PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pregnancy Outcomes: Effects of Metformin (POEM) study: a protocol for a long-term, multicentre, open-label, randomised controlled trial in gestational diabetes mellitus
AUTHORS	van Hoorn, Eline; van Dijk, Peter; Prins, Jelmer; Lutgers, Helen; Hoogenberg, Klaas; Erwich, Jan Jaap H.M.; Kooy, Adriaan

VERSION 1 – REVIEW

REVIEWER	Balani, Jyoti Epsom & St Helier University NHS Hospital, Diabetes
REVIEW RETURNED	05-Nov-2021

GENERAL COMMENTS	General comments: This is an interesting study which will provide high quality long term data on mother and offspring outcomes after metformin treatment in pregnancy. The composite primary outcome includes instrumental delivery and Caesarean delivery and I note that obstetric care is to be performed according to the usual practice of the participating centre (page 9/85). This might introduce some confounding if centres have different practices concerning timing of delivery, indications for Caesarean section and induction of labour. There is great interest in the long term effects on the offspring and in particular, fat distribution. MiG TOFU has reported body composition outcomes at 2 years and more recently (BMJ Open Diab Res Care 2018 6 (1) at 7-9 years. This study offers an opportunity to provide further information and I would urge the investigators to consider anthropometric measures in the children as well as overall body weight (Tables 3, 4). Specific Comments: Page 9/85 Line 42 In both groups, insulin rescue will be started at the discretion of the internist if the allocated treatment is not sufficient to achieve the target values of glycaemic control at least more than two times (FPG ≤ 5.3 mmol/l and PG < 7.8 mmol/l). According to normal standard of care, the internist may choose to commence insulin rescue only temporarily if there is a reversible factor for dysregulation (medication/food/stress/fever). Reviewer Comments- Please specify- “High target values at least more than two times- in what time frame, at least more than two times a week or a month or just two times in the whole of pregnancy? If target values are not met more than two times in Phase B or C (FPG ≤ 7.0 mmol/l or PG ≤10.0 mmol/l), anti-hyperglycaemic

	treatment will be started (or extended) according to national guidelines for the treatment of T2DM Reviewer Comment- Please specify- “High target values at least more than two times in phase B or C- In what time frame- a week, a month, or 6 months Please provide details of frequency of self monitoring of blood glucose in phase B and phase C Page 45/85 Line 19/20 Change in body composition- Impedance Reviewer comment: Please provide details of procedure used for measuring body composition, whether it is safe in pregnancy and whether body water redistribution in pregnancy will affect the measurements of body composition during the different trimesters. Page 55/85- Line 18 Exclusion criteria Reviewer comment -- Add Hyperemesis Gravidarum Page 12/85 line 32 Drug safety Metformin should be stopped if evidence of intrauterine growth restriction. In the "Metformin in obese non-diabetic pregnant women" trial (NEJM 2016 374:434-443), for example, this was defined as estimated fetal weight lower than the fifth percentile and abnormal fetal Doppler studies. Page 60/85 Line35 Self monitoring of blood glucose in phase B and phase C Reviewer comments- Please give details of frequency of self monitoring of blood glucose in phase B and phase C How many 7 point blood glucose profiles in phase B and phase C- what frequency- please mention details Page 68/75 Line 15& 16 Reviewer comments -Potential risks of using Metformin if eGFR between 30 and 45 in pregnancy? Metformin should be avoided avoided or stopped if eGFR falls below 45 in pregnancy. Preferable additions: Inclusion of Birth centile along with birth weight Page 7/85 line 53, page 54/85 l11: Hindus are not an ethnic group; they are followers of the Hindu religion. The term women of South Asian descent includes women of any religion or none who are at increased risk. I would like to acknowledge Dr Steve Hyer, Consultant Endocrinologist at Epsom & St Helier Hospital NHS Trust, Carshalton, Surrey, UK for his contribution in the review of this article.

REVIEWER	Yeung, Roseanne University of Alberta
REVIEW RETURNED	08-Nov-2021

GENERAL COMMENTS	Thank you for your work in this area. A few considerations: - there is increasing data to suggest differing GDM phenotypes with resultant implications for treatment (ie IFG= increased insulin resistance, IGT= more insulin deficient) (ref DOI:

	10.1111/eci.13628; DOI: 10.1111/dme.14173) --> perhaps it is worth adding stratified analyses to consider those with IFG vs IGT as per OGTT in response where IFT would be hypothesized to have more benefit In regard to safety monitoring--sexual endocrine disruption has not been brought up much in human studies/implications, but given your long term follow up--consider impact on sexual development/sexual preference in offspring; https://doi.org/10.1016/j.chemosphere.2015.03.060

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

General comments

This is an interesting study which will provide high quality long term data on mother and offspring outcomes after metformin treatment in pregnancy. The composite primary outcome includes instrumental delivery and Caesarean delivery and I note that obstetric care is to be performed according to the usual practice of the participating centre (page 9/85). This might introduce some confounding if centres have different practices concerning timing of delivery, indications for Caesarean section and induction of labour. There is great interest in the long term effects on the offspring and in particular, fat distribution. MiG TOFU has reported body composition outcomes at 2 years and more recently (BMJ Open Diab Res Care 2018 6 (1) at 7-9 years. This study offers an opportunity to provide further information and I would urge the investigators to consider anthropometric measures in the children as well as overall body weight (Tables 3, 4).
First of all, we want to thank the reviewer for the willingness to review our paper, and for the kind compliments concerning the importance of this trial. We agree that because care is performed according to usual practice in the participating centre, some confounding could be introduced. This is partially controlled by extensive population characterization, randomization being performed per site, and the availability of a national (Dutch) GDM obstetric guideline, to which the participating centers adhere. Additionally, the aim of this study is to evaluate the role of metformin in addition to usual care in real-life practice.

We agree that the long-term effects are of particular interest in the GDM population receiving metformin. We look forward to additional data from the MiG trial, and hope that the POEM study provides important additional information on the long-term effects of in utero metformin exposure on the offspring in a Dutch GDM population. We will definitely consider other anthropometric measures in children at certain time points in the long term follow up.

Specific comments

Page 9/85 Line 42. In both groups, insulin rescue will be started at the discretion of the internist if the allocated treatment is not sufficient to achieve the target values of glycaemic control at least more than two times (FPG ≤ 5.3 mmol/l and PG < 7.8 mmol/l). According to normal standard of care, the internist may choose to commence insulin rescue only temporarily if there is a reversible factor for dysregulation (medication/food/stress/fever).

1. Please specify- “High target values at least more than two times- in what time frame, at least more than two times a week or a month or just two times in the whole of pregnancy?
Thank you for this comment. Target glycaemic control is defined by the NICE guidelines as a fasting glucose concentration < 5.3 mmol/L and 1-hour postprandial < 7.8 mmol/L. The aim of this study is to

evaluate the role of metformin on top of standard care for GDM. We therefore chose to leave standard of care up the discretion of the treating internist.

In accordance with Dutch guidelines, standard care consists of insulin rescue, if glycemic targets are not met. In line with real-life practice, in the participating centers, insulin therapy is not commenced based on a single abnormal value. Therefore, our protocol places an emphasis on a minimum of two abnormal glucose values, leaving usual care unaffected as much as possible, and we realize that this could differ depending on the center, treating physician, and clinical status of the patient. We agree with the reviewer that the current protocol (perhaps unnecessarily) specifies insulin rescue therapy.

If target values are not met more than two times in Phase B or C (FPG ≤ 7.0 mmol/l or PG ≤10.0 mmol/l), anti-hyperglycaemic treatment will be started (or extended) according to national guidelines for the treatment of T2DM.

2. Please specify- “High target values at least more than two times in phase B or C- In what time frame- a week, a month, or 6 months Please provide details of frequency of self monitoring of blood glucose in phase B and phase C

Thank you for your remark.
In Dutch guidelines T2DM is diagnosed if someone has fasting plasma glucose levels ≥ 7,0 mmol/l on two different days or a fasting glucose level ≥ 7,0 mmol/l in combination with symptoms of hyperglycemia or a random glucose value of ≥11,1 mmol/l in combination with symptoms of hyperglycemia. A time frame is not specified and hence we did not specify this in our protocol, leaving this up to the discretion of the treating internist/general practitioner. In general practice this time frame is mostly within one month. We adjusted the value of 10 mmol/l to 11,1 mmol/l.

We would like to further clarify the frequency of self-monitoring:
In Phase B we ask participants to measure 2 days 7-point blood glucose curves in the week before every visit. Every visit (fasting) plasma glucose levels will be determined in the research regular blood panel.
In Phase C no blood glucose curves have to be measured. In Phase C (fasting) plasma glucose levels will be determined in the research regular blood panel.

Page 45/85 Line 19/20 Change in body composition- Impedance

3. Please provide details of procedure used for measuring body composition, whether it is safe in pregnancy and whether body water redistribution in pregnancy will affect the measurements of body composition during the different trimesters.
Our apologies, there is a slight discrepancy between the protocol admitted to the institutional review board and the manuscript submitted. We are not measuring body composition of the mother, apart from height and weight. Therefore, we will exclude the term body composition (impedance) from this page in the protocol and have removed this outcome from the appendix.

Page 55/85- Line 18. Exclusion criteria

4. Add Hyperemesis Gravidarum
We have added hyperemesis gravidarum to our exclusion criteria.

Page 12/85 line 32 Drug safety

5. Metformin should be stopped if evidence of intrauterine growth restriction. In the "Metformin in obese non-diabetic pregnant women" trial (NEJM 2016 374:434-443), for example, this was defined as estimated fetal weight lower than the fifth percentile and abnormal fetal Doppler studies.
We agree that in this study metformin should be stopped in case of intrauterine growth restriction. Different definitions for fetal growth restriction exist. In the northern part of the Netherlands, the most used definition is from a Delphi consensus (Gordijn et al. Consensus definition of fetal growth restriction: a Delphi procedure, 2016).

We added the following to the protocol considering stopping metformin and referenced the study provided above:

“Additionally, metformin will be stopped in case of fetal growth restriction, as was also done in previous studies. Fetal growth restriction will be defined according to the criteria proposed by Delphi consensus.”

Page 60/85 Line 35 Self monitoring of blood glucose in phase B and phase C

6. Please give details of frequency of self monitoring of blood glucose in phase B and phase C How many 7 point blood glucose profiles in phase B and phase C - what frequency - please mention details
In Phase B we ask participants to measure two separate 7-point blood glucose curves in the week before every visit. A 7 point glucose curve consists of 7 glucose measurements: before and after each main meal (with the first measurement being a fasting glucose value) and before bedtime. In addition, every visit (fasting) plasma glucose levels will be determined in the research regular blood panel.
In Phase C no blood glucose curves have to be measured. In Phase C (fasting) plasma glucose levels will be determined in the research regular blood panel.

7. Page 68/75 Line 15& 16 Potential risks of using Metformin if eGFR between 30 and 45 in pregnancy? Metformin should be avoided or stopped if eGFR falls below 45 in pregnancy.
Thank you for your remark. We recognize that in pregnancy the e-GFR is usually higher due to different renal physiology, fluid distribution and weight. Although metformin can be commenced safely (with dose reduction) in non-pregnant populations up with e-GFR as low as 30 mL/min/1.73 m2 (KDIGO 2020, Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease), we agree caution should be taken in a pregnant population. Therefore, an e-GFR below 45 mL/min/1.73 m2 is an exclusion criterium in our study.

In addition, the guideline ‘Clinical practice guideline on pregnancy and renal disease’ (BMC Nephrology, 2019) states that metformin can be used in pregnancy for women with a pre-pregnancy eGFR>30 mls/min/1.73m2 and stable renal function during pregnancy.

However, your questions concerns a decline in renal function (e-GFR below 45 mls/min/1.73m2), when a patient is already included and using metformin. A detailed instruction for handling this is described in the IRB protocol. We chose to allow continuation of the drug for the following reasons:

1. Patients participating in the POEM study are subjected to regular visits including laboratory measurements, side-effects are detected in an early stage, and proper action can be taken.
2. Potentially the biggest concern regarding a decline in e-GFR is lactate acidosis. Under stable circumstances, without intercurrent disease, the risk therefore is very low. However, in case of intercurrent disease, we will be alert, and have a specified dose reduction in the protocol in case of decline in e-GFR.

3. In case of intercurrent disease and decline in e-GFR, the dose of metformin is reduced, and clinical status of the patient will be monitored, implying further action (stopping) can be taken if serious effects are seen.
4. Although no data on pregnant patients taking metformin and showing eGFR decline exists, in T2DM outside of pregnancy continuation with an eGFR > 30 mls/min/1.73m2 has been proven safe (Lipska et al: Diabetes Care 2011 and Lazarus et al: JAMA 2018), if dosing metformin is appropriate, according to our algorithm in the protocol.
5. Finally, (transient) discontinuation of the drug is up to the discretion of the treating physician if a patient is admitted with a significant eGFR decline – as described in our algorithm in the protocol, with or without intercurrent disease.

References:
Lipska KJ, Bailey CJ, et al. Use of Metformin in the Setting of Mild-to-Moderate Renal Insufficiency. Diabetes Care 2011: 34 (6): 1431-1437.
Lazarus B, Wu A et al. Association of Metformin Use With Risk of Lactic Acidosis Across the Range of Kidney Function: A Community-Based Cohort Study. JAMA 2018: 178(7):903-910.

Preferable additions

8. Inclusion of Birth centile along with birth weight
We added birth centile as well as birth weight.

9. Page 7/85 line 53, page 54/85: Hindus are not an ethnic group; they are followers of the Hindu religion. The term women of South Asian descent includes women of any religion or none who are at increased risk.
Thank you for this important remark. We have adjusted this in the revised protocol.

Reviewer: 2

1. Thank you for your work in this area. A few considerations:
There is increasing data to suggest differing GDM phenotypes with resultant implications for treatment (ie IFG= increased insulin resistance, IGT= more insulin deficient) (ref DOI: 10.1111/eci.13628; DOI: 10.1111/dme.14173) --> perhaps it is worth adding stratified analyses to consider those with IFG vs IGT as per OGTT in response where IFT would be hypothesized to have more benefit
We would like to thank reviewer 2 for taking the time to review our protocol and we agree that it would be very interesting to do a stratified analysis considering the different phenotypes, as we hypothesize the IFG group would benefit the most from metformin. We have added this to the protocol.

In regard to safety monitoring--sexual endocrine disruption has not been brought up much in human studies/implications, but given your long term follow up--consider impact on sexual development/sexual preference in offspring
Thank you for your valuable remark. We agree sexual development is a topic of interest especially given the emerging data in animal studies. The current study plans to evaluate gonadal and gender development as well as puberty and maturation as described in the protocol. We will definitely consider to taking sexual development and preference into account as well.

VERSION 2 – REVIEW

REVIEWER	Balani, Jyoti Epsom & St Helier University NHS Hospital, Diabetes
REVIEW RETURNED	12-Jan-2022

GENERAL COMMENTS	I would like to thank the authors for accepting our suggestions and making changes to the paper accordingly. I would like to mention that Dr Steve Hyer, Consultant Endocrinologist at Epsom & St Helier Hospital has also helped in the review of this article.

REVIEWER	Yeung, Roseanne University of Alberta
REVIEW RETURNED	27-Jan-2022

GENERAL COMMENTS	Looking forward to seeing the study results! Thank you for your submission.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

I would like to thank the authors for accepting our suggestions and making changes to the paper accordingly. I would like to mention that Dr Steve Hyer, Consultant Endocrinologist at Epsom & St Helier Hospital has also helped in the review of this article.

We would like to thank Dr. Jyoti Balani and Dr. Steve Hyer for their thorough assessment that improved the quality and clarity of this manuscript.

Reviewer: 2

Dr. Roseanne Yeung, University of Alberta Comments to the Author:

Looking forward to seeing the study results! Thank you for your submission.

We would like to thank Dr. Roseanne Yeung for the compliments and for her solid assessment of this manuscript.