Author’s response to reviews

Title: Views and preferences of medical professionals and pregnant women about a novel primary prevention intervention for hypertensive disorders of pregnancy: a qualitative study

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Version: 1 Date: 10 Feb 2019

Author’s response to reviews:

Dear editor(s),

We thank the reviewers for their relevant and constructive feedback. Please find below our point-by-point response to the issues raised.

Reviewer #1.

Comment 1.

As calcium supplementation is recommended for pregnant women with low dietary calcium intake and those at high risk of preeclampsia, and aspirin is recommended in pregnant women at high risk of preeclampsia, I wonder whether those interviewed were representative of the populations for whom calcium and aspirin is recommended.

Response

We thank the reviewer for this interesting comment. Indeed, while calcium supplementation is recommended for women with low dietary calcium intake, in this study it was the aim to explore
women’s view regardless of dietary intake and/or risk. We acknowledge we might not have been clear on this and therefore have amended the aim (line 121 and 347) in the background and discussion section. The participants in this study were recruited as they are ‘potential future users of the polypill’ if it were to be implemented as a public health intervention. A public health approach primarily includes the general pregnant population classified as ‘low risk’. Therefore the women in this study were women with low risk pregnancies and as such thus not representatives of the population to whom aspirin is recommended at this moment. As we did not assess their calcium intake we cannot say if they were representatives of the population for whom calcium is currently recommended. However, the aim of this study was to explore the views and preferences for a potential future intervention, in anticipation of further quantitative assessment and possible implementation. To clarify the rationale behind the population selection of this study we have amended a part of the text in the background section and study participants section.

Changes

Line 114-122: As such a public health approach with an unselected population of pregnant women – i.e. including low risk women – could further reduce the burden of HDP.13,19

The strategy to offer a polypill to an unselected population has not been explored yet. This qualitative study was conducted in anticipation of further quantitative assessment of the impact of the polypill concept (i.e. safety, efficacy, cost-effectiveness) and possible implementation of a polypill as a public health intervention in the general pregnant population. It explores the acceptability, views and preferences of (low-risk) pregnant women and primary healthcare providers.

Line 151-153: Women’s current calcium intake and other additional risk factors for HDP were not included as in-or exclusion criteria. For in a public health approach, the population for whom the polypill is hypothetically intended, is not selected by these risk factors either.

Line 345-347: The aim of this study was to explore the acceptability, views and preferences of (low-risk) pregnant women and primary healthcare providers about a polypill with aspirin and calcium as a public health intervention in the general pregnant population to prevent hypertensive disorders of pregnancy.

Comment 2.

Was any form of assessment of pregnant participants preeclampsia risk or of their dietary calcium intake performed?

Response
As a public health approach primarily includes the general pregnant population classified as ‘low risk’, this study focused on these women and their healthcare providers (see background section line 114-16 and study participants section line 141-143). Within the Dutch perinatal care system ‘low risk’ care is under supervision of primary care practitioners. This study was nested in routine primary antenatal care. In which risk assessment as well as general dietary advice is given by midwives at the primary care level. All participants were under care at a primary care facility and were as such classified as ‘low risk’. By means of a questionnaire we collected additional information on their obstetric history. Women who had a history of hypertension in previous pregnancies or the current pregnancy were excluded from the study. Women who had had any other complications during this pregnancy or a previous pregnancy were excluded as well. As the population for whom the polypill is hypothetically intended is not selected by additional risk factors for hypertensive disorders of pregnancy, we did not select on that either. This information has been added to the study participants section (line 151-153) During the interviews the use of pregnancy related supplements such as folic acid and multi-vitamins was discussed.

Changes

Line 151- 153: Women’s current calcium intake and other additional risk factors for HDP were not included in the in-or exclusion criteria. For in a public health approach, the population for whom the polypill is hypothetically intended, is not selected by these risk factors either.

Comment 3.

The evidence on calcium and/or aspirin supplementation as a PE preventive strategy for all pregnant women is limited, so it seems rather irrelevant to investigate what stakeholders from an unselected pregnant population would think of a combined pill in the absence of evidence on effectiveness and safety in this population. Counselling about a healthy diet that includes calcium rich foods would be more appropriate intervention for this Dutch population perhaps?

Response

Recently, evidence suggests that women in countries considered to have high calcium intake such as the Netherlands, also frequently have inadequate calcium intake and studies have explored whether all pregnant women should be advised to take calcium supplements. This, combined with the recommendations in the current guidelines to advice women with moderate risk factors (i.e nulliparity, BMI >35, family history), resulted in this study in which we aimed to explore whether a polypill intervention could be appropriate for this population, from their point of view. We believe that women-centered care starts during the research phase and before implementation. This study was thus conducted in anticipation of future quantitative assessment of the polypill impact and possible implementation. By exploring views and preferences of
stakeholders during this phase we could study the acceptability of such an intervention before implementation. To clarify this we have made a few amendments in the background section and changed the title of the recommendations section of the manuscript.

Changes

Line 117-122: The strategy to offer the polypill to an unselected population has not been explored yet. This qualitative study was conducted in anticipation of further quantitative assessment the impact of the polypill concept (i.e. safety, efficacy, cost-effectiveness) and possible implementation of the polypill as a public health intervention in the general pregnant population. It explores the acceptability, views and preferences of (low-risk) pregnant women and primary healthcare providers. This is essential knowledge to meet healthcare-users’ needs and contribute to women-centred care.20–23

Line 428: Recommendations for future research and information provision

Comment 4.

It would be helpful to the reader to include the information that was provided to participants with regard to preeclampsia and the role of calcium and aspirin within the paper, instead of as a supplementary file. How accurate/certain is the evidence contained in the supplementary file? What are the confidence intervals for the estimates on effect? What duration of treatment was being 'recommended' to women in the focus groups - are we really sure aspirin is safe throughout pregnancy? Were women informed of the WHO recommendations (which include different doses and specify the context for the supplements)?

Response

We agree with the reviewer we might not have been clear on the content of the informational video shown to the participants. The information video that was shown to the participants is produced by the Dutch patient organisation, the HELLP Foundation, and is publicly accessible via their website (www.hellp.nl). This video provides information on prevalence and signs and symptoms of HDP (amended line 180-181) and was made in collaboration with the Dutch Society of Obstetrics and Gynaecology and the Royal Dutch Association for Midwives.

Subsequently, information was given on the ‘hypothetical scenario’ in which the characteristics of the polypill were explained, based on the evidence collected in the literary review “Prevention of Hypertensive Disorders of Pregnancy: a Novel Application of the Polypill Concept” by Browne et al.(see reference 5), a comprehensive review of systematic reviews on drug and dietary interventions to prevent hypertensive disorders of pregnancy. As reference and clarification we have added their results table as supplementary file to the manuscript.
Furthermore, during the interviews it was explained that most studies are performed in high risk populations. Participants were informed that as such the evidence regarding safety and efficacy based on these studies was only partly applicable to them. We have included an extra sentence in the data collection section to elaborate on the content of the ‘hypothetical scenario’. In the scenario women are ‘recommended’ to use the pill during the first 34 weeks of pregnancy. Women were informed about the Dutch antenatal care guidelines for calcium and aspirin supplementation. These guidelines are based on the WHO guidelines.

Changes

Line 181-185: Subsequently, an information video with general information on prevalence and signs and symptoms of HDP was shown to ensure all participants had a similar understanding of the conditions. The video was made in collaboration with the Dutch Society of Obstetrics and Gynaecology and the Royal Dutch Association for Midwives and produced by the Dutch patient organisation, the HELLP Foundation. It is publicly accessible via their website (www.hellp.nl).

Line 186-197: As the polypill concept is not yet implemented in the Dutch perinatal care system, a hypothetical scenario with explanation about the polypill concept as a public health intervention was presented similarly to the participants to provide focus and promote a more in-depth discussion. In this scenario, amongst other polypill characteristics current evidence on safety and effectiveness of calcium and aspirin supplementation was discussed. Participants were explained that virtually all studies have been performed in high risk populations. They were informed that as such this evidence is only partly applicable to them (see Additional file 1).

Additional file 1

Line 2

Summary of information provided on hypothetical scenario polypill

Line 11

Both substances are safe to use during pregnancy (tested in high risk pregnancies)

Additional file 2

Results table Browne et al (see reference 5)

Comment 5.

This combined pill is referred to in the paper as ‘the’ polypill, as if it has already been manufactured – is this the case? If not, perhaps refer to it as ‘a’ instead of ‘the’. If it has already been manufactured or is in development, please provide more details of it for the reader.
Response

We agree with the reviewer and have changed ‘the’ polypill into ‘a’ polypill as suggested. As ‘the polypill concept’ refers to the specific concept of a public health intervention we have changed references to the concept accordingly.

Change

Line 80-82: This study aimed to explore the acceptability, views and preferences of pregnant women and primary healthcare providers for the concept of a polypill as a public health intervention for the prevention of HDP.

Line 117-122: The strategy to offer a polypill to an unselected population has not been explored yet. This qualitative study was conducted in anticipation of further quantitative assessment of the impact of the polypill concept (i.e. safety, efficacy, cost-effectiveness) and possible implementation of a polypill as a public health intervention in the general pregnant population.

Line 223-225: We identified two major themes that shaped medical professionals’ and women’s preferences for and views on the polypill concept: ‘Informed Choice’ and ‘Medicalisation’. Each theme could be divided into subthemes for both groups separately (Figure 1).

Line 244: This made them reluctant towards the polypill concept.

Line 316-317: As the polypill concept is a new intervention most women preferred a medical professional to inform them about it.

Line 336-338: Under the strict condition of it being scientifically proven to be a harmless method that could benefit their child, they had a positive stance towards the polypill concept (Beneficial).

Line 363-365: If the polypill concept is implemented, this information was considered essential to provide to women, and made health professionals more reluctant towards a public health approach.

Line 407-10: While expressing the importance of safety of a polypill and vigilance towards medicalisation, most participants, healthcare practitioners and women, considered a polypill with calcium and aspirin to be a simple, presumably harmless method to decrease the risk of a serious condition.

Comment 6.

Further, to my mind, ‘poly’ refers to ‘multiple’ components, which in the case of this pill is two components - so I think ‘combined pill’ or alternative would be better that ‘poly’ which sounds like ‘multi’.
Response

In the prevention of cardiovascular diseases, fixed-dose combination pills or polypills, are currently explored as a novel strategy to simultaneously address various risk factors at once and facilitate optimal adherence (see reference 8-12). As polypill is a known concept and this specific polypill concept originates in cardiovascular disease management, we have chosen for the term ‘polypill’. We have added the term fixed-dose combination pill, which was now only mentioned in the abstract, in the background section of the manuscript.

Changes

Line 104 – 106: These can be combined in a fixed-dose preparation – further referred to as ‘a polypill’– to target several causal risk factors at once and promote adherence.

Comment 7.

I don't think it's appropriate to make any recommendations, as the benefits and harms of a combined pill in an unselected population have not been proven and so the information provided in the figure is not accurate. Also, I do not agree that it is like folic acid supplementation.

Response

The recommendations are made with regard to future research, the potential implementation strategy and information provision. We refrain from making any recommendations whether the polypill should be implemented or not given the current available evidence. To clarify this we have amended the title of the recommendations section.

Changes

Line 428-430

Recommendations for future research implementation and information provision

Applying the results of this research, a number of recommendations can be made for future research on the implementation of a public health intervention for an unselected pregnant population.

Comment 8.

Lines 349/350 - I don't understand this sentence. Do you mean more research should be done, or shouldn't be done?
“It is debatable if the possible benefits of 350 aspirin and calcium should not be explored further, based on the results of one study.”

Response

We agree with the reviewer that this sentence is formulated rather confusing. We have amended the sentence to clarify its meaning.

Changes

Line 398-400: As such there is clinical equipoise to justify future studies to explore the possible benefits and potential harms of aspirin and calcium supplementation.

Comment 9.

Lines 357-359 - "most participants, healthcare practitioners and women, considered the polypill to be a simple, presumably harmless method to decrease the risk of a serious condition. " - I feel that this will really depend on what the women have been told about the intervention....I suggest deleting this sentence.

Response

We have amended the section on data collection, elaborating on the information that was given to the participants. We hope that this justifies the use of this statement in the manuscript.

Changes

Line 186-197: As the polypill concept is not yet implemented in the Dutch perinatal care system, a hypothetical scenario with explanation about the polypill concept as a public health intervention was presented similarly to the participants to provide focus and promote a more in-depth discussion. In this scenario, amongst other polypill characteristics current evidence on safety and effectiveness of calcium and aspirin supplementation was discussed. Participants were informed that virtually all studies have been performed in high risk populations. They were informed that as such this evidence is only partly applicable to them (see Additional file 1).

Comment 10.

The conclusions - that study participants thought it would be an improvement in care if the pill was offered, provided it is shown to be effective and safe (i.e. an improvement in care) - seems a bit nonsensical.

Response
Participants agreed that provided more research on effectiveness and safety is conducted, the polypill concept could be an improvement of care. In other words stating that they support further research, rather than writing the concept completely off beforehand. We amended this sentence in the conclusions section.

Change

Line 437-440: As preeclampsia is considered a serious condition that could harm both mother and child, most medical professionals and pregnant women in this study thought it had the potential to be an improvement of care to offer a polypill as a public health intervention, provided that three conditions are met. First, more research on effectiveness and safety of this polypill should be conducted.

Comment 11.

General: - I would be interested to know what are the beliefs and position of the investigators of this study regarding introducing a polypill to women in the Netherlands? Did you include a reflexive statement in your protocol?

Response

We acknowledge that our beliefs and positions regarding the introduction of a polypill in the Dutch antenatal care system are not negligible. Prior to the interviews the researchers explicitly discussed their personal views about the polypill concept and on how subjective and intersubjective elements could influence data collection, analysis and interpretation. Influence by conflict of interest was minimised as both the researcher who conducted the interviews and focus groups and the researcher who helped with analysing the data were not involved in the development of the polypill (see competing interest line 464-468). We added a sentence in the data collection section that the moderator was not involved in the development of the polypill.

All investigators agree that more research is needed before introduction of a polypill into the Dutch antenatal care system could be considered. This study was in anticipation of and aimed to contribute to the design of future research.

All of this was included and reflected on in the study protocol.

Changes

Line 177: This moderator is not involved in the development of the polypill.
Reviewer #2

I found this manuscript interesting and relevant to current obstetric practice with important and generalisable themes including person-centred care and joint decision-making highlighted. Overall the study is well presented and thought through, drawing some interesting conclusions regarding current antenatal education in the thematic analysis. The issue of a lack of education around HDP in a high income setting and user preference for more knowledge is highlighted. The idea of midwives as information 'gatekeepers' to women in an attempt to minimise anxiety provides interesting material for discussion. Further evidence to support the use of shared and informed decision making is useful in this area. Minor amendments suggested below

Response:

We thank the reviewer for acknowledging the relevance of the subject.

Comment 1

I would suggest the authors consider revising the statement made in the Plain English summary 'offering all women the polypill (as) a way to prevent HDP (a public health approach) should be considered'. In my opinion there is currently no robust evidence base for the implementation of aspirin and calcium prophylaxis in low risk populations. In high risk populations the evidence base is still being established in terms of optimal dosing and regimens. Current international guidelines recommend the use of low dose aspirin and calcium in high risk populations and in populations with low dietary calcium intake, which I assume isn't relevant to the Dutch population. It may be useful if the authors framed this study within the current clinical practice undertaken in the Netherlands with regards to the use of aspirin and calcium prophylaxis and describe briefly the current national guidelines in the background.

Response

We agree with the reviewer that this statement is formulated rather strongly. As such we have adjusted the phrase as stated below. We have also added a brief statement on the current national guidelines on aspirin and calcium supplementation.

Recently, evidence suggests, however, that women in countries considered to have high calcium intake such as the Netherlands, also frequently have inadequate calcium intake and studies have explored whether all pregnant women should be advised to take calcium supplements. This, combined with the recommendations in the current guidelines to advice women with moderate risk factors (i.e nulliparity, BMI >35, family history), resulted in this study in which we aimed to explore whether a polypill intervention could be appropriate for this population, from their point of view.
Changes:

Line 78-79: Instead, offering all women a polypill as a way to prevent HDP (a public health approach) could be considered.

Line 111 -112: In the Netherlands use of low-dose aspirin is recommended to high-risk women (REF NVOG dec 2018). Dietary advice regarding calcium intake (minimum of 1000mg per day) is given to women at moderate risk or higher (REF KNOV).

Comment 2.

There is also no reference to the importance of establishing the cost effectiveness of this approach. Although cost effectiveness has been evaluated in a high risk population this does not necessarily translate into a whole population approach. I would also recommend the authors justify more clearly their reasoning for sampling low risk women and the providers caring for them exclusively.

Response:

Some studies have performed cost-effectiveness analysis of offering low-dose aspirin to the general pregnant population (see reference 19). However, we agree that cost-effectiveness is indeed a factor that should be further explored before implementation of a new intervention. As such this study was in anticipation of further quantitative assessment including a cost-effectiveness analysis (line 119). We have chosen to focus on low risk women as a public health approach primarily includes the general pregnant population, classified as ‘low risk’. To clarify this we have made some amendments in the background section as stated below.

Changes

Line 112-122: However, current risk prediction and stratification performance by history taking remains limited.16–18 Futhermore, complex risk prediction models with biomarkers and uterine artery Dopplers cannot be readily included in routine antenatal care. As such a public health approach with an unselected population of pregnant women – i.e. including low risk women – could further reduce the burden of HDP.13,19

The strategy to offer a polypill to an unselected population has not been explored yet. This qualitative study was conducted in anticipation of further quantitative assessment the impact of the polypill concept (i.e. safety, efficacy, cost-effectiveness) and possible implementation of a polypill as a public health intervention in the general pregnant population. It explores the acceptability, views and preferences of (low-risk) pregnant women and primary healthcare providers.
Comment 3.
Consider rewording the following sentence in the background as difficult to read. "However, given the persistent burden of these disorders, primary prevention - i.e before the onset of disease - of HDP from occurring is key.'

Change:
Line 100-102: However, given the potential fulminant course of disease, primary prevention – i.e. preventing HDP from occurring – is key.

Comment 4.
Consider rephrasing ' However, as risk prediction and stratification performance remain limited and cannot be readily included in antenatal care, a public health approach with an unselected population of pregnant women could further reduce the burden of HDP'. The authors could elaborate as risk stratification based on maternal history is currently undertaken in some settings as part of routine antenatal care e.g in the UK as per NICE guidance and is arguably easier to implement that the suggested 'public health approach'.

Response
Current risk stratification is indeed based on maternal history. Yet, its performance remains limited as still women classified as ‘low risk’ get HDP later in their pregnancies. Risk prediction improves slightly by combining history with serum biomarkers and uterine artery Dopplers (see reference 16-18). However, such an approach cannot be readily included in antenatal care (see reference 18). Therefore a public health approach with an unselected population of pregnant women could further reduce the burden of HDP. We have amended the text in order to make a distinction between risk prediction by history taking and models that include biomarkers and Dopplers.

Changes
Line 112-116: However, current risk prediction and stratification performance by history taking remains limited.16–18 Furthermore, complex risk prediction models with biomarkers and uterine artery Dopplers cannot be readily included in routine antenatal care. As such a public health approach with an unselected population of pregnant women – i.e. including low risk women – could further reduce the burden of HDP.13,19
Comment 5.

Can the authors clarify the justification for the participant selection (Study participants). The implementation strategy being explored in this study would include the general pregnant population (aiming to capture high risk women) however these women have not been sampled nor have the clinicians managing them.

Response:

We agree that in the broadest sense of the word the general pregnant population does include high risk women. However high-risk women are already offered supplemental calcium and aspirin and are under stricter control than women with low-risk pregnancies. The aim of a public health approach would be to capture those women who would have been classified as low risk by current risk stratification methods but get HDP even still. As such it is this ‘general’ population that includes these low risk women that we aimed to represent in our study. We have made some amendments in the background section in addition to the study participant section to clarify this.

Change:

Line 111 -114 : In the Netherlands use of low-dose aspirin is recommended to high-risk women (REF NVOG dec 2018). Dietary advice regarding calcium intake (minimum of 1000mg per day) is given to women at moderate risk or higher (REF KNOV).

Line 114-116: As such a public health approach with an unselected population of pregnant women – i.e. including low risk women – could further reduce the burden of HDP.13,19

Line 122-124: It explores the acceptability, views and preferences of (low-risk) pregnant women and primary healthcare providers.

Comment 6.

Consider revision of the sentence in Data Collection section 'Subsequently, an information video with general information of HDP was shown to ensure all participants had equal understanding of the conditions.' Purely showing a video would not ensure equal understanding of all participants.

Change:

Line 181-183: Subsequently, an information video with general information on HDP was shown to ensure all participants had a similar understanding of the conditions.
Comment 7.

Consider being more specific in Results sections with regards to balance of respondents expressing certain views. Is it possible to give the numbers of respondents within each group. e.g regarding risk reduction vs over medicalisation

Response

We understand how specificity in numbers could give more clarity to the results, yet this does not fit the qualitative nature of this research. As the aim of this study was not to make generalisable statistical statements, but to gain an in-depth understanding of the various views and preferences of pregnant women and primary health providers.

Changes

Line 437-439:

As preeclampsia is considered a serious condition that could harm both mother and child, most medical professionals and pregnant women in this study thought it had the potential to be an improvement of care to offer a polypill as a public health intervention, provided that three conditions are met.

Reviewer #3

Comment 1

Could you give the evidence and rationale to use Calcium plus aspirin to prevent HDP compared to each agent?

Response:

Recently, evidence suggests that women in countries considered to have high calcium intake such as the Netherlands, also frequently have inadequate calcium intake, and studies have explored whether all pregnant women should be advised to take calcium supplements. This, combined with the recommendations in the current guidelines to advice women with moderate risk factors (i.e nulliparity, BMI >35, family history), resulted in this study in which we aimed to explore whether a polypill intervention could be appropriate for this population, from their point of view. For calcium and aspirin target different pathophysiological pathways and as such different risk factors. Aspirin inhibits the results of preeclampsia-associated placental damage. Calcium reduces the effect of relatively low serum calcium levels on blood pressure. This is based on the evidence collected in the literary review “Prevention of Hypertensive Disorders of
Pregnancy: a Novel Application of the Polypill Concept” by Browne et al. (see reference 5). The authors performed a comprehensive review of systematic reviews on drug and dietary interventions to prevent hypertensive disorders of pregnancy. As reference and clarification, we have added their results table as supplementary file to the manuscript.

Changes

Additional file 2

Results table Browne et al. (see reference 5)

Comment 2

Is there any evidence of beneficial data and safety data of each agent & the combination?

Response

See response of comment 1.

Changes

Additional file 2

Results table Browne et al. (see reference 5)

Comment 3

How to ensure that each interview gives the same information to the each participants group ?

Response

Each interview started with a video and presentation with the hypothetical scenario of the polypill as public health intervention including the information given in additional file 1. To give more information on the hypothetical scenario we have amended the text in the data collection section.

Changes

Line 186-197: As the polypill concept is not yet implemented in the Dutch perinatal care system, a hypothetical scenario with explanation about the polypill concept as a public health intervention was presented similarly to the participants to provide focus and promote a more in-depth discussion In this scenario, amongst other polypill characteristics current evidence on safety and effectiveness of calcium and aspirin supplementation was discussed. Participants were
explained that virtually all studies have been performed in high risk populations. They were informed that as such this evidence is only partly applicable to them (see Additional file 1).