PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Ibrahim, Ibrahim; Abdullahi, Hala; Fagier, Yassin; Ortashi, Osman; Terrangera, Annalisa; Okunoye, Gbemisola

VERSION 1 – REVIEW

REVIEWER	McCowan, Lesley University of Auckland
REVIEW RETURNED	03-Aug-2021

GENERAL COMMENTS	This is an important RCT that aims to reduce GDM in a population from Qatar with a high prevalence of GDM. There are some issues that I think need clarification and /or more detail provided. The definition of the primary outcome (GDM) is not specified in the protocol (or in the trial registration document). From reading reference 3 it appears that WHO (IADPSG) criteria are used in Qatar but this should be specified and referenced. Secondary outcome-pregnancy weight gain is not defined. Is it total weight gain, excessive weight gain, weight gain /week etc? I can't see any description of measurements of pregnancy weight in the study schedule. Is the measure of weight gain adjusted for gestation? This should be included in methods. What definitions are being used for hypertension in pregnancy? Will preeclampsia be separated from gestational hypertension- references needed. Other secondary outcomes for the baby also need to be defined and or referenced for example- what birthweight centiles are being used, similarly for shoulder dystocia- presumably this is from clinical record. Also how is RDS defined, hypoglycaemia definition. Polyhydramnios is included as a secondary outcome and exclusion- presume exclusion is polyhydramnios at randomisation- please clarify. Sample size and power- the study has 80% power to detect a 40% reduction in GDM which is ambitious but in keeping with the effect size in in the Cochrane review. The type of t-test is not specified- presumably one sided? Please clarify.

REVIEWER	Hong, Jesrine University of Malaya, Obstetrics & Gynaecology
REVIEW RETURNED	06-Oct-2021

GENERAL COMMENTS	This is a study protocol for a RCT evaluating the effect of antenatal dietary myoinositol supplementation on incidence of GDM . Below are my comments: Title: I suggest some minor changes to the title to be more concise " The effect of antenatal dietary myo-inositol supplementation on the incidence of GDM (and fetal outcome): A double-blind randomized controlled trial. I am not convinced that fetal outcome should be included in the study title as it is the secondary outcome and the study is not powered to test this. From what I gathered from Introduction, the study focus on reducing incidence of GDM in Qatari women. Abstract: Introduction can be more concise. Methods and analysis: Describe more on the study protocol rather than the sample size calculation - this may be more appropriate in the main text. Page 3 line 3-6: Author mentioned study aim to develop a predictive model of response to myoinositol supplementation in pregnancy - this differs from study hypothesis and objective Ethics and dissemination: Please include ethics approval number/ID and date. Trial registration date. Whether this is a prospectively registered trial - has the trial started? Limitations: originality of study, as already 5 similar RCTs and systematic reviews done with significant result, albeit lower sample size. Introduction: Author mentioned there were previous RCTs/ systematic reviews/ meta-analysis on use of myoinositol in pregnancy with significant result. This study is a similar study design as previous RCTs - single centre, on Qatari population (which is likely not generalizable to other population - previous studies on Caucasian population as author mentioned) and looking at reduction of GDM. How will this study's result add to existing published data? Outcomes: Primary outcome: Define GDM in author's setting. beneficial to add pre-eclampsia as well Inclusion criteria: no.4 can be removed, since exclusion criteria has been listed Exclusion: 1. More suitable to put as Type 2 DM or pre existing DM beneficial to add known allergy to myoinositol? 7. is redundant as inclusion no.3 has mentioned May be better to add known fetal abnormalities - since author is looking at neonatal outcome as well. Randomization methods need to be more elaborated. intervention packs are given by pharmacist not involved in the study to maintain blinding of investigator. however, participants need to come monthly to get supply by research nurse - are they blinded?

	as mentioned pharmacist is the only sole healthcare provider have access to randomization data. 2g of myoinositol - how many tablets are they - are they similar in quantity as placebo? Compliance: what is the rate considered as compliant? and effective. What is the intervention period? - Page 11 Line 3-4 mentioned at least 12 weeks. WOmen will be advised to continue using the trial packs - so how about those not continuing? will this affect the outcomes Sample size: Kindly have a check again. from the explanation, each arm after rounding up should be 325 at least. Based on the author guide, discussion is not required in protocols

REVIEWER	Hegerty, Christopher Queensland Health, Warwick Hospital
REVIEW RETURNED	13-Oct-2021

GENERAL COMMENTS	This looks like a good and worthwhile trial. I do have a few minor thoughts. Regarding the primary and secondary outcomes. As the main aim is to decrease the diagnosis of GDM something to consider is the reason for diagnosis. If it is to improve outcomes, then it is important to measure outcomes to see if the 'treatment' has improved or worsened outcomes. More on secondary outcomes below. If an aim is early recognition of women who are more likely to later develop diabetes in order to allow closer monitoring in their pregnancy and also give them a 'heads up' and allow lifestyle change post pregnancy, this raises a different question regarding decreasing the diagnosis. Unfortunately the study is unlikely to have the power to detect changes in most of the secondary outcomes, in particular shoulder dystocia associated injuries, small for gestational age babies and hypertension. I mention these because shoulder dystocia and hypertension are two of the three outcomes which meta-analyses seem to show are changed by GDM treatment, and SGA is an important outcome when we are undertaking treatment primarily aimed at decreasing the intrauterine growth of babies. With regard to shoulder dystocia, although many studies include this as an outcome in my opinion it is meaningless in itself and the important thing is harm to babies as a result. I am unclear from your description whether you are looking at 'shoulder associated birth injuries' or at 'shoulder dystocia' without injury plus 'shouder dystocia with injury' combined. Unfortunately there will not be enough power to find a difference. It would be wonderful if you could increase your power by increasing your numbers or by collaborating with another group, although I realize this may not be possible. On this topic, I was a bit alarmed at the plan to stop the trial if a review at 50% enrollment finds a difference in your primary outcome. This would effectively eliminate the chance of finding any result in any of the other outcomes.

	Regarding neonatal hypoglycaemia, I was unclear when after delivery unblinding would occur. It would have to be at least a couple of days to allow a meaningful assessment of hypoglycaemia. Also, the assessment of neonatal hypoglycaemia in studies is as you know bedevilled by ascertainment bias and hospital protocols etc.. Will you be using a protocol which is applied equally to all babies entered in the trial, not just those of mothers diagnosed with GDM? An issue you might consider discussing is placental passage, or otherwise, of myo inositol. The histories of metformin and glyburide use are interesting in this regard. Some would say that if we are treating mothers in pregnancy with a substance with any placental passage then we have an obligation to follow up the children. I look forward to the results of your study.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Lesley McCowan, University of Auckland

Comments to the Author:
This is an important RCT that aims to reduce GDM in a population from Qatar with a high prevalence of GDM.
There are some issues that I think need clarification and /or more detail provided.
The definition of the primary outcome (GDM) is not specified in the protocol (or in the trial registration document). From reading reference 3 it appears that WHO (IADPSG) criteria are used in Qatar but this should be specified and referenced.
GDM definition included and referenced
Secondary outcome-pregnancy weight gain is not defined. Is it total weight gain, excessive weight gain, weight gain /week etc? I can't see any description of measurements of pregnancy weight in the study schedule. Is the measure of weight gain adjusted for gestation?
This should be included in methods.
Section on gestational weight gain is added to the method (We use the last recorded weight at the time of delivery to calculate total gestational weight gain corrected for gestational age at delivery.)
What definitions are being used for hypertension in pregnancy? Will preeclampsia be separated from gestational hypertension- references needed.
Will use Hypertension definition based on the American College of Obstetrics and Gynecology (included and referenced
Hypertensive disorders of pregnancy which includes gestational hypertension and pre-eclampsia will be subdivided in the analysis

Other secondary outcomes for the baby also need to be defined and or referenced for example- what birthweight centiles are being used, similarly for shoulder dystocia- presumably this is from clinical record.
Also how is RDS defined, hypoglycaemia definition. Definitions of secondary outcomes measures included in the revised manuscript
Polyhydramnios is included as a secondary outcome and exclusion- presume exclusion is polyhydramnios at randomisation- please clarify.
Those who have evidence of polyhydramnios at randomization will be excluded however polyhydramnios is an outcome measure.

Sample size and power- the study has 80% power to detect a 40% reduction in GDM which is ambitious but in keeping with the effect size in in the Cochrane review.
We agree and this is in keeping with the effect size in in published literature.

The type of t-test is not specified- presumably one sided?
Please clarify.two sided t-test will be used

Reviewer: 2
Dr. Jesrine Hong, University of Malaya

Comments to the Author:
This is a study protocol for a RCT evaluating the effect of antenatal dietary myoinositol supplementation on incidence of GDM .

Below are my comments:
Title: I suggest some minor changes to the title to be more concise "The effect of antenatal dietary myo-inositol supplementation on the incidence of GDM (and fetal outcome): A double-blind randomized controlled trial.See Please see our earlier esponse to editor and title changed as suggested

I am not convinced that fetal outcome should be included in the study title as it is the secondary outcome and the study is not powered to test this.
From what I gathered from Introduction, the study focus on reducing incidence of GDM in Qatari women.
See our response to editor
Abstract: Introduction can be more concise.
Methods and analysis: Describe more on the study protocol rather than the sample size calculation - this may be more appropriate in the main text.
Page 3 line 3-6: Author mentioned study aim to develop a predictive model of response to myoinositol supplementation in pregnancy - this differs from study hypothesis and objective
Thank you, Revised as suggested
Ethics and dissemination: Please include ethics approval number/ID and date. Trial registration date. Whether this is a prospectively registered trial - has the trial started? Thank you, Revised as suggested
Limitations: originality of study, as already 5 similar RCTs and systematic reviews done with significant result, albeit lower sample size.
Strengths and limitation bullet points revised and updated see response to editor
Introduction: Author mentioned there were previous RCTs/ systematic reviews/ meta-analysis on use of myoinositol in pregnancy with significant result. This study is a similar study design as previous RCTs - single centre, on Qatari population (which is likely not generalizable to other population - previous studies on Caucasian population as author mentioned) and looking at reduction of GDM. How will this study's result add to existing published data?
Introduction revised
Outcomes: Primary outcome: Define GDM in author's setting.
beneficial to add pre-eclampsia as well
See response to reviewer 1 and definition of GDM , hypertension and pre-eclampsia included in the revised version
Inclusion criteria: no.4 can be removed, since exclusion criteria has been listed
Revised as suggested
Exclusion: 1. More suitable to put as Type 2 DM or pre existing DM
The word pre-existing is added

beneficial to add known allergy to myoinositol?
Revised as suggested
7. is redundant as inclusion no.3 has mentioned
May be better to add known fetal abnormalities - since author is looking at neonatal outcome as well.
Revised as suggested
Randomization methods need to be more elaborated. intervention packs are given by pharmacist not involved in the study to maintain blinding of investigator. however, participants need to come monthly to get supply by research nurse - are they blinded? as mentioned pharmacist is the only sole healthcare provider have access to randomization data.
Research nurse is blinded, a sentence is added to make this clearer
2g of myoinositol - how many tablets are they - are they similar in quantity as placebo? It is in a form of sachet and not tablet, please read the revised version which is more clearer

Compliance: what is the rate considered as compliant? and effective.
Studies suggest that people who are prescribed to take home medications usually take about 50% of their prescribed doses. For the purpose of this study, we consider at least 80% completion of the trial pack as compliant and this will form the basis of our inference with regards to effectiveness. We believe this level of compliance is achievable with the study structure and follow up plan.
What is the intervention period? - Page 11 Line 3-4 mentioned at least 12 weeks. WOmen will be advised to continue using the trial packs - so how about those not continuing? will this affect the outcomes
The data will be analyzed based on intention to treat and its effects on outcomes depends on the number of patients who didn't continue to take it.

Sample size: Kindly have a check again. from the explanation, each arm after rounding up should be 325 at least.Thank you for pointing this out , we have ran the numbers again through our biostatistician and the numbers are correct
Based on the author guide, discussion is not required in protocols
Discussion is removed
Reviewer: 3
Dr. Christopher Hegerty, Queensland Health, Queensland Government Department of Health and Ageing
Comments to the Author:
This looks like a good and worthwhile trial.
I do have a few minor thoughts.
Regarding the primary and secondary outcomes. As the main aim is to decrease the diagnosis of GDM something to consider is the reason for diagnosis. If it is to improve outcomes, then it is important to measure outcomes to see if the 'treatment' has improved or worsened outcomes. More on secondary outcomes below.
If an aim is early recognition of women who are more likely to later develop diabetes in order to allow closer monitoring in their pregnancy and also give them a 'heads up' and allow lifestyle change post pregnancy, this raises a different question regarding decreasing the diagnosis.
Unfortunately the study is unlikely to have the power to detect changes in most of the secondary outcomes, in particular shoulder dystocia associated injuries, small for gestational age babies and hypertension.
I mention these because shoulder dystocia and hypertension are two of the three outcomes which meta-analyses seem to show are changed by GDM treatment, and SGA is an important outcome when we are undertaking treatment primarily aimed at decreasing the intrauterine growth of babies.
Thank you for comments, which we are in agreement with and now included in the limitation of the study bullet points section
With regard to shoulder dystocia, although many studies include this as an outcome in my opinion it is meaningless in itself and the important thing is harm to babies as a result.

I am unclear from your description whether you are looking at 'shoulder associated birth injuries' or at 'shoulder dystocia' without injury plus 'shouder dystocia with injury'
The definition of shoulder Dystocia encompasses neonates with or without birth injuries combined. Unfortunately there will not be enough power to find a difference.
It would be wonderful if you could increase your power by increasing your numbers or by collaborating with another group, although I realize this may not be possible.
Thanks, notes see above
On this topic, I was a bit alarmed at the plan to stop the trial if a review at 50% enrollment finds a difference in your primary outcome. This would effectively eliminate the chance of finding any result in any of the other outcomes.
We are in total agreement; however, this has been enforced on us by the regulatory authorities (MOPH)
Regarding neonatal hypoglycaemia, I was unclear when after delivery unblinding would occur. It would have to be at least a couple of days to allow a meaningful assessment of hypoglycaemia. Also, the assessment of neonatal hypoglycaemia in studies is as you know bedevilled by ascertainment bias and hospital protocols etc.. Will you be using a protocol which is applied equally to all babies entered in the trial, not just those of mothers diagnosed with GDM?
The diagnosis of GDM will not be blinded.
We do agree with your comment and this is why we used a very objective definition of hypoglycaemia, with neonates requiring intravenous glucose administration;
An issue you might consider discussing is placental passage, or otherwise, of myo inositol. The histories of metformin and glyburide use are interesting in this regard.
Some would say that if we are treating mothers in pregnancy with a substance with any placental passage then we have an obligation to follow up the children.
This is a very valid point; however, we do not have the means to measure Myo-inositol in cord blood
I look forward to the results of your study.

VERSION 2 – REVIEW

REVIEWER	McCowan, Lesley University of Auckland
REVIEW RETURNED	22-Nov-2021

GENERAL COMMENTS	Your revisions have resulted in a marked improvement in your protocol .I have a few further minor points. Regarding pregnancy weight gain- self reported pre-pregnancy weight is likely to be unreliable. In addition you can use early pregnancy measured weight to determine pregnancy weight gain. For the analysis of weight gain you will need to adjust for gestation at recruitment as well as gestation at last weight measurement. Suggest you reference the growth charts to diagnose SGA and LGA so others can reproduce in future. Regarding hypoglycaemia-suggest you include the numerical values and timing for diagnosis in the protocol. is glucose gel not used for treatment? If it is include in the treatment. Which dietary questionnaires are being used- reference so that your study is reproducible. What lifestyle data are you collecting- reference this . Are you collecting information about mental health such as EPDS? This would probably be useful if feasible.

REVIEWER	Hong, Jesrine University of Malaya, Obstetrics & Gynaecology
REVIEW RETURNED	23-Nov-2021

GENERAL COMMENTS	Thank you authors for the response to most of the reviewers'/ editor's comment. The study protocol has improved after the revision.

REVIEWER	Hegerty, Christopher Queensland Health, Warwick Hospital
REVIEW RETURNED	25-Nov-2021

GENERAL COMMENTS	It looks like a good and interesting trial. There is no problem with the primary outcome, however I wonder if a weakness in interpreting secondary outcomes is inherent in the structure. If myo-inositol for example is successful in changing the number of women with a positive OGTT at 24-28 weeks from 20% t0 10% for example this is a good outcome for the primary outcome. From then on however won't the GDM groups be different? The group with a positive OGTT despite taking myo-inositol will presumably be more insulin resistant than the placebo GDM group and so comparison of secondary outcomes may be affected by this. If the myo-inositol group has better outcomes this will probably still be a valid result, but if outcomes are worse it may be difficult to know what to make of it. These are just my thoughts and the trial should go ahead as planned.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Lesley McCowan, University of Auckland

Comments to the Author:

Your revisions have resulted in a marked improvement in your protocol .I have a few further minor points.

Regarding pregnancy weight gain- self reported pre-pregnancy weight is likely to be unreliable. In addition you can use early pregnancy measured weight to determine pregnancy weight gain. For the analysis of weight gain you will need to adjust for gestation at recruitment as well as gestation at last weight measurement.

There is a linked Electronic medical records system between the primary health care (PHCC) and the study site such that pre-pregnancy records and laboratory results are accessible. This provides a reliable source for measured pre-pregnancy weight to validate self-reported weight. This is the current

routine practice. In the absence of a validated pre-pregnancy weight, the measured weight at first hospital visit will be used and appropriate adjustment for gestation at recruitment and end of study.

Suggest you reference the growth charts to diagnose SGA and LGA so others can reproduce in future.

The study site currently uses an Electronic medical records system (cerner) with a built in WHO Growth charts which calculate the percentile for the birth weight according to Gestational age at birth and gender.

Regarding hypoglycaemia-suggest you include the numerical values and timing for diagnosis in the protocol. is glucose gel not used for treatment? If it is include in the treatment.

Definition of hypoglycemia and Values added to the protocol.

In our protocol: 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

Which dietary questionnaires are being used- reference so that your study is reproducible.

What lifestyle data are you collecting- reference this.

We use standard questionnaires that they have been adapted for our population, they are added as supplementary files.

Are you collecting information about mental health such as EPDS?

This would probably be useful if feasible.

The EPDS is part of standard antenatal screening for all patients booked at the study site and no additional mental health screening is being collected during the study. The EPDS is built in the Electronic medical records system (Cerner)

Reviewer: 2

Dr. Jesrine Hong, University of Malaya

Comments to the Author:

Thank you authors for the response to most of the reviewers'/ editor's comment. The study protocol has improved after the revision.

Reviewer: 3

Dr. Christopher Hegerty, Queensland Health, Queensland Government Department of Health and Ageing

Comments to the Author:

It looks like a good and interesting trial.

There is no problem with the primary outcome, however I wonder if a weakness in interpreting secondary outcomes is inherent in the structure.

If myo-inositol for example is successful in changing the number of women with a positive OGTT at 24-28 weeks from 20% t0 10% for example this is a good outcome for the primary outcome.

From then on however won't the GDM groups be different? The group with a positive OGTT despite taking myo-inositol will presumably be more insulin resistant than the placebo GDM group and so comparison of secondary outcomes may be affected by this. If the myo-inositol group has better outcomes this will probably still be a valid result, but if outcomes are worse it may be difficult to know what to make of it.

These are just my thoughts and the trial should go ahead as planned.

These are very fascinating thoughts and similar to some of our theoretical curiosity.These thoughts strengthen the need to undertake this trial and the outcome of the trial will shed more light on which of these lines of theoretical possibilities are closer to the actual effect.