and varying risk factors (13). Recent systematic reviews and meta-analyses have shown that Myo-inositol supplementation is associated with a significantly reduced incidence of GDM and preterm delivery (14)(15).

Given the ready availability of Myo-inositol as a dietary supplement and its relatively low cost compared to traditional interventions for preventing GDM, exploring its potential role in reducing GDM is a much needed and timely study in a different socio-economic and population context such as Qatar. Qatar's population is of multi-ethnic origin, including Qataris and non-Qatari Arabs (residents of the Middle East and North Africa Region), Asian (residents from the India sub-continent and the Philippines), and Caucasian expatriates.A large RCT in this diverse population with high GDM risk will add to the available evidence of the role of nutritional supplements to prevent GDM.

Methods/Design

Aim and Hypothesis

This is a prospective, randomized, double blind, placebo controlled clinical trial to either Myo-inositol supplementation or placebo. The study plans to enroll 640 pregnant women attending antenatal care at Sidra Medicine, with 320 pregnant women in each arm. The study overview is summarized in Figure 1 .

The hypothesis for the study is that Myo-inositol in pregnancy reduces the risk of developing Gestational Diabetes.

Outcome Measures

Primary Outcome:

1. The occurrence of Gestational Diabetes in both groups

Secondary outcomes:

Maternal:

1. Gestational weight gain.
2. Need for Metformin or insulin therapy.
3. Mode of delivery.
4. Hypertensive disorders of pregnancy

Fetal:

1. Large for Gestational Age at delivery (weight >95th centile for Gestation)
2. Small for Gestational Age at delivery (weight< 10th centile for Gestation)
3. Macrosomia (fetal weight ≥ 4000 g at delivery)
4. Shoulder dystocia and birth injury
5. Polyhydramnios.
6. NICU Admission for > 24 hours
7. Neonatal hypoglycaemia requiring intravenous glucose
8. Preterm delivery (<37 weeks gestation)
9. Transient Tachypnea of the newborn
10. Respiratory distress syndrome (RDS)

Gestation diabetes (GDM) diagnosis is based on WHO (IADPSG) , one or more abnormal glucose values; (fasting blood glucose ≥ 5.1 mmol/l; 1-hour post 75 grams OGTT ≥10.0 mmol/ l; and 2-hours post 75 grams OGTT ≥ 8.5 mmol/l (16).

Pre-pregnancy weight is recorded in the initial visit based on patient self-report and is entered into the electronic medical records. We will use the last recorded weight at the time of delivery to calculate total gestational weight gain corrected for gestational age at delivery.

Macrosomia is defined as birth weight > 4000 grams. LGA (Large for gestational age) is defined as birth weight >95th percentile, and SGA (small for gestational age) is defined as birth weight <10th percentile using the locally adapted growth charts. Preterm delivery is defined as delivery < 37 weeks' Gestation.

Hypertensive disorders in pregnancy will be diagnosed based on the American College of Obstetrics and Gynaecology (17). Gestational hypertension is defined as a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure. Women with gestational hypertension with severe range blood pressures (a systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher) are diagnosed with preeclampsia with severe features. Pre-eclampsia is any raised blood pressure as above with significant Proteinuria of 300 mg or more per 24 hour urine collection or protein/creatinine ratio of 0.3 mg/dL or more or urine dipstick reading of 2+ of protein (17) .

Shoulder dystocia is the use of any additional manoeuvres for the delivery of the baby after the delivery of the head, as documented by the delivering medical staff.

The diagnosis of neonatal hypoglycemia and respiratory distress syndrome (RDS) will be extracted from the diagnosis section of the neonatal electronic medical records.

Neonatal hypoglycemia will be diagnosed based on the Paediatric Endocrine Society and British Association of Perinatal Medicine (BAPM). We will only include neonatal hypoglycemia requiring intravenous glucose (18). Respiratory distress syndrome (RDS) is coded in accordance with -ICD-10-CM Diagnosis Code.

Inclusion and Exclusion criteria

All pregnant women booking for antenatal care at Sidra Medicine before 16 weeks of gestation will be approached to participate in the study. Comprehensive written and verbal information will be provided in both English and Arabic. This will ensure early commencement of the study supplementation or placebo with a sufficient period prior to undertaking the OGTT, thus optimizing any potential effect of the intervention. The following are the inclusion and exclusion criteria for the study:

Inclusion criteria:

1. Pregnant women booked for prenatal care at Sidra Medicine.
2. Gestational age less than 16 weeks.
3. Capacity to provide informed consent.

Exclusion criteria:

1. Pre-gestational diabetes / pre-existing diabetes.
2. Fasting glucose of ≥5.1 mmol/l (92 mg/dl)
3. Women on steroids during pregnancy.
4. Women using Metformin for any other disorder, e.g., PCOS.

5. Women taking Myo-inositol as part of any supplementation.
6. Cancer- Not in remission.
7. Known allergy to Myo-inositol
8. Women who had bariatric surgery.
9. Involvement in another interventional trial.
10. Polyhydramnios.

Study participants

Women who agree to participate will be invited to attend the research clinic. They will be provided with detailed information about the study by the Principal Investigator or delegated Co-investigators, and, if agreeable, a written consent form will be obtained.

An acceptance rate of 50-60% is anticipated; hence, the target is to approach about 1000 women with a view to enrolling them in the study. The average obstetric antenatal booking patient rate is between 8 to 14 per day, and this translates into a projected average of 2860 patients annually, well above the recruitment target for this study. The study protocol is consistent with the principles of the Declaration of Helsinki (IRB number 1538656), and participants will be required to provide written informed consent prior to trial enrollment. The study overview is summarized in supplementary figure 1.

Randomization and Study schedule

Randomization will be performed using computer-generated numbers, which would allocate participants into either Myo-inositol or Placebo arms. Both Myo-inositol and Placebo will have identical packaging prepared at the source and supplied through Sidra pharmacy. All research team members and research participants will be blinded to the content of the

research packs. The pharmacist shall seal, randomly number the sachets according to the computer-generated scheme, and be the sole healthcare provider to access this data until blinding is broken. Breaking blinding is possible after delivery and in cases of adverse reactions or if severe side effects are encountered.

The Myo-inositol pack will contain 2 g of Myo-inositol in the form of a sachet. The placebo pack will contain a pharmacologically inert substrate in a similar packing to the Myo-inositol sachets. Both Myo-inositol and Placebo sachets are to be taken twice a day.The pharmacist will provide a monthly (30 days) supply of the trial packs. All participants will complete at least 12 weeks of intervention or supplementation before undertaken OGTT. The Research nurse, blinded to the research supplements, will arrange scheduled contacts with all participants every month to arrange additional trial packs and check on compliance. These scheduled contacts will be linked to the regular antenatal clinic schedules so that participants do not have to make extra visits. All participants will have standard antenatal care as per Sidra's prenatal care pathway.

Participants will be advised to stop study supplements only when admitted in spontaneous labour, for Induction of Labour or Lower Segment Caesarean Section, whichever comes earlier. The remaining and unused sachets will be collected on admission for delivery to evaluate patient compliance. The study schedule is summarised in the supplementary Table1.

Clinical assessment

The Oral Glucose Tolerance Test (OGTT) will be performed at 24-28 weeks as per Sidra protocol for routine screening for GDM, and additional blood samples for C-peptide and Insulin will also be taken at the same time. All participants will complete at least 12 weeks of intervention or supplementation prior to undertaking the OGTT. Women will be advised to continue using the trial packs regardless of OGTT results. Those who are diagnosed as having GDM will have standard antenatal care as per Sidra prenatal care pathway.

Data regarding pregnancy course and delivery outcome will be collected by the research nurse. Lifestyle and dietary data will be collected at each visit by a dietician using 24hrs dietary recall and questionnaires and correlated with the study outcomes.

Participants who withdraw from the study or who fail to return for follow-up assessments shall continue to have data collected from their routine diabetic or obstetrics clinic visits unless they specifically withdraw consent for this. Data collected during the trial will be stored securely with appropriate data security governance in the hospital electronic System for Health records as a source document.

Sample size and Statistical Analysis

The overall prevalence of newly detected diabetes in pregnancy in Qatar is 23.6%. A sample size of 640 pregnant women, with 320 in each arm, is sufficient to detect a clinically significant reduction of 40% in the incidence of GDM between groups using a two-tailed z-test of proportions between two groups with 80% power and a 95% level of confidence, accounting for 20% drop out rate. This 40% reduction represents a 23.6 % incidence of

newly detected diabetes in pregnancy in the placebo group and a maximum of 14.2% in the Myo-inositol group. All randomized subjects will be included in the analysis.

All statistical analyses will be applied using R and SAS v9.4 (SAS Institute). Statistical analyses will include both descriptive (numerical and graphical) and inferential statistics. Graphical analyses, where deemed appropriate, will be included in the analyses. Frequencies and proportions will be used to summarize qualitative variables, whereas means, median, standard deviation, and quartiles will be used to summarize quantitative variables. Two sided Student's t-test and chi-squared test will be used to evaluate the differences between continuous and categorical variables, respectively. Spearman's correlation coefficients will be estimated to determine associations between quantitative variables. Logistic regression analysis will be performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor. ORs and their 95% confidence intervals (95% CI) for associated factors will be estimated, and all statistical assessments will be considered significant at P-value < 0.05. The statistical analyses are directed towards the assessment of the objectives of the study.

Data Monitoring Plan

The data-monitoring plan for this study includes the appointment of an independent expert to perform and oversee the interim analysis for the study. An interim analysis is planned at 12 months and or at 50% of enrolment, whichever comes earlier. If the interim analysis shows that the difference between the two arms reaches statistical significance, the result of the analysis and recommendation for stopping the trial will be communicated to the IRB.

List of Abbreviations

GDM- Gestational Diabetes

FDA-Food and drugs administration

IDF-International Diabetes Federation

T2DM-Type 2 Diabetes Mellitus

PCOS-Polycystic Ovarian syndrome

OGTT-Oral Glucose Tolerance Test

NICU-Neonatal intensive care unit

RDS-Respiratory distress syndrome

Declarations

Ethics approval and consent to participate: This study was approved by the Sidra Medicine IRB on 12th April 2021 with the approval reference number 1538656.

Consent for publication: Written informed consent will be obtained for publication

Publication and dissemination plan: Planned publication in a peer-reviewed journal.

All data generated or analyzed during this study will be included in the publication of the subsequent results.

Competing interests: The authors declare that they have no competing interests.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Funding: The study is funded by Sidra Medicine through the competitive Internal Research Grant fund, following the external peer review of the study. The funding arm of Sidra Medicine is not involved in the design of the study, management, analysis, interpretation of data; writing of the report; the decision to submit the report for publication or writing of the protocol manuscript.

Patient and public involvement: No patient involved in the study.

Authors' contributions:

HA initiated the idea for the study, II , GO and HA produced the initial study design, GO prepared the draft manuscript. HA, II, OO, YF, AT, and GO contributed to the manuscript review. All authors read and approved the final manuscript.

Acknowledgments: Not applicable

Word count: 2580 words

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Diagram 1: A study overview

Subjects

Randomization

Randomize Before 16 weeks of gestation

ARM 1 N=320

Control

ARM 2 N=320

Placebo

Timelines

6-16 weeks
20 weeks
24 weeks
OGTT
28 weeks
32 weeks
36 weeks
37 weeks
38 weeks
39 weeks
40 weeks
Delivery

Data Collection At Delivery

- **Maternal outcomes**
- **Neonatal outcomes**

Inclusion criteria:

1. **Pregnant women booked for prenatal care at Sidra Medicine.**
2. **Gestational age less than 16 weeks.**
3. **Capacity to provide informed consent**

Exclusion criteria:

1. Pre-Gestational diabetes / pre-existing diabetes.
2. Fasting Glucose of ≥5.1 mmol/l (92 mg/dl)
3. Women on steroids during pregnancy.
4. Women using Metformin for any other disorder, e.g., PCOS.
5. Women taking Myo-inositol as part of any supplementation.
6. Cancer- Not in remission.
7. Known allergy to Myo-inositol
8. Women who had bariatric surgery.
9. Involvement in another interventional trial.
10. Polyhydramnios.

Basic Information

- **Demographics**
- **Family history**
- **Pre-Pregnancy BMI**
- **Basic Observations(BP, Pulse, BMI)**
- **Physical activity**
- **Dietary History**

Table 1. MiGDM Study Overview

Time point	6-16 wks	20 wks	24 wks	28 wks	32 wks	36 wks	37 wks	38 wks	39 wks	40 wks	Delivery
Measurement											
Demographics	X										
Family history	X										
Pre-Pregnancy BMI	X										
BP and HR	X	X	XX	X	X	X	X	X	X	X	X
Physical activity	X										
Maternal outcomes											X
Neonatal outcomes											X
C-peptide Insulin, OGTT			X	X							
Routine clinic tests	X										
Ultrasound scan		X		X	X	X					

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry , Trial registration section
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable
Protocol version	3	Date and version identifier Not applicable
Funding	4	Sources and types of financial, material, and other supportFunding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors , Authors , Authors affiliation and Authors contributions
	5b	Name and contact information for the trial sponsor Funding
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Not applicable
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Background and introduction
	6b	Explanation for choice of comparators Background and Introduction
Objectives	7	Specific objectives or hypotheses Aim and Hypothesis

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Method/Design
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Method/Design
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Inclusin and exclusion criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Randomization and Study schedule
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) , Randomization and Study schedule
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) , Randomization and Study schedule
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Randomization and Study schedule
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Outcomes measures
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Attachment: Table 1. MiGDM Study Overview , and Diagram 1; study overview
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations Sample size and Statistical Analysis
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Study plan

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions) Randomization and Study schedule
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Randomization and Study schedule
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Randomization and Study schedule
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Randomization and Study schedule
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Randomization and Study schedule

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Table 1. MiGDM Study Overview
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Page 11 second paragraph
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Informed consent ; Confidentially section 16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol Sample size and Statistical Analysis

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) Sample size and Statistical Analysis
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Randomization and Study schedule , Sample size and Statistical Analysis
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Data monitoring
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Data monitoring
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct IRB Research proposal under section Safety reporting:
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor IRB Research proposal under section Quality assurance and Reporting
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 13, Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) IRB Research proposal under section Reporting:
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 9, Study plan first paragraph
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Consent form section 23,24,25
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Consent form section 16

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 13 and 14 Declarations and Competing interests :
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Consent form section 16 confidentiality
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Consent form section 14, 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 14 Publication and dissemination plan
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 14 Authors' contributions
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates IRB 400 Informed consent form attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Relevant information are included in IRB 400 Informed consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The effect of antenatal dietary Myo-inositol supplementation on the incidence of Gestational Diabetes Mellitus and fetal outcome: Protocol for a double blind randomized controlled trial.

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Title Page

Title of Study:

The effect of antenatal dietary Myo-inositol supplementation on the incidence of Gestational Diabetes Mellitus and fetal outcome: Protocol for a double-blind randomized controlled trial.

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) affects 23.6% of Qatari women and is associated with maternal and perinatal morbidity and long-term risk of developing type 2 diabetes (T2DM).A number of challenges exist with current interventions, including non-compliance with dietary advice, the reluctance of mothers to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies. Myo-inositol is readily available as an FDA-approved food supplement with emerging but limited evidence suggesting it may be beneficial in reducing the incidence of GDM. Further studies, such as this one, from different ethnic contexts and with differing risk factors, are urgently needed to assess Myo-inositol effects on maternal and neonatal outcomes.

Methods and analysis: This study is a prospective, randomized, double-blinded, placebo controlled clinical trial to either Myo-inositol supplementation or placebo.

We plan to enrol 640 pregnant women attending antenatal care at Sidra Medicine, Doha, Qatar, 320 in each arm. All participants will complete at least 12 weeks of supplementation prior to undertaking the OGTT at 24-28 weeks. The daily use of the trial supplementation will continue until the end of pregnancy. All outcome measures will be collected from the electronic medical records.

Ethics and dissemination: Ethical approval for the study was obtained on 12/04/2021 from Sidra Medicine (IRB number 1538656). Results of the primary trial outcome and secondary endpoints will be submitted for publication in a peer-reviewed journal.

Trial Registration: Prospectively registered on 26/05/2021. Registration number ISRCTN16448440 (ISRCTN registry).

Article Summary:

Strengths and limitations of this study

- To our knowledge, this is the first large RCT in an ethnic population with a high prevalence of GDM to test the effectiveness of Myo-inositol supplementation.
- The early screening of diabetes in pregnancy used in Qatar ensures that women with pre-existing diabetes are excluded before enrolment.
- The duration of Myo-inositol supplementation prior to OGTT is variable, between 12 and 20 weeks and this is a potential limitation of the study.
- The study may not have enough power to address some of the secondary outcome measures.

Keywords:

Gestational Diabetes, Pregnancy, Myo-inositol, perinatal morbidity, Dietary supplementation

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). Identified risk factors for GDM include maternal age, maternal body mass index (BMI), ethnic background, family history, and previous history of GDM (1). Globally, the International Diabetes Federation (IDF) estimates that 14% of all deliveries are affected by GDM (2). Diabetes is a significant public health issue in Qatar with increasing prevalence over the years. A recent study from Qatar showed that the prevalence of GDM among Qatari women was 23.6% (3). GDM is a major pregnancy complication associated with both maternal and perinatal morbidity and long-term risk of the development of type 2 diabetes (T2DM). The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multi-centric, observational study, evaluated the relationship between maternal hyperglycemia and adverse pregnancy outcomes and identified elevated maternal serum glucose level during pregnancy as a major risk factor for adverse pregnancy outcomes, increasing rates of large-for-gestational-age infants, fetal hyperinsulinemia, neonatal hypoglycemia, and caesarean delivery (4). During pregnancy, GDM is associated with an increased risk of pre-eclampsia, preterm labor, Caesarean-section, macrosomia, shoulder dystocia, and a substantial increase in medical cost (5), (6). Exposure to hyperglycemia in pregnancy is shown to be associated with an increased risk to the offspring of abnormal glucose tolerance, Type 2 diabetes, obesity, and higher blood pressure (7), (8).

In the last decade, multi-modal evidence-based measures and interventions have been introduced to improve the outcome of pregnancy in women with GDM. It has also been shown that both lifestyle modifications and Metformin therapy effectively delay or prevent diabetes in women with a history of GDM (9). Whilst significant progress has been made,

several challenges remain with current interventions, including non-compliance with dietary advice and mothers' reluctance to ingest Metformin tablets or use Insulin injections. These challenges highlight the importance of pursuing evidence-based prevention strategies.

Inositol has been proposed as a food supplement that might reduce GDM incidence in high-risk pregnant women. Myo-inositol, an isomer of inositol, is a naturally occurring sugar commonly found in cereals, corn, legumes, and meat. The US Food and Drug Administration class it as a dietary supplement. It is one of the intracellular mediators of the insulin signaling pathway and correlated with insulin sensitivity in T2DM. It is an insulin-sensitizing mediator, which is reported to reduce plasma glucose levels in polycystic ovary syndrome (PCOS), where it has gained increasing attention and is used for its unique property of reducing insulin resistance. Inositol isoforms were reported to improve insulin sensitivity and ovulatory function in young women affected by PCOS (10). Chiro- and Myo-inositol are major components of the two inositol phosphoglycan mediators of insulin action. Patients with T2DM, compared to controls, have less active chiro-inositol-containing mediator fractions form and a significantly reduced chiro-inositol to Myo-inositol ratio (11). Myo-inositol supplementation is shown in an RCT to reduce the incidence of GDM in pregnant women with a parent with type 2 diabetes (6 %vs. 15.3%, P = 0.04) as well as the incidence of the delivery of a macrocosmic fetus (12). The potential beneficial effect on improving insulin sensitivity suggests that it may be useful for preventing GDM. Although Myo-inositol shows promise in preventing GDM, there is not enough evidence at this stage to support its routine use. A more recent Cochrane Database Systematic Review looked at the antenatal dietary supplementation with Myo-inositol in women during pregnancy for preventing GDM, concluded that there is evidence from four trials of a potential benefit for reducing the incidence of GDM. However, there was no consensus on neonatal outcomes. The

authors recommended further studies to include pregnant women of different ethnicities and varying risk factors (13). Recent systematic reviews and meta-analyses have shown that Myo-inositol supplementation is associated with a significantly reduced incidence of GDM and preterm delivery (14) (15).

Given the ready availability of Myo-inositol as a dietary supplement and its relatively low cost compared to traditional interventions for preventing GDM, exploring its potential role in reducing GDM is a much needed and timely study in a different socio-economic and population context such as Qatar. Qatar's population is of multi-ethnicorigin, including Qataris and non-Qatari Arabs (residents of the Middle East and North Africa Region), Asian (residents from the India sub-continent and the Philippines), and Caucasian expatriates.A large RCT in this diverse population with high GDM risk will add to the available evidence of the role of nutritional supplements to prevent GDM.

Methods/Design

Aim and Hypothesis

This is a prospective, randomized, double blind, placebo controlled clinical trial to either Myo-inositol supplementation or placebo. The study plans to enroll 640 pregnant women attending antenatal care at Sidra Medicine, with 320 pregnant women in each arm. The study overview is summarized in Supplementary Figure 1.

The hypothesis for the study is that Myo-inositol in pregnancy reduces the risk of developing Gestational Diabetes.

Outcome Measures

Primary Outcome:

1. The incidence of Gestational Diabetes in both groups

Secondary outcomes:

Maternal:

1. Gestational weight gain.
2. Need for Metformin or insulin therapy.
3. Mode of delivery.
4. Hypertensive disorders of pregnancy

Fetal:

1. Large for Gestational Age at delivery (weight >95th centile for Gestation)
2. Small for Gestational Age at delivery (weight< 10th centile for Gestation)
3. Macrosomia (fetal weight ≥ 4000 g at delivery)
4. Shoulder dystocia and birth injury
5. Polyhydramnios.
6. NICU Admission for > 24 hours
7. Neonatal hypoglycaemia requiring intravenous glucose
8. Preterm delivery (<37 weeks gestation)
9. Transient Tachypnea of the newborn
10. Respiratory distress syndrome (RDS)

Gestation diabetes (GDM) diagnosis is based on WHO (IADPSG) , one or more abnormal glucose values; (fasting blood glucose ≥ 5.1 mmol/l; 1-hour post 75 grams OGTT ≥10.0 mmol/ l; and 2-hours post 75 grams OGTT ≥ 8.5 mmol/l (16).

Pre-pregnancy weight is recorded in the initial visit based on patient self-report and is entered into the electronic medical records. In the absence of a validated pre-pregnancy weight, the measured weight at first hospital visit will be used with appropriate adjustment for gestation at recruitment. We will use the last recorded weight at the time of delivery to calculate total gestational weight gain corrected for gestational age at delivery.

Macrosomia is defined as birth weight > 4000 grams. LGA (Large for gestational age) is defined as birth weight >95th percentile, and SGA (small for gestational age) is defined as birth weight <10th percentile. The percentile for growth will be extracted from the built in growth charts (WHO birth to 24 months weight for age chart) within the Electronic medical records system. Preterm delivery is defined as delivery < 37 weeks' Gestation.

Hypertensive disorders in pregnancy will be diagnosed based on the American College of Obstetrics and Gynaecology (17). Gestational hypertension is defined as a systolic blood pressure of 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure. Women with gestational hypertension with severe range blood pressures (a systolic blood pressure of 160 mm Hg or higher, or diastolic blood pressure of 110 mm Hg or higher) are diagnosed with preeclampsia with severe features. Pre-eclampsia is any raised blood pressure as above with significant Proteinuria of 300 mg or more per 24 hour urine collection or protein/creatinine ratio of 0.3 mg/dL or more or urine dipstick reading of 2+ of protein (17).

Shoulder dystocia is the use of any additional manoeuvres for the delivery of the baby after the delivery of the head, as documented by the delivering medical staff.

The diagnosis of neonatal hypoglycemia and respiratory distress syndrome (RDS) will be extracted from the diagnosis section of the neonatal electronic medical records.

Neonatal hypoglycemia will be diagnosed based on the Paediatric Endocrine Society and British Association of Perinatal Medicine (BAPM) (18). If the blood glucose is less than 45 mg/dL (2.5mmol/L), Glucogel with a milk feed is to be given up to 3 times. If blood glucose remains at 25 mg/dl (1.4 mmol/l) up to 2 times, then the neonate will be admitted to NICU for Intravenous dextrose. In symptomatic patients with glucose < 45 mg/dl (2.5 mmol/l), the neonate will be admitted to NICU for IV dextrose . We will only include neonatal hypoglycemia requiring intravenous glucose for this study Respiratory distress syndrome (RDS) is coded in accordance with -ICD-10-CM Diagnosis Code.

Inclusion and Exclusion criteria

All pregnant women booking for antenatal care at Sidra Medicine before 16 weeks of gestation will be approached to participate in the study. Comprehensive written and verbal information will be provided in both English and Arabic. This will ensure early commencement of the study supplementation or placebo with a sufficient period prior to undertaking the OGTT, thus optimizing any potential effect of the intervention.

The following are the inclusion and exclusion criteria for the study:

Inclusion criteria:

1. Pregnant women booked for prenatal care at Sidra Medicine.
2. Gestational age less than 16 weeks.

3. Capacity to provide informed consent.

Exclusion criteria:

1. Pre-gestational diabetes/ pre-existing diabetes.
2. Fasting glucose of ≥5.1 mmol/l (92 mg/dl)
3. Women on steroids during pregnancy.
4. Women using Metformin for any other disorder,e.g., PCOS.
5. Women taking Myo-inositol as part of any supplementation.
6. Cancer- Not in remission.
7. Known allergy to Myo-inositol
8. Women who had bariatric surgery.
9. Involvement in another interventional trial.
10. Polyhydramnios.

Study participants

Women who agree to participate will be invited to attend the research clinic. They will be provided with detailed information about the study by the Principal Investigator or delegated Co-investigators, and, if agreeable, a written consent form will be obtained (supplementary file 1).

An acceptance rate of 50-60% is anticipated; hence, the target is to approach about 1000 women with a view to enrolling them in the study. The average obstetric antenatal booking patient rate is between 8 to 14 per day, and this translates into a projected average of 2860 patients annually, well above the recruitment target for this study. The study protocol is consistent with the principles of the Declaration of Helsinki (IRB number 1538656), and

participants will be required to provide written informed consent prior to trial enrollment. The study overview is summarized in supplementary figure 1.

Randomization and Study schedule

Randomization will be performed using computer-generated numbers, which would allocate participants into either Myo-inositol or Placebo arms. Both Myo-inositol and Placebo will have identical packaging prepared at the source and supplied through Sidra pharmacy. All research team members and research participants will be blinded to the content of the research packs. The pharmacist shall seal, randomly number the sachets according to the computer-generated scheme, and be the sole healthcare provider to access this data until blinding is broken. Breaking blinding is possible after delivery and in cases of adverse reactions or if severe side effects are encountered.

The Myo-inositol pack will contain 2 g of Myo-inositol in the form of a sachet. The placebo pack will contain a pharmacologically inert substrate in a similar packing to the Myo-inositol sachets. Both Myo-inositol and Placebo sachets are to be taken twice a day.The pharmacist will provide a monthly (30 days) supply of the trial packs. All participants will complete at least 12 weeks of intervention or supplementation before undertaken OGTT. The Research nurse, blinded to the research supplements, will arrange scheduled contacts with all participants every month to arrange additional trial packs and check on compliance. These scheduled contacts will be linked to the regular antenatal clinic schedules so that participants do not have to make extra visits. All participants will have standard antenatal care as per Sidra's prenatal care pathway.

Participants will be advised to stop study supplements only when admitted in spontaneous labour, for Induction of Labour or Lower Segment Caesarean Section, whichever comes

earlier. The remaining and unused sachets will be collected on admission for delivery to evaluate patient compliance. The study schedule is summarised in the supplementary Table1.

Clinical assessment

The Oral Glucose Tolerance Test (OGTT) will be performed at 24-28 weeks as per Sidra protocol for routine screening for GDM, and additional blood samples forC-peptide and Insulin will also be taken at the same time.All participants will complete at least 12 weeks of intervention or supplementation prior to undertaking the OGTT. Women will be advised to continue using the trial packs regardless of OGTT results. Those who are diagnosed as having GDM will have standard antenatal care as per Sidra prenatal care pathway.

Data regarding pregnancy course and delivery outcome will be collected by the research nurse. Lifestyle and dietary data will be collected at each visit by a dietician using 24hrs dietary recall and questionnaires and correlated with the study outcomes (supplementary file 2, 3 and 4)

Participants who withdraw from the study or who fail to return for follow-up assessments shall continue to have data collected from their routine diabetic or obstetrics clinic visits unless they specifically withdraw consent for this. Data collected during the trial will be stored securely with appropriate data security governance in the hospital electronic system for health records as a source document.

Sample size and Statistical Analysis

The overall prevalence of newly detected diabetes in pregnancy in Qatar is 23.6%. A sample size of 640 pregnant women, with 320 in each arm, is sufficient to detect a clinically

significant reduction of 40% in the incidence of GDM between groups using a two-tailed z-test of proportions between two groups with 80% power and a 95% level of confidence, accounting for 20% drop out rate. This 40% reduction represents a 23.6 % incidence of newly detected diabetes in pregnancy in the placebo group and a maximum of 14.2% in the Myo-inositol group. All randomized subjects will be included in the analysis.

All statistical analyses will be applied using R and SAS v9.4 (SAS Institute). Statistical analyses will include both descriptive (numerical and graphical) and inferential statistics. Graphical analyses, where deemed appropriate, will be included in the analyses. Frequencies and proportions will be used to summarize qualitative variables, whereas means, median, standard deviation, and quartiles will be used to summarize quantitative variables. Two sided Student's t-test and chi-squared test will be used to evaluate the differences between continuous and categorical variables, respectively. Spearman's correlation coefficients will be estimated to determine associations between quantitative variables. Logistic regression analysis will be performed to estimate odds ratios (ORs) and to examine the predictive effect of each factor. ORs and their 95% confidence intervals (95% CI) for associated factors will be estimated, and all statistical assessments will be considered significant at P-value < 0.05. The statistical analyses are directed towards the assessment of the objectives of the study.

Data Monitoring Plan

The data-monitoring plan for this study includes the appointment of an independent expert to perform and oversee the interim analysis for the study. An interim analysis is planned at 12 months and or at 50% of enrolment, whichever comes earlier. If the interim analysis shows that the difference between the two arms reaches statistical significance, the result of the analysis and recommendation for stopping the trial will be communicated to the IRB.

List of Abbreviations

GDM- Gestational Diabetes

FDA-Food and drugs administration

IDF-International Diabetes Federation

T2DM-Type 2 Diabetes Mellitus

PCOS-Polycystic Ovarian syndrome

OGTT-Oral Glucose Tolerance Test

NICU-Neonatal intensive care unit

RDS-Respiratory distress syndrome

Declarations

Ethics approval and consent to participate: This study was approved by the Sidra Medicine IRB on 12th April 2021 with the approval reference number 1538656.

Consent for publication: Written informed consent will be obtained for publication

Publication and dissemination plan: Planned publication in a peer-reviewed journal.

All data generated or analyzed during this study will be included in the publication of the subsequent results.

Competing interests: The authors declare that they have no competing interests.

Provenance and peer review: Not commissioned; externally peer-reviewed.

Funding: The study is funded by Sidra Medicine through the competitive Internal Research Grant fund, (grant number SDR200067), following the external peer review of the study. The funding arm of Sidra Medicine is not involved in the design of the study, management, analysis, interpretation of data; writing of the report; the decision to submit the report for publication or writing of the protocol manuscript.

Patient and public involvement: No patient involved in the study.

Authors' contributions:

HA initiated the idea for the study, II , GO and HA produced the initial study design, GO prepared the draft manuscript. HA, II, OO, YF, AT, and GO contributed to the manuscript review. All authors read and approved the final manuscript.

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Word count: 2580 words

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Diagram 1: A study overview

Subjects

Randomization

Randomize Before 16 weeks of gestation

ARM 1 N=320

Control

ARM 2 N=320

Placebo

Timelines

6-16 weeks
20 weeks
24 weeks
OGTT
28 weeks
32 weeks
36 weeks
37 weeks
38 weeks
39 weeks
40 weeks
Delivery

Data Collection At Delivery

- **Maternal outcomes**
- **Neonatal outcomes**

Inclusion criteria:

1. **Pregnant women booked for prenatal care at Sidra Medicine.**
2. **Gestational age less than 16 weeks.**
3. **Capacity to provide informed consent**

Exclusion criteria:

1. Pre-Gestational diabetes / pre-existing diabetes.
2. Fasting Glucose of ≥5.1 mmol/l (92 mg/dl)
3. Women on steroids during pregnancy.
4. Women using Metformin for any other disorder, e.g., PCOS.
5. Women taking Myo-inositol as part of any supplementation.
6. Cancer- Not in remission.
7. Known allergy to Myo-inositol
8. Women who had bariatric surgery.
9. Involvement in another interventional trial.
10. Polyhydramnios.

Basic Information

- **Demographics**
- **Family history**
- **Pre-Pregnancy BMI**
- **Basic Observations(BP, Pulse, BMI)**
- **Physical activity**
- **Dietary History**

Table 1. MiGDM Study Overview

Time point	6-16 wks	20 wks	24 wks	28 wks	32 wks	36 wks	37 wks	38 wks	39 wks	40 wks	Delivery
Measurement											
Demographics	X										
Family history	X										
Pre-Pregnancy BMI	X										
BP and HR	X	X	XX	X	X	X	X	X	X	X	X
Physical activity	X										
Maternal outcomes											X
Neonatal outcomes											X
C-peptide Insulin, OGTT			X	X							
Routine clinic tests	X										
Ultrasound scan		X		X	X	X					

IRB-400 Informed Consent Form For Research Study

Protocol Title:	**Effect of antenatal dietary Myo-inositol supplementatiom in women during pregnancy on the incidence of gestational diabetes mellitus and fetal outcome : A randomized controlled trial (MiGDM TRIAL)**
Protocol Number:	**1538656**
Sponsor:	**Sidra Medicine-IRF**
Principal Investigator:	**Dr Ibrahim Mamoun Ibrahim**
Site Address:	**Sidra Medicine, Doha, Qatar**
Telephone Number:	**30016566**

1. Introduction

Before agreeing to participate in this research study, please read and understand the following explanation of the proposed study. This informed consent form describes the purpose, procedures and risks of the study. It also describes your right to withdraw from the study at any time, and that you are volunteering. Also, that no guarantees or assurances can be made as to the results of the study. Please feel free to ask questions.

2. Background and Purpose

The background and purpose of this research study is to ascertain whether we can reduce the chances of developing diabetes during pregnancy through the use of simple nutritional supplement in women who are pregnant.

Diabetes is a relatively common health problem in Qatar and during pregnancy up to one in four pregnant women are affected by diabetes in Qatar. Pregnancies affected by diabetes carry additional problems for the expectant mother and her unborn baby. Some of these problems can be prevented or reduced through the use of currently available treatments. Treatments currently used for diabetes during pregnancy include targeted dietary and lifestyle changes as well as the use of tablets or injection (insulin) to keep blood sugar level within a healthy range. Whilst these treatments are helpful , they can be time-consuming , inconvenient and carry potential side-effects particularly treatment by injection. In addition, the problems caused by diabetes to the mother and her unborn baby are not always preventable even when current treatments are used. Therefore, the ideal goal if possible, is the to prevent diabetes during pregnancy altogether, and this is the reason we are undertaking this research study. By reducing the chances of developing diabetes during pregnancy, problems associated with having diabetes can also be reduced or prevented altogether.

3. Number of Subjects

About 640 subjects will participate in this study and this is the only site for the entire study nationally.

4. Study Duration and Length of Participation

Your participation in this study will last approximately 32 weeks and will include a maximum of 8 visits to the study center. We also expect that this research study will last approximately two years to complete althoughyour involvement will only be till the end of your pregnancy.

5. Procedures

Your participation will involve attendance at the Sidra Obstetric clinic which is located on the fourth floor of the Sidra outpatient building. There will be monthly attendances from the time you enroll to participate in the study until delivery of the baby and this will coincide with your regular antenatal visits. Each attendance will last for approximately 45 minutes to one hour and includes your normal antenatal appointment with a Doctor or midwife. The first two appointments may be longer to allow a detailed explanantion of the purpose of this research and seek your written permission. The reseach coordinator will meet with you at your first visit and provide a detailed explanation of the research and also provide you with a direct contact telephone number and additional written information about the research in addition to arranging the follow up visit. A clinical dietician will call you after each visit to ask about your lifestyle and dietary habits using short questionnaries.

Your participation will involve the collection of a packet of research supplements to be taken daily throughout the duration of your involvement in the research. The supplement could either be myoinositol or an inactive supplement, both of which are safe to use during pregnancy.

You will be offered a test for diagnosing diabetes during pregnancy called the Oral Glucose Tolerance test(OGTT), between 6 and 7 months of pregnancy (24-28 weeks). This test is part of the standard antenatal care and will be offered even if you were not taking part in this research. The test usually takes about two hours to complete and involves three blood samples, about table spoonful to be taken at hourly intervals. An additional blood sample, half a table spoonful (5 mls) will be taken specifically for the purpose of this research, this will measure the precursor of the Insulin hormone (C-peptide), to find out the resons why some women develop diabetes in pregnancy and how to prevent it. All the visits related to this research will take place in the outpatient clinic setting, there will be no admission or overnight stay in the hospital related to this research.

If you agree to participate, the researchers will also collect details of your medical history, previous pregnancy history and the outcome of your current pregnancy from the hospital electronic medical records. The details of the baby including birth weight and condition at birth and mode of delivery will also be collected .You will have your standard antenatal care whether or not you choose to participate in the research. Your standard antenatal care will consist of scheduled blood tests, ultrasound scan of the baby and antenatal consultations. If you choose to take part in the research, you will be required to take the research supplement on a daily basis. The research supplement contains either Myoinositol or an inactive supplement. The researchers and yourself will not know which of these supplements you will receive to avoid unitended bias. The decision on which of the supplement you will receive will be determined by chance, with every one having an equal chance of receiving the Myoinositol or the inactive supplement.

6. Alternative Procedures

This study is for research purposes only. The only alternative is to not participate in this study and you will have your standard anatenatal care as usual

7. Risks, Side Effects and/or Discomforts

The potential risks and side effects associated with procedures involved in the research are as follows:

- Blood samples: possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Taking the research supplements: There is no known risk we are aware of that is associated with taking the research supplement , having been used widely around the world.

8. Unforeseen Risks

There are no known risk for study participation . The safety to the fetus is not studied well, but there is no known or foreseeable risk to the fetus from myo-inositol or placebo.

9. Pregnancy *(include if applicable)*

This research is designed specifically for participants who are currently pregnant.

10. New Findings

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be made available to you. This might include changes in procedures, changes in the risks or benefits of participation, or any new alternatives to participation that the researchers learn about.

11. Individual Results from the Research Tests/Surveys

Generally, tests done for research purposes are not meant to provide results or clinical information that apply to you alone

12. Benefits

This study is for research purposes only. There could be potential benefits if it happens that you are assigned to one of the 2 treatment arms (Myoinositol or placebo), however neither you nor the Principal investigator knows which arm of the study you are assigned into until the end of the study.
A brief fact sheet about Myoinositol is provided along with this consent form for information only.

13. Costs

There will be no charge to you for your participation in this study. The study-related procedures will be provided at no charge to you or your insurance company. The study visits will be aligned with your standard antenatal care visits according to the agreed care plan with Sidra Medicine.The cost of the routine visit will be according to the agreed care plan with Sidra Medicine and will not be paid by the research funds.

14. Compensation for Participation

You will not receive any monetary compensation for your participation in this study.

15. Research Related Injuries

If you are injured or made sick from taking part in this research study, call Dr Ibrahim Ibrahim immediately, T. +974-30016566, or alternatively contact Sidra Medicine Emergency Department.
Medical care will be provided to you at Sidra Medicine at no charge. In case we were unable to provide care to you at Sidra, we will arrange and pay for your care at Hamad Medial Corporation (HMC). If you receive care at another institution, you or your insurance will have to pay for that care in accordance with the

policies of that institution. Sidra Medicine has no program or funds set aside to compensate you for research-related injuries or to pay for medical care for research-related injuries at institutions other than HMC or Sidra. Contact the Principal Investigator for more information

16. Confidentiality

Records of your participation in this study will be held confidential except as disclosure is required by law or as described in this informed consent document. Efforts will be made to limit your personal information, including research study and medical records, to people who have a need to review this information.

The investigator, authorized research personnel, the sponsor or persons working on behalf of the sponsor, monitors, auditors, MOPH, other regulatory agencies (when applicable) and the Institutional Review Board (IRB) will be able to inspect and copy confidential study-related records which identify you by name. They will be granted direct access to your medical records for verification of the research procedures and date. Therefore, absolute confidentiality cannot be guaranteed. By signing this document, you are authorizing this access.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We will take careful steps to keep your information confidential.We will store your identifiable information, in a password-protected database; encrypted file which changes it to another format to protect it from being accessed by anyone outside of the approved staff.

We will remove your name or other direct identifiers from your information or samples. We will label your information or samples with a code. We will store the key that links the code to your identity separately. Only select staff will have access to the list that links the code to you.

The staff follow procedures to keep your identity secret to the extent allowed by law. In very unusual cases, staff may be required to release your identifiable medical and research information to the extent allowed by law.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

17. Commercial Gain

Your information or samples collected during this study will no longer belong to you. Information or samples may be used for the development of new products, treatments, processes or services for commercial sale. There are no plans to offer you financial compensation or share any profits with you or your relatives should this occur.
You will not, however, lose any legal rights to which you are entitled by signing this consent.

18. Research Team Contact

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, contact the investigator Dr Ibrahim Ibrahim on +974 30016566

19. IRB Contact

An Institutional Review Board (IRB) is an independent committee established to help protect the rights of research subjects. IRB at Sidra has reviewed and approved this study. Both the IRB at Sidra and the Qatari Ministry of public helath(MOPH) will be promptly notified in the event of research related injury. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, Email: irb@sidra.org, or T. +974-4003-7747 during business hours Sunday- Thursday 7:30 a.m. to 4:00 p.m.

20. Voluntary Participation/Withdrawal

Your decision to participate in this study is voluntary. You may choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care.

If you choose to withdraw from the study after a period of participation, you will continue to receive your pregnancy care according to the standard schedule of antenatal, intrapartum and postpartum care. You will be asked to return the unused trial packs to the research nurse to complete the appropriate documentation.The research nurse will return the unused packs to the trial Pharmacist.

The investigator or the sponsor can stop your participation at any time without your consent for the following reasons:

- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements;
- If the study is cancelled.

21. Place and Duration of Storage of Information or Samples

The information will be stored at Sidra Medicine, Doha, Qatar for no longer than 3 years. Only the Investigator or authorized Sidra research team members will have access to the information.

22. Providing Information or Samples to Recipient Researchers (include if applicable)

Before sharing your information we will replace identifiers such as (e.g., your name, medical record number, or date of birth) with a code. Your coded information may be shared with other Sidra researchers and researchers outside of Sidra, without your additional informed consent.

23. Optional Future Use:

Do you give permission for Dr Ibrahim Ibrahim under the auspices of Sidra Medicine to store and share your information for future research in compliance with applicable regulations and institutional policies?

☐ **Yes** ☐**No** Initials

Remember, you can still be in the main study even if you even if you do not wish to allow your information and/or specimens stored for this investigator's future research.

24. Participating in Future Studies

The research staff would like to contact you with information about participating in future studies.
You give your permission for the investigator or staff to contact you regarding your willingness to participate in future research studies? ☐ **Yes** ☐**No** Initials

25. Consent

I have read and understand the information in this informed consent document. I have had an opportunity to ask questions. All my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document. I will receive a copy of this signed consent document.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

_____
Printed Name of the Person Conducting the Consent Discussion

_____ _____
Signature of the Person Conducting the Consent Discussion Date

26. Consent for Subjects Who Cannot Read *(include if applicable)*

The study subject has indicated that he/she is unable to read. The consent document has been read to the subject by a member of the study staff, discussed with the subject by a member of the study staff, and the subject has been given an opportunity to ask questions of the study staff.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness* Date

**Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent and any other written information supplied to the subject. Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance*

27. For Children Who Become Adults *(include if applicable)*

Not applicable

Subject ID: _____ Interview date (dd/mm/yy): --/--/--

Lifestyle

1- During the **last 7 days**, how many times did you **walk** for at least 10 minutes?

a. None
b. Once
c. Twice
d. 3 times
e. 4 times
f. 5 times
g. 6 times
h. 7 times and more

2- How much time did you usually spend **walking** per day?

_____ **hours per day**

_____ **minutes per day**

3- During the **last 7 days**, on how many times did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming?

a. None
b. Once
c. Twice
d. 3 times
e. 4 times
f. 5 times
g. 6 times
h. 7 times and more

4- How much time did you usually spend doing **vigorous** physical activities?

_____ **hours per day**

_____ **minutes per day**

5- During the **last 7 days**, on how many times did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis?

a. None
b. Once
c. Twice
d. 3 times
e. 4 times
f. 5 times
g. 6 times
h. 7 times and more

6- How much time did you usually spend doing **moderate** physical activities?

_____ **hours per day**

_____ **minutes per day**

7- During the **last 7 days**, how much time did you usually spend watching a screen (TV, computer, phone, or other devices)?

a. ½ hour or less
b. 1 hour
c. 2 hours
d. 3 hours
e. 4 hours
f. 5 hours
g. more than 5 hours

8- On average, how many hours per day do you spent in sleeping?

a. 3 hours or less

b. 4 hours

c. 5 hours

d. 6 hours

e. 7 hours

f. 8 hours

g. 9 hours or more

FOOD FREQUENCY **Research patient ID** **XXX**

Date __ __ - __ __-20 __ __

○ 1st Trimester ○ 2nd Trimester ○ 3rd Trimester ○ Delivery

How frequently do you **DRINK** the following?		Frequency and Quantity per day
Milk products: • Full fat cow milk	○ No	Yes, how many Cups/day _____
• low fat cow milk	○ No	Yes, how many Cups/day _____
• skimmed cow milk	○ No	Yes, how many Cups/day _____
• Soya milk	○ No	Yes, how many Cups/day _____
• Sweetened milk/condensed milk	○ No	Yes, how many Cups/day _____
Water	○ No	Yes, how many glasses/day _____
Tea/coffee	○ No	Yes, how many Cups/day _____
Soft drinks (coca, sprite, fanta)	○ No	Yes, how many Cups/day _____
Freshly pressed fruit/vegetable juice	○ No	Yes, how many Cups/day _____
Alcohol	○ No	Yes, how many glasses/day _____
How frequently do you **EAT** the following?		Frequency and Quantity per day Tablespoon (TBS), Teaspoon (TSP)
Bread	○ No	○ slice ○ whole bread, how many/day_____
Cereals	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Rice	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Biscuit, pancake, rusks slice	○ No	○ how many/day_____
Legumes, beans	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Fresh vegetables	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Cooked vegetables	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Fruits	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Nuts	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Tubers, potatoes, sweet potatoes	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Noodles, Pasta	○ No	○ Cup ○ TBS ○ TSP, how many/day_____
Red meat	○ No	○ Cup ○ TBS ○ TSP, how many/day_____

Poultry	O No	O Cup O TBS O TSP, how many/day_____
Fish, seafood	O No	O Cup O TBS O TSP, how many/day_____
Processed food (roast chicken, turkey, beef sausage)	O No	O slice, how many/day _____
Dairy products (cheese, yogurt, leban, labnaa)	O No	O Cup O TBS O TSP, how many/day_____
Eggs	O No	O how many/day_____
Pizza	O No	O whole O slice, how many/day_____
Do you use oil? Which one? • olive oil • corn oil • sunflower oil • other oil	O No	O Cup O TBS O TSP, how many/day_____ O Cup O TBS O TSP, how many/day_____ O Cup O TBS O TSP, how many/day_____ O Cup O TBS O TSP, how many/day_____
Do you use fats? Which one? • butter • ghee • lard	O No	O Cup O TBS O TSP, how many/day_____ O Cup O TBS O TSP, how many/day_____ O Cup O TBS O TSP, how many/day_____
Do you use salt?	O No	O Cup O TBS O TSP, how many/day_____
Do you use sugar?	O No	O Cup O TBS O TSP, how many/day_____
How frequently do you **have the** following **habit** ?		**Frequency per week**
Do you eat fast food?	O No	Yes, how many times/week _____
Do you eat fried potatoes (French fries and chips)	O No	Yes, how many times/week _____
Do you eat chocolate, cookies, cake and donuts	O No	Yes, how many times/week _____

24HDR

Patient ID:	
Dates of recorded intake:	
Nutritionist:	
Nutritionist Contact Information:	

Instructions for Keeping Your 24Hrs Food Record

- Please keep your 24hr food record for one day.
- Select day that closely resemble your usual eating habits.
- Each time you eat or drink anything (meals, snacks, etc.) during the day, write down what and how much was served and what and how much was eaten.
- To measure how much was eaten, use a set of **measuring cups and spoons** to help estimate amounts. Also see the examples below to estimate portion sizes.
- Note if food choices are homemade or purchased. Please include brand names whenever possible.

Amounts and Conversions

1/4 cup = 50 ml or 4 Tablespoons

1/3 cup = 75 ml or 5 1/2 Tablespoons

1/2 cup = 125 ml or 8 Tablespoons

2/3 cup = 150 ml or 10 1/2 Tablespoons

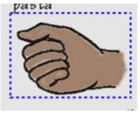
3/4 cup = 175 ml or 12 Tablespoons

1 cup = 250 ml or 16 Tablespoons

1 glass = 200 ml

30 gr = 1 slice of processed cheese or lunchmeat

How to Estimate Your Portion Size

Meat Ninety (90) gr of meat are about the size and thickness of a deck of playing cards	
Fruit A medium apple or peach is about the size of a tennis ball	
Grains One cup of rice or pasta is about the size of your fist	
Cheese Thirty (30) gr of cheese is about the size of four dice	

Three-Day Food Record Checklist

Beverages	What kind of milk? Homo, 2%, 1%, skim, other. Was it fruit juice or fruit beverage or drink?
Breads	Did you spread on butter or margarine?
Cereal	Did you add milk? Did you add sugar or fruit?
Dairy	What brand or kind of yogurt? What brand or kind of cheese?
Vegetables	Was it raw or cooked? Was it fresh, frozen or canned? Did you add any butter, margarine or sauce?
Fruit	Was it a small, medium or large fruit? Was it fresh, frozen or canned?
Grains	Did you add any butter, margarine, peanut butter, jam or honey? Was it a half or whole sandwich? Was it a small or large muffin or bagel?
Fish	Was your canned fish packed in water or oil How did you cook your fish?
Meats	How did you cook your meat? What kind of cut was it e.g. chicken leg or chicken breast?
Soups	Was your soup prepared with milk, water or cream?
Restaurants	What restaurant was it?
Packaged food	What brand was it?

SAMPLE MENU – 24 HRS

Day 1: Tuesday, May 14, 2015				
Time of Meal or Snack	**Type of Food or Beverage Offered**	**Amount Eaten**	**Method of Preparation or Brand**	**Comments** (e.g. amount of food served, too tired to eat)
Breakfast	Cereal	½ cup	Honey Nut Cheerios	
	Milk 2%	½ cup		On cereal
	Banana	½ med		
AM Snack	Animal Crackers	10	Christie	
	Apple juice	120 gr	Allen's pure apple juice-canned	
Lunch	Grilled cheese sandwich			
	Whole wheat bread	1 slice	Dempsters	No crusts
	Cheese slice	1 slice	Kraft slices	
	Butter on bread	1 Tbsp		
	Yogurt – strawberry	75 ml	Mini-go	
	Milk	½ cup	2%	
PM Snack	Granola bar	1 bar – 35 g	Quaker Chewy, Trail Mix – tropical fruit	Ate half of it
Dinner	Chicken fingers	1 ½	President's Choice	
	French fries	10	McCain regular	
	Honey	2 Tbsp		For dipping
	Ketchup	2 Tbsp	Heinz	
	Carrots	½ medium	Raw, cut in sticks	
	Milk	½ cup	2%	
Evening Snack	Ice cream	1 cup	Chocolate Nestle	

Was this day's intake considered: [ ] Poor [X] Average [ ] Very Good

24 HRS

Date:				
Time of Meal or Snack	**Type of Food or Beverage Offered**	**Amount Eaten**	**Method of Preparation or Brand**	**Comments** (e.g. amount of food served, too tired to eat)
Breakfast				
AM Snack				
Lunch				
PM Snack				
Dinner				
Evening Snack				

Was this day's intake considered: [ ] Poor [ ] Average [ ] Very Good

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry page 3 , Trial registration section
	2b	All items from the World Health Organization Trial Registration Data Set Not applicable
Protocol version	3	Date and version identifier Not applicable
Funding	4	Sources and types of financial, material, and other support Page 14, Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors , Page 1 , Authors , Authors affiliation and Page 14 Authors contributions
	5b	Name and contact information for the trial sponsor Page 14, Funding
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities Page 14, Funding
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) Not applicable
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention Page 4, Background
	6b	Explanation for choice of comparators Page 4, Background
Objectives	7	Specific objectives or hypotheses Page 7, Aim and Hypothesis

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) Page 7, Method/Design
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained Page 7, Method/Design
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) Page 8,Inclusin and exclusion criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered Page 10 , Randomization and Study schedule
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) Page 11 , Randomization and Study schedule , first paragraph in the page
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Page 10 , Randomization and Study schedule , second paragraph
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Page 10 and 11 , Randomization and Study schedule
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended Page 7,Outcomes measures
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) Attachment: Table 1. MiGDM Study Overview , and Diagram 1; study overview
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations page 11, Sample size and Statistical Analysis

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Page 9, Study plan
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions) Page 10 and 11 , Randomization and Study schedule
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned Page 10 and 11 , Randomization and Study schedule
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Page 10 and 11 , Randomization and Study schedule
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how Page 10 and 11 , Randomization and Study schedule
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Page 10 and 11 , Randomization and Study schedule
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol Table 1. MiGDM Study Overview **and data collection sheet**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols Page 11 second paragraph
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol Informed consent ; Confidentially section 16

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol page 11, Sample size and Statistical Analysis
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) page 11, Sample size and Statistical Analysis
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) Page 11 , Randomization and Study schedule , second paragraph in the page and page 11, Sample size and Statistical Analysis
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed Page 12, Data monitoring
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial Page 12, Data monitoring
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct IRB Research proposal under section Safety reporting:
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor IRB Research proposal under section Quality assurance and Reporting
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval Page 13, Ethics approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) IRB Research proposal under section Reporting:
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) Page 9, Study plan first paragraph

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Consent form section 23,24,25
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial Consent form section 16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site Page 13 and 14 Declarations and Competing interests :
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators Consent form section 16 confidentiality
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation Consent form section 14, 15
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions Page 14 Publication and dissemination plan
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 14 Authors' contributions
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates IRB 400 Informed consent form attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable Relevant information are included in IRB 400 Informed consent form

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.