PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and acceptability of myo-inositol nutritional supplement in the prevention of gestational diabetes (EMmY): a protocol for a randomised, placebo-controlled, double-blind pilot trial
AUTHORS	Amaefule, Chiamaka; Drymoussi, Zoe; Dodds, Julie; Sweeney, Lorna; Pizzo, Elena; Daru, Jahnavi; Robson, John; Poston, Lucilla; Khalil, Asma; Myers, Jenny; Harden, Angela; Hitman, Graham; Khan, Khalid; Zamora, Javier; Huda, Mohammed; Thangaratinam, Shakila

VERSION 1 – REVIEW

REVIEWER	Rosario D'Anna University Hospital of Messina, Italy
REVIEW RETURNED	18-Apr-2018

GENERAL COMMENTS	This will be a multi-centre, placebo controlled, double-blind pilot randomized study which aims to assess the acceptability prior to undertaking a full-scale trial on myo-inositol supplementation (2 g of myo-inositol powder twice daily from 12-16 weeks gestation until delivery) to prevent gestational diabetes in high risk pregnancies. The Authors claim that they will assess the maternal, fetal and neonatal outcomes. The objectives are ambitious and the Authors should address the following: _In the introduction, line 42, the Authors consider the existing randomized trial on myo-inositol of poor quality and with small samples size, but in the main RCT 220 women were involved for each study, certainly more than 200 women who will randomized in this study. Please clarify it. _ In the study participants section, the risk factors considered have different impact in determining gestational diabetes. How the Authors may match them adequately? _ In the outcomes section the Authors claim that secondary outcomes will be maternal, fetal and neonatal outcomes. Please include a sample size calculation to justify that this study is adequately powered to show a difference in these outcomes. _ In the data analysis section the Authors contradict themselves admitting that they “cannot reliably assess the effect of the intervention on outcomes, given the pilot sample size”. Probably is better to admit that there is only a primary outcome in this study

	about the acceptability of the protocol _ In the Discussion section at line 8 the Authors reported that in previous RCT studies GDM rate decreased of about 60%, thus 1500 women are needed to demonstrate that myo-inositol supplementation prevents the incidence of GDM in high risk women. This statement is not supported by a sample size calculation that probably could reveal that for an expected reduction of 60% in GDM rate 200 women are enough; instead 1500 women are probably needed to show a difference in maternal, fetal and neonatal outcomes. In conclusion, carrying out a study only on the acceptability, safety and women adherence to myo-inositol supplementation is a missed opportunity because a large multicentre randomized, double-blind, controlled trial to confirm the results obtained in the previous trials would be necessary. The protocol is well done, but in the previous single studies and meta-analysis it has been never reported an adverse event following myo-inositol supplementation. Thus, should be strongly encouraged a large multicentre trial supported by a sample size calculation which consider the low incidence of GDM clinical complications. Reducing GDM rate is an important result, but obstetricians are more interested whether GDM complications such as macrosomia, preterm birth and gestational hypertension may be reduced.

REVIEWER	Basilio Pintaudi Diabetes Unit, Niguarda Hospital, Milan, Italy
REVIEW RETURNED	07-Jun-2018

GENERAL COMMENTS	This is the protocol of a pilot trial the Authors are going to perform during this and next year. The trial fosuses on the use of myo-inositol in preventing gestational diabetes. It will evaluate trial processes, assess acceptability to mothers and obtain preliminary estimates of effects and costs. The paper is well written and it addresses a very important topic.

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments	**Authors' Response**
Reviewer #1	
The Authors claim that they will assess the maternal, fetal and neonatal outcomes. The objectives are ambitious and the Authors should address the following:	

a) In the introduction, line 42, the Authors consider the existing randomized trial on myo-inositol of poor quality and with small samples size, but in the main RCT 220 women were involved for each study, certainly more than 200 women who will randomized in this study. Please clarify it.

Yes, we agree with the reviewer. However, our proposed protocol is for a pilot trial designed to assess the feasibility of conducting a future definitive large scale trial. For this reason, a sample size of 200 women is appropriate.

We expect some of the women recruited with a previous history of gestational diabetes to have undiagnosed type 2 diabetes, who will be identified in the OGTT test in the first trimester. Hence we will plan to recruit 220 to obtain the 200 eligible women.

We have described the above in the manuscript. See the section titled *"sample size calculation, page 10, Line 4 – 18"* It reads as follows; *"We expect that 1500 women will be booked for antenatal care each month at the participating hospitals, and at least 300 of those will be eligible. Assuming 1000 eligible women were approached, we expect about 25% (250/1000) to be consented. We expect that 20% (50) of women who consent to the study will have a previous history of gestational diabetes. These women will undergo an early HbA1C and/ or an OGTT test before 16 weeks gestational age to rule out any potentially pre-existing but undiagnosed type 2 diabetes or early pre-gestational diabetes. Any of these women with abnormal HbA1C (> 48mmol/l) and/ or OGTT (fasting blood glucose ≥ 5.6mmol/l and/or a 2-hour 75g blood glucose level ≥7.8 mmol/l) results and hence a diagnosis of early gestational diabetes will be excluded from the study. This will result in 200 women being randomised to either the myo-inositol or placebo arm".*

b) In the study participants section, the risk factors considered have different impact in

We agree that the risk factors may affect gestational diabetes. But being a pilot trial, we are not powered to assess the impact of myo-

determining gestational diabetes. How may the Authors match them adequately?	inositol on gestational diabetes. However, the pilot trial enables us to assess the feasibility of recruiting and randomising an adequate number of high risk women to the trial. Therefore, only feasibility outcomes will be reported using proportions and descriptive statistics.
c) In the outcomes section the Authors claim that secondary outcomes will be maternal, fetal and neonatal outcomes. Please include a sample size calculation to justify that this study is adequately powered to show a difference in these outcomes	Being a pilot trial, a sample size of 200 is adequate to assess feasibility outcomes but inadequate to show a difference in clinical outcomes between groups. However, we will be collecting these outcomes in this pilot trial to inform the future definitive full scale trial on the feasibility of collecting and assessing these outcomes in our population groups. The rationale for a pilot trial in this regard has been described in detail in the following paper (Eldridge, S.M., Chan, C.L., Campbell, M.J., Bond, C.M., Hopewell, S., Thabane, L. and Lancaster, G.A., 2016. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *Pilot and feasibility studies*, *2*(1), p.64.
d) In the data analysis section the Authors contradict themselves admitting that they "cannot reliably assess the effect of the intervention on outcomes, given the pilot sample size". Probably is better to admit that there is only a primary outcome in this study about the acceptability of the protocol	We are proposing a pilot trial and our primary outcome is on the rate of recruitment and randomisation of eligible participants to this trial. See the section titled *"Primary and secondary outcome measures and outcome assessment", "Line 1 – 3".* It reads as follows; "*The primary outcomes are the proportion of eligible, consented, and randomised participants. The secondary outcomes include the acceptability of the study and the intervention as well as the proportion of outcome measures obtained in the trial".*
e)In the Discussion section at line 8 the Authors	We have removed this sentence, as our focus is

reported that in previous RCT studies GDM rate decreased of about 60%, thus 1500 women are needed to demonstrate that myo-inositol supplementation prevents the incidence of GDM in high risk women. This statement is not supported by a sample size calculation that probably could reveal that for an expected reduction of 60% in GDM rate 200 women are enough; instead 1500 women are probably needed to show a difference in maternal, fetal and neonatal outcomes.	on the pilot study. The sample size estimation will be informed by the pilot data.

Reviewer #2

This is the protocol of a pilot trial the Authors are going to perform during this and next year. The trial focuses on the use of myo-inositol in preventing gestational diabetes. It will evaluate trial processes, assess acceptability to mothers and obtain preliminary estimates of effects and costs. The paper is well written and it addresses a very important topic.	Thank you for the positive comment.

VERSION 2 – REVIEW

REVIEWER	Rosario D'ANNA Department of Human Pathology. Universiti of Messina, Italy
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	The Authors insist on doing their pilot study. I hope that after this first step, a large, prospective, randomized trial on the efficacy of myo-inositol in preventing GDM could be performed.