PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The SUGAR-DIP trial: oral medication strategy versus insulin for diabetes in pregnancy, study protocol for a multicenter, open label, non-inferiority, randomized controlled trial
AUTHORS	de Wit, Leon; Rademaker, D.; Voormolen, D.; Akerboom, B.; Kiewiet-Kemper, R.; Soeters, M.; Verwij-Didden, M.; Assouiki, F.; Schippers, D.; Vermeulen, M.; Kuppens, S.; Oosterwerff, M.; Zwart, J.; Diekman, M.; Vogelvang, T.; Gallas, P.; Galjaard, S.; Visser, W.; Horree, N.; Klooker, T.; Laan, R.; Heijligenberg, R.; Huisjes, A.; van Bemmel, T.; van Meir, C.; van den Beld, A.; Hermes, W.; Vidarsdottir, S.; Veldhuis-Vlug, A.; Dullemond, R.; Jansen, H. J.; Sueters, M.; de Koning, E.; van Laar, J.; Wouters-van Poppel, P.; Sanson-van Praag, M.; van den Akker, E.; Brouwer, C.; Hermsen, B.; Potter van Loon, B.; van der Heijden, O.; de Galan, B.; van Leeuwen, M.; Wijbenga, J.; de Boer, K.; van Bon, A.; van der Made, F.; Eskes, S.; Zandstra, M.; van Houtum, W.; Braams-Lisman, B.; Daemen-Gubbels, C.; Wouters, Maurice; IJzerman, R.; Mensing van Charante, N.; Zwertbroek, R.; Bosmans, J; Evers, I.; Mol, Ben; de Valk, H.; Groenendaal, Floris; Naaktgeboren, CA; Painter, Rebecca; de Vries, Hans; Franx, Arie; van Rijn, Bas

VERSION 1 - REVIEW

REVIEWER	Delia Bogdanet Galway University Hospital
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	Very well written protocol. Just a few comments mostly aimed at the Introduction/Background and less at the protocol itself which, as I said , is well thought out. 1. The prevalence of gestational diabetes mellitus (GDM) is rising and currently affects approximately 5-10% of all pregnancies.[1,2] - page 8 The prevalence can be higher in certain parts of the world. I would either change the prevalence ranges to the correct ones or I would specify what part of the world you refer to that has this prevalence. Also - I think in terms of prevalence references there are papers which are focused on this topic only and might provide better referencing 2. GDM carries significant perinatal risks for pregnancy and childbirth, such as large-for-gestational-age infants, stillbirth,

	shoulder dystocia, obstructed labor, preeclampsia and neonatal hypoglycemia - page 8 I would also add macrosomia , SGA, polyhydramnios. Neonatal hypoglycemia - in GDM women that are treated - i would mention that. I think reference 3 doesn t belong here.I would take it out or replace it with something more relevant. 3. Reference 7 - maybe not the most relevant reference. Would you consider referencing the HAPO FUS study? 4. The rising number of women diagnosed with GDM requiring treatment is increasingly putting pressure on health care - page 8 All women diagnosed with GDM require intervention - would you consider rephrasing this?Do you mean pharmacological treatment? - If yes you would need to reference that 5. multidisciplinary approach by endocrinologists, obstetricians and diabetes nurse specialists. - page 8 I would add in midwives and dietetician 6. As pharmacologic treatment subcutaneous insulin injections have traditionally been used as firstchoice treatment for GDM and is still advocated in many, but not all, guidelines I would expand on this and state what guidelines recommend insulin as first line therapy and which ones don t. Especially that you ve stated this a few times in the manuscript. 7. Both are already widely used in the treatment of GDM and accepted as a safe firstline pharmacological treatment option in several guidelines - page 8 True that they are safe but they are not both accepted as first line therapy. Also the references you provided only include on guideline - the FIGO one which suggest metformin (not glyburide) might be first line but high risk pregnancies clearly have first line therapy insulin in the document. Please rephrase and review references. 8. A recent statement by the Society of Maternal-Fetal Medicine (SMFM) Committee further endorses OGLDs as a reasonable and safe first-line pharmacologic treatment in GDM.[21] They endorse Metformin but uncertainty still remains regarding glyburide. WOuld you consider rephrasing 9. any NICU admission and interventions used to regulate neonatal glucoses. - page 14 Would you consider NICU admissions for any reason not just hypoglycemia 10. As secondary outcomes would you consider looking at polyhydramnios, malformations and SGA as well? 11. I m not sure I understand – will you give the GDM women a list of all the possible side effects they can experience? (Would it be possible to make that more clear in the manuscript, please?) If yes, I don t think that is very wise – it will involve a lot of bias. What about just simple self-reporting of any symptoms? 12. What do you expect your timeline to be? The numbers seem reasonable to adequately power the study. 13. Who will fill in the report form? The doctors involved in the study?Or is there a database where all these details are inputted by midwives since first visit? It s a a very complete form but it will be very time consuming if one has to do it from zero

REVIEWER	Diane Farrar Bradford Institute for Health Research Bradford Teaching Hospitals Bradford UK
REVIEW RETURNED	26-Feb-2019

GENERAL COMMENTS	There are significant side effects associated with glibenclamide use other than hypoglycaemia that you do not mention and should to give a balanced appraisal of the drugs in your trial (disturbances of the gut such as diarrhoea, constipation, nausea, vomiting or abdominal pain, temporary visual disturbances at start of treatment, weight gain, allergic skin rashes and disturbance in liver function) 34 weeks as the upper limit for inclusion seems quite late, although it is a balance between allowing diet treatment to fail before recruitment, it is unlikely that treatment will affect LGA, your primary outcome, if women only receive pharmacological treatment sufficient to lower hypergycaemia for 3 or 4 weeks. If OGTT were conducted at 24 weeks and two weeks allowed for diet treatment to be assessed, you could recruit at 26 to 28 weeks and thus have more chance for pharma treatments to influence LGA. This may be a tight timeline but I think you should discuss timing of OGTT and GDM diagnosis and the balance between that and treatment length and influence on adverse outcomes

REVIEWER	TITUS BEYUO School of Medicine and Dentistry, University of Ghana. Ghana
REVIEW RETURNED	05-Mar-2019

GENERAL COMMENTS	My fundamental issue with this trial protocol is the use of different diagnostic cutoffs in enrollments of participants. How will this be controlled for in analysis? is there matching based on diagnostic criteria? Participants with Diabetes Mellitus in Pregnancy (DIP) and Gestational Diabetes Mellitus (GDM) may respond differently due to difference in the disease entity. Authors admit this as the third point on limitations of the study, but plan to do subgroup analysis based on diagnostic criteria and treatment targets, will this cure the inherent differences the different disease entities poses.? how many centers are using either diagnostic criteria? why is both 75g OGTT and 100gOGTT being proposed as part of the protocol? will there be matching at enrollment based on this|?

VERSION 1 – AUTHOR RESPONSE

Reviewer comments:

Reviewer: 1

Reviewer Name: Delia Bogdanet

Institution and Country: Galway University Hospital

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Very well written protocol.

Just a few comments mostly aimed at the Introduction/Background and less at the protocol itself which, as I said , is well thought out.

1. The prevalence of gestational diabetes mellitus (GDM) is rising and currently affects approximately 5-10% of all pregnancies.[1,2] - page 8

The prevalence can be higher in certain parts of the world. I would either change the prevalence ranges to the correct ones or I would specify what part of the world you refer to that has this prevalence. Also - I think in terms of prevalence references there are papers which are focused on this topic only and might provide better referencing

P8. Introduction.

We have adjusted the prevalence ranges to 1-28% to reflect global estimates and added a remark that the prevalence varies by region and diagnostic criteria used. For referencing we added additional papers.

“The prevalence of gestational diabetes mellitus (GDM) is rising and currently affects approximately 1-28% of all pregnancies, varying by region and diagnostic criteria used.”

2. GDM carries significant perinatal risks for pregnancy and childbirth, such as large-for-gestational-age infants, stillbirth, shoulder dystocia, obstructed labor, preeclampsia and neonatal hypoglycemia - page 8

I would also add macrosomia , SGA, polyhydramnios. Neonatal hypoglycemia - in GDM women that are treated - i would mention that. I think reference 3 doesn t belong here.I would take it out or replace it with something more relevant.

P8. Introduction.

We added the complications you mention to the list of GDM associated perinatal risks. Reference 3 (Zeng et al.) was replaced with a systematic review on gestational diabetes mellitus and pregnancy outcomes (Wendland et al. reference 5).

“GDM carries significant perinatal risks for pregnancy and childbirth, such as polyhydramnios, small- and large-for-gestational-age infants, macrosomia, stillbirth, shoulder dystocia, obstructed labor, preeclampsia and neonatal hypoglycemia.”

3. Reference 7 - maybe not the most relevant reference. Would you consider referencing the HAPO FUS study?

P8. Introduction.

Reference 7 (Wouldes et al.) was replaced with the reference to the HAPO follow-up study by Scholtens et al. (reference 10), as suggested by the reviewer. In accordance with this follow-up study, we added glucose and insulin resistance to the long-term risks in offspring in the first paragraph of the introduction.

Additionally a reference of follow-up study of a sub-group of the HAPO study was added, that reported on increased risk for obesity in offspring (Tam et al., reference 12) .

“In addition, increasing concern exists about the impact of GDM on offspring development and associated long-term risks for glucose and insulin resistance, obesity and chronic disease in children born to mothers with GDM.”

4. The rising number of women diagnosed with GDM requiring treatment is increasingly putting pressure on health care - page 8

All women diagnosed with GDM require intervention - would you consider rephrasing this? Do you mean pharmacological treatment? - If yes you would need to reference that

P8. Introduction.

We sought to make a statement on the rising number of women diagnosed with GDM, which is increasingly putting pressure on health care resources, rather than an increase in women requiring additional (pharmacological) treatment. As indeed the reviewer mentions, all women with GDM require treatment and monitoring (either diet alone or in combination with pharmacological agents). We therefore rephrased this statement to the following:

“The rising number of women diagnosed with GDM is increasingly putting pressure on health care resources.”

5. multidisciplinary approach by endocrinologists, obstetricians and diabetes nurse specialists. - page 8

I would add in midwives and dietetician

P8. Introduction.

We added midwives and dieticians, as they are indeed members of the multidisciplinary team.

“Effective treatment for GDM treatment requires a multidisciplinary approach by midwives, obstetricians, dieticians, endocrinologists, and diabetes nurse specialists.”

6. As pharmacologic treatment subcutaneous insulin injections have traditionally been used as firstchoice treatment for GDM and is still advocated in many, but not all, guidelines

I would expand on this and state what guidelines recommend insulin as first line therapy and which ones don t. Especially that you ve stated this a few times in the manuscript.

P8. Introduction.

We have included additional guidelines in the manuscript from the United States (ACOG, ADA, SMFM), Canada, Australia, United Kingdom and the Netherlands.

Furthermore we separated the guidelines that recommend insulin as first-line therapy and others that include oral agents as first-line therapy.

“As pharmacologic treatment subcutaneous insulin injections have traditionally been used as first-choice treatment for GDM and is still advocated in many [15–18], but not all [19–21] guidelines.”

7. Both are already widely used in the treatment of GDM and accepted as a safe firstline pharmacological treatment option in several guidelines - page 8

True that they are safe but they are not both accepted as first line therapy. Also the references you provided only include on guideline - the FIGO one which suggest metformin (not glyburide) might be first line but high risk pregnancies clearly have first line therapy insulin in the document. Please rephrase and review references.

P8. Introduction.

We have rephrased this sentence to:

“Both are already widely used in the treatment of GDM, considered to be safe and have been incorporated in several guidelines as treatment options alongside insulin.[19–21,24,25]”

The references now include 4 guidelines that acknowledge oral agents as alternative treatment options alongside insulin (rather than first-line), and a paper that includes safety and provides an overview on the potential role of the various antihyperglycemic agents in GDM (ref. 24).

8. A recent statement by the Society of Maternal-Fetal Medicine (SMFM) Committee further endorses OGLDs as a reasonable and safe first-line pharmacologic treatment in GDM.[21]

They endorse Metformin but uncertainty still remains regarding glyburide. WOuld you consider rephrasing

P9. Introduction

We have rephrased our statement to the following:

“The International Federation of Gynecology and Obstetrics (FIGO) and more recently the Society of Maternal-Fetal Medicine (SMFM) Committee further endorsed OGLDs as a reasonable and safe first-line pharmacologic treatment option in GDM, with metformin being preferred over glibenclamide.[21,27]”

9. any NICU admission and interventions used to regulate neonatal glucoses. - page 14

Would you consider NICU admissions for any reason not just hypoglycemia

P14. Study procedures, neonatal care.

We indeed monitor NICU (and Medium Care) admission for any reason, not just for hypoglycemia. This is also part of our secondary outcome measures (stated on page 15).

We therefore rephrased the sentence to clarify that neonatal admissions for any reason are documented:

“Time and plasma glucose values are documented as well interventions used to regulate neonatal glucoses. Furthermore, any admission to a neonatal Medium Care or Intensive Care Unit is documented.”

10. As secondary outcomes would you consider looking at polyhydramnios, malformations and SGA as well?

P15. Outcome measures: secondary outcome measures

The outcomes presented in this paragraph as secondary outcomes were selected based on their clinical relevance and/or observed differences in previous studies specifically comparing insulin to oral agents and this selection is listed as such to portray this focus.

Besides these secondary outcomes, there are additional characteristics and outcomes of interest. Polyhydramnios, congenital malformations and small-for-gestational-age are incorporated as outcomes of interest, see supplemental files 1 (additional study parameters) and 2(eCRF). These will be monitored and collected during the trial and subsequently reported.

We added the following remark to the paragraph on secondary outcome measures:

“These secondary outcomes were selected based on their clinical relevance and/or observed differences in previous studies comparing OGLDs and insulin.”

11. I m not sure I understand – will you give the GDM women a list of all the possible side effects they can experience? (Would it be possible to make that more clear in the manuscript, please?) If yes, I don t think that is very wise – it will involve a lot of bias. What about just simple self-reporting of any symptoms?

P16. Patient perspective and treatment satisfaction.

We have indeed constructed a list of side effects, not including all possible side effects but limited to the most commonly reported and furthermore allow for self-reporting of any other experienced undesirable effects. Both treatment arms receive the same questionnaire. Because we are offering the same list to both treatment arms, we do not anticipate this will result in selective overreporting or bias.

For clarification we have rephrased the statement regarding the monitoring of side effects and added a sentence that an identical form is issued to both treatment arms:

“Side effects will be monitored using a custom made form consisting of a short list of the most common side effects and the possibility to self-report any other experienced undesirable effects. The form will also address the actions taken as a response to side effects. Both treatment arms receive the same side effect form.”

12. What do you expect your timeline to be? The numbers seem reasonable to adequately power the study.

Recruitment at the first trial site was initiated in 2017 and currently over 25 sites are actively recruiting participants. In our initial work, the patients have shown high willingness to participate in the trial and we expect to be running at reasonable inclusion rates once all study sites are active.

13. Who will fill in the report form? The doctors involved in the study?Or is there a database where all these details are inputted by midwives since first visit? It s a a very complete form but it will be very time consuming if one has to do it from zero

P19. Data handling

The trial is set up in setting of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology – NVOG Consortium 2.0. This is a research network that includes trained research nurses, who will be responsible for filling in the report form. There is an electronic database, accessible at any time, which allows for inputting data from the first visit onwards. Our eCRF is based on a standardized piloted eCRF that has been used in many other multicenter trials that ran within the NVOG Constortium 2.0, and has therefore demonstrated feasibility.

We added the following statement to the paragraph concerning data handling:

“The eCRF is based on a standardized piloted eCRF that has been used in other multicenter trials within the NVOG Consortium 2.0 network and will be filled in by trained research nurses.”

Reviewer: 2

Reviewer Name: Diane Farrar

Institution and Country: Bradford Institute for Health Research, Bradford Teaching Hospitals, Bradford, UK

Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below

1. There are significant side effects associated with glibenclamide use other than hypoglycaemia that you do not mention and should to give a balanced appraisal of the drugs in your trial (disturbances of the gut such as diarrhoea, constipation, nausea, vomiting or abdominal pain, temporary visual disturbances at start of treatment, weight gain, allergic skin rashes and disturbance in liver function)

P9. Introduction.

We have now included several significant undesirable effects associated with glibenclamide use in the manuscript in addition to the already mentioned hypoglycemia in mothers and newborns: gastro-intestinal disorders, allergic skin reactions, altered liver enzyme values, visual disturbances and weight gain.

“Other undesirable effects include gastro-intestinal reactions, allergic skin reactions, altered liver enzyme values, visual disturbances and weight gain.”

2. 34 weeks as the upper limit for inclusion seems quite late, although it is a balance between allowing diet treatment to fail before recruitment, it is unlikely that treatment will affect LGA, your primary outcome, if women only receive pharmacological treatment sufficient to lower hypergycaemia for 3 or 4 weeks. If OGTT were conducted at 24 weeks and two weeks allowed for diet treatment to be assessed, you could recruit at 26 to 28 weeks and thus have more chance for pharma treatments to influence LGA. This may be a tight timeline but I think you should discuss timing of OGTT and GDM diagnosis and the balance between that and treatment length and influence on adverse outcomes

We agree with the reviewer that in the women recruited at 34 weeks the effect of treatment on the primary outcome may be limited, however in constructing the inclusion criteria we have taken several factors into account:

In the Netherlands a risk factor based screening policy is used. Women with predefined risk factors are screened by means of an OGTT at mostly around 24 and up to 28 weeks of pregnancy.

Given the timing of the OGTT with the current guidelines we expect that the majority of women will be included in the SUGAR-DIP trial at approximately 26 to 30 weeks of gestation, allowing for 10-12 weeks of pharmacological treatment prior to delivery.

However, if clinical symptoms occur suggestive for GDM (e.g. suspected macrosomia on ultrasound), an OGTT can be performed at any time during pregnancy, also in women without risk factors. This results in a portion of women diagnosed later than the abovementioned 26-30 weeks. As this is part of clinical practice, we felt that these women should not be excluded from the trial, also taking into account that the results from our study will most likely also be applied to these women. Also, initiation of treatment in the last trimester may still influence several important secondary outcomes, such as neonatal hypoglycemia.

Furthermore, restriction of the gestational age at which participants can be included poses practical inconvenience by limiting the number of eligible women, prolonging completion of the trial.

Lastly, several large trials on oral glucose lowering agents for gestational diabetes mellitus have used similar upper limits of 33-34 weeks (Langer et al. NEJM 2000, Rowan et al. NEJM 2008, Sénat et al. JAMA 2018), with a median gestational age at enrollment ranging from 27 to 32 weeks.

We have added the following statement to Methods section, under Participants and eligibility criteria (p11):

“For the SUGAR-DIP trial we have set the upper limit for inclusion to 34 weeks, in line with previous trials [22,23,40], allowing for at least 4 weeks of exposure to pharmacological treatment. With the timing of the OGTT in current guidelines it is expected that the majority of women will be treated for over 8 weeks. Although in women diagnosed later in pregnancy exposure to treatment may have less of an effect on the primary outcome, treatment may still influence several important secondary outcomes, such as neonatal hypoglycemia.”

Reviewer: 3

Reviewer Name: TITUS BEYUO

Institution and Country: School of Medicine and Dentistry, University of Ghana. Ghana

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

1. My fundamental issue with this trial protocol is the use of different diagnostic cutoffs in enrollments of participants. How will this be controlled for in analysis? is there matching based on diagnostic criteria? Participants with Diabetes Mellitus in Pregnancy (DIP) and Gestational Diabetes Mellitus

(GDM) may respond differently due to difference in the disease entity. Authors admit this as the third point on limitations of the study, but plan to do subgroup analysis based on diagnostic criteria and treatment targets, will this cure the inherent differences the different disease entities poses? how many centers are using either diagnostic criteria?

why is both 75g OGTT and 100gOGTT being proposed as part of the protocol? will there be matching at enrollment based on this|?

We agree with the reviewer that both national and international variation in diagnostic criteria for the diagnosis of GDM are of interest and of importance for clinical research on this subject. We would like to elaborate on the current situation in the Netherlands and the actions taken on this matter in the SUGAR-DIP trial.

Currently most centers in the Netherlands adhere to the WHO 1999 criteria and use a 75g OGTT to diagnose GDM. A limited number of centers has adopted the WHO 2013 criteria, or use hybrid cut-offs. Given that worldwide diagnostic thresholds vary (NICE, ADIPS, WHO etc.), allowing variation in the SUGAR-DIP trial promotes external validity. To provide insight on this matter, we plan to perform subgroup analyses that take into account the OGTT values and criteria used, for instance by pooling data from centers that use the same criteria and identify the interaction term

In the Dutch national guideline on GDM, both reference values for the 75g and 100g OGTT are given. Nationwide the 75g OGTT is by far the most commonly used test and currently no participating site is using the 100gr version. The 100g OGTT is stated in the study protocol, as it is still part of the national guideline, and we sought to have the inclusion criteria reflect current clinical practice in the Netherlands. We are collecting data from each participant on which test was used for the diagnosis.

Although thresholds for the diagnosis of GDM in the Netherlands and therefore in the trial are divergent to some extent, the target glucose values to define insufficient glycemic control (while on diet) as the additional inclusion criterium for enrollment in the trial apply to all centers. It is thus expected that patients eligible for enrollment form a homogenous group despite the differences in screening tools.

We acknowledge the difficulties regarding diagnostic criteria for GDM, however we feel that the current setup of the SUGAR-DIP trial reflects clinical practice with all its variation. The proposed sub group analyses will provide additional insight in the study results and aid in interpretation of the data.

We added the following statement to the Methods section, heading Participants and eligibility criteria, to elaborate on the 100-gram OGTT and variation of diagnostic thresholds: p.12

“The 100-gram OGTT is incorporated in the study protocol, as it is part of the Dutch national guideline, however this test is not commonly used in the Netherlands. Although thresholds for the diagnosis of GDM in the Netherlands and therefore in the trial are divergent to some extent, the target

glucose values to define insufficient glycemic control (while on diet) as the additional inclusion criterium for enrolment in the trial apply to all centers. It is thus expected that patients eligible for enrolment form a homogenous group despite differences in screening tools."

VERSION 2 – REVIEW

REVIEWER	Delia Bogdanet Galway University Hospital National University of Ireland Galway
REVIEW RETURNED	15-Apr-2019

GENERAL COMMENTS	Well designed study. Looking forward to the results.

REVIEWER	Titus Beyuo School of Medicine and Dentistry, University of Ghana
REVIEW RETURNED	30-Apr-2019

GENERAL COMMENTS	Explanations are satisfactory. The concept and protocol is well written.