Author's response to reviews

Title: Pregnancy outcome after use of cranberry in pregnancy - the Norwegian Mother and Child Cohort Study

Authors:

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Version: 2
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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised manuscript 3319569911032191 "Pregnancy outcome after use of cranberry in early pregnancy – the Norwegian Mother and Child Cohort Study", that we would like to resubmit for publication in the BMC Complementary and Alternative Medicine.

The revised version of the manuscript is based on the reviewers’ comments. Please find our specific replies to the reviewers’ comments below. We hope these changes will make the manuscript suitable for publication in your journal.

Additional requests:
- Please confirm whether the data used in your study is publicly available. If not, please provide details in your manuscript on who granted you permission to access it.

Response:

The data used in this study is not publicly available. The following information is included in the Methods-section: Access to MoBa was granted by the MoBa steering committee at the National Institute of Public Health.

In addition to the changes described below, we have decided to change the title of the manuscript into “Pregnancy outcome after use of cranberry in pregnancy – the Norwegian Mother and Child Cohort Study”.

Reviewer Jean-Jacques Dugoua recommended that the additional file 1 should be included in the manuscript. We will leave that decision to you.

Sincerely yours,

Kristine Heitmann

on behalf of the authors
We would like to thank the reviewers for their valuable comments. Changes to the manuscript are described below as a response to the reviewers’ comments.

Reviewer's report

Title: Pregnancy outcome after use of cranberry in early pregnancy – the Norwegian Mother and Child Cohort Study

Version: 1 Date: 8 August 2013

Reviewer: Jean-Jacques Dugoua

Reviewer's report:

General comment:
A well conducted and written study. There is a large knowledge gap on cranberry safety during pregnancy.

Response:
We thank you for the review of our manuscript, and encouraging comments.

Major compulsory revisions:
The addition of vaginal bleeding findings in the abstract and conclusion. Further discussion of vaginal bleeding findings in the discussion.

Response:
We have revised the abstract as suggested and elaborated on the vaginal bleeding findings in the discussion.

The comments fall under minor essential revisions:

Abstract
1. I disagree with the statement that cranberry is “one of the most frequently prescribed herbs during pregnancy”. The references cited do not support this claim. Please rephrase to “commonly prescribed”.

Response:
We have rephrased this sentence to “Cranberry is one of the most commonly used herbs during pregnancy. The herb has been used traditionally against urinary tract infections.”

2. Please rephrase “No studies are found that specifically address the safety of use of cranberry during pregnancy.” See comment #2 under the introduction.

Response:
This sentence has been rephrased: No studies are found that specifically address the risk of malformations after use of cranberry during pregnancy.

3. Please state the dates of the Norwegian Mother and Child Cohort Study.
Response:
The first sentence of the Methods-section in the abstract is changed to: “The study is based on data from The Norwegian Mother and Child Cohort Study including more than 100,000 pregnancies from 1999 to 2008.”

4. Present your results on vaginal bleeding in the 1st, 2nd and 3rd trimesters.

Response:
Unfortunately, including all this information in the abstract will result in a word count exceeding the maximum limit set by the journal. However, the following sentence is now included: “Although an association was found between use of cranberry in late pregnancy and vaginal bleeding after pregnancy week 17, further sub-analyses of more severe bleeding outcomes did not support a significant risk.”

5. Please rephrase: “Nevertheless, pregnant women should be strongly encouraged to use antibiotics against any detected urinary tract infection”. I suggest: “Although treatment guidelines on asymptomatic bacteriuria in pregnancy recommend antimicrobial therapy as the first line treatment, cranberry appears to be a safe adjunctive therapy.”

Response:
The sentence is rephrased, however, as we only studied a selected number of outcomes, we cannot conclude that it is definitively safe. We now state that: “Treatment guidelines on asymptomatic bacteriuria in pregnancy recommend antimicrobial therapy as the first line treatment. According to our data and the outcomes studied, cranberry does not appear to be a harmful adjunctive self-treatment.

Introduction
1. I disagree with the statement that cranberry is “one of the most frequently prescribed herbs during pregnancy”. The references cited do not support this claim. Please rephrase to “commonly prescribed”.

Response:
We have changed the sentence into the following: “Cranberry is one of the most commonly used herbs during pregnancy, and five studies report prevalence rates of over 5 % [3-7].”

2. Wing et al (2008) address neonatal safety from cranberry exposure during pregnancy: “There were no differences between the groups with regards to obstetrical or neonatal outcomes (Table 4). No preterm deliveries less than 34 weeks’ occurred in women with UTIs during this investigation.” This study is the first to address malformations, not pregnancy safety. Please rephrase with this in mind

Response:
Thank you for pointing this out. This text has been changed into: “This (Wing et al. (2008)) study did not detect any differences between the groups with regards to obstetrical or neonatal outcomes such as preterm delivery, route of delivery, birth weight, Apgar score or admission to neonatal intensive care unit. No studies are found that specifically address the risk of malformations of use of cranberry during pregnancy.”

Methods
1. No comments.
Results
1. “To be included in the current study, the women had to have a record in MBRN and to have answered the first questionnaire (n = 69,930)” and “Among the included women, 92.5 % had answered the second questionnaire and 87.3 % had answered the third questionnaire.” Were the ORs adjusted for timing of exposure in Table 2? Did you find a significant observation by isolating cranberry exposure in the 3rd trimester? For example, what if cranberry has uterine stimulating properties; an increase in preterm birth may be observed.

Response:
Sub-analyses stratifying on timing of use were performed. The obtained adjusted ORs did not reveal any significant associations with the selected pregnancy outcomes by isolating cranberry exposure in early or late pregnancy. Use of cranberry during early pregnancy did not increase the risk of stillbirth/neonatal death (adjusted OR 0.9, 95% CI 0.2-3.5), low birth weight (adjusted OR 0.7, 95% CI 0.4-1.3), small for gestational age (adjusted OR 0.9, 95% CI 0.6-1.3), preterm birth (adjusted OR 0.8, 95% CI 0.5-1.2), low Apgar score (<7) (adjusted OR 0.9, 95% CI 0.4-2.0) or neonatal infections (adjusted OR 1.0, 95% CI 0.5-2.1).

Sub-analyses with exposures of cranberry in late pregnancy only did not reveal any significantly increased risk of stillbirth/neonatal death (adjusted OR 1.2, 95% CI 0.4-3.8), low birth weight (adjusted OR 0.6, 95% CI 0.4-1.1), small for gestational age (adjusted OR 0.8, 95% CI 0.6-1.2), preterm birth (adjusted OR 1.1, 95% CI 0.8-1.6), low Apgar score (<7) (adjusted OR 1.1, 95% CI 0.6-2.1) or neonatal infections (adjusted OR 0.7, 95% CI 0.3-1.6), either.

However, due to no statistically significant results we have chosen to write “data not shown” in the manuscript. The paragraph now reads: “Use of cranberry during pregnancy did not seem to increase the risk of any of the selected negative pregnancy outcomes: stillbirth/neonatal death, low birth weight, small for gestational age, preterm birth, low Apgar score (<7) or neonatal infections (data not shown).”

2. “The mean birth weight was 3605 g (standard deviation 590 g) and the median gestational age was 40 among the live born infants.” Please use SD for standard deviation.

Response:
The “Instructions for Authors” provided by the journal state that if abbreviations are used in the text they should be defined in the text at first use. However, we agree that “SD” should be written after “standard deviation”: “The mean birth weight was 3605 gram (standard deviation (SD) 590 gram) and the median gestational age was 40 among the live born infants”

3. “The women who had used cranberry, were more likely to have experienced UTI during pregnancy compared to women who did not use cranberry.” Delete “,”.

Response:
This comma has been deleted.

4. I hope appendix 1 is included in the final publication, it provides useful data.

Response:
Additional file 1 will be available as a supplementary e-table. However, according to your advice, we will ask the editor if he prefers to have it as a table in the printed article.

**Discussion**

1. **First study to investigate risk of malformations. First paragraph. Please edit.**

Response:

The sentence has been rephrased into: “To the best of our knowledge, this is the first study to investigate the risk of malformations after use of cranberry during pregnancy.”

2. **These results are in agreement with a prior pilot study of the efficacy for the prevention of asymptomatic bacteriuria in pregnancy showing no differences between the cranberry group and the control group with regard to obstetric or neonatal pregnancy outcomes [28].” I assume you mean the apparent safety findings. Please state this. This study did not assess the effectiveness of cranberry for ASB in pregnancy.**

Response:

We have changed the text into: “These results are in agreement with the safety findings of a prior pilot study of the efficacy for the prevention of asymptomatic bacteriuria in pregnancy showing no differences between the cranberry group and the control group with regard to obstetric or neonatal pregnancy outcomes [28].”

3. **However, we did find an increased risk of vaginal bleeding occurring after pregnancy week 17 among the women who used ginger during late pregnancy.** Is this an error? Your study is on cranberry, this is the first mention of ginger. Please correct.

Response:

This is indeed an error, thank you for pointing this out to us. The sentence has been corrected into: “However, we did find an increased risk of vaginal bleeding occurring after pregnancy week 17 among the women who used cranberry during late pregnancy.”

4. **With respect to vaginal bleeding after cranberry exposure at the 2nd and 3rd trimesters, your p values are at 0.08. You have a non-significant trend. Cranberry contains a significant amount of salicylic acid, which has anti-platelet activity. You need to discuss the vaginal bleeding findings and possible causes. The vaginal bleeding outcome should also be stated in your abstract and conclusion.**

Response:

We have elaborated on the vaginal bleeding findings and the paragraph now reads: “Previous studies have indicated an interaction between cranberry and Warfarin [20, 32, 33, 44]. The mechanism of the interaction remains elusive, and different mechanisms are mentioned in the literature [32, 33, 44]. Cranberry contains significant amounts of salicylic acid, and might increase the risk of bleeding through its capacity to inhibit platelet aggregation [20, 32, 45]. On the contrary, others state that salicylic acid does not share the antiplatelet effect of acetylsalicylic acid [44, 46]. Another biologically plausible mechanism of action has been proposed by Abdul et al. who observed a non-significant trend towards decreased activity of clotting factors when cranberry was co-administered with warfarin [33]. However, the authors did not find any significant independent effect on the clotting system when cranberry was
administered alone during the pre-treatment period. Consequently, a clear explanation of the findings with regards to bleeding in this current study is difficult to obtain, but it cannot be completely ruled out that use of cranberry during pregnancy might increase the risk of maternal vaginal bleeding. In the current study, the doses and form of administration were unknown. Vaginal bleeding was self-reported and included spotting in addition to more severe bleeding incidents. We did not find a statistically significant association between use of cranberry during early pregnancy and maternal vaginal bleeding, or between use of cranberry during late pregnancy and more severe bleeding outcomes such as vaginal bleeding more than spotting after pregnancy week 17 and hospitalization due to vaginal bleeding after pregnancy week 12. These findings are reassuring. Nevertheless, a non-significant trend was seen between use of cranberry during late pregnancy and vaginal bleeding more than spotting after pregnancy week 17. Consequently, maternal vaginal bleeding is something that should be explored in later studies with respect to administration form and dosage.”

5. **One study limitation is the patient’s self-reporting of a UTI. There is no confirmed medical diagnosis of ASB or SB. Please include a brief sentence to this fact.**

Response:
We agree. We have already mentioned this under limitations at the end of the discussion-section. However, we have now deliberated it further, and it now reads: “Another limitation of the study is that MoBa is based upon self-reporting. Therefore, information on use of cranberry and the diagnosis UTI may not be complete as the medical diagnosis of ASB or symptomatic bacteriuria have not been confirmed.”

6. **Another limitation is dosing: form (capsules, tablets, liquid), total daily dose, duration of treatment, frequency of treatment and adjunct herbals along with cranberry. In the methods, you stated that you retained patients that used cranberry; what if cranberry was only in small amount, and the other herbal ingredients in their combinations, e.g. uva ursi, berberis, etc? Please include a brief sentence to this fact.**

Response:
We agree with your comment, and have changed the text into the following: “Additionally, the doses and administration forms were not available. The total daily dose, duration of treatment, frequency of treatment and adjunct herbals ingested along with cranberry, are therefore uncertain.”

7. **The survey did not address regular cranberry juice consumers who consume cranberry as a juice, this is a potential confounder. Please include a brief sentence to this fact.**

Response:
The following sentence has now been included “Furthermore, we did not include dietary intake of cranberry products (i.e. juice, berries) in our study, although this could have been a potential important confounder to adjust for.”

8. **“Since the mechanism of interaction between cranberry and warfarin is unknown, it cannot be ruled out that cranberry might increase the risk of bleeding via a pharmacodynamic mechanism of action.” Cranberry might inhibit the cytochrome P450 2C9 (CYP2C9). The mechanism of action you are discussing refers to the pharmacokinetic effects on the clearance via CYP2C9 rather than pharmacodynamics. Please edit.**
A potential inhibiting effect on platelet aggregation can be seen as a pharmacodynamic mechanism. The section including this sentence has been changed with regard to your suggestion under point 4 under discussion.

9. “The risk of recall bias was avoided as a consequence of the prospective nature of data collection.” There is always a risk recall bias when data is reported retrospectively. This statement may only apply to your data collected in the 2nd trimester and during breastfeeding where women were aware (I assume) that 2 additional questionnaires were forthcoming and were more attentive to their symptoms, regimens, health and so on. Please modify this statement.

Response:
The statement is modified, and now reads: “The risk of recall bias was reduced as a consequence of the prospective nature of data collection. However, as the third questionnaire was completed 6 months after giving birth, there might be some recall bias. This could only occur among the 69 women who reported cranberry use between completion of the second questionnaire and delivery in the third questionnaire. This represents 7.5% of the women who used cranberry in pregnancy.”

10. Van Trigt et al (1994) found that 37% of women discontinued drug use during pregnancy due to a perceive risk of teratogenicity. There are other such studies in the literature with similar findings. This perception is likely the answer to your statement: “The proportion of women who report treatment with antibiotics in relation to UTI (55.9 %) is worryingly low.”

Response:
Thank you for this comment. The following text is now included in the discussion: “The proportion of women who report treatment with antibiotics in relation to UTI (55.9 %) is worryingly low. Pregnant women are previously found to overestimate the risk of medicines [53, 54], which may explain this finding.

Conclusion
1. Include vaginal bleeding conclusions.

Response:
The following sentence has been included in the conclusions: “However, maternal vaginal bleeding should be investigated further before any firm conclusions can be drawn.”

References

• Ref 19 and 20: These are not referenced properly. Author, name, date and additional detail can be provided for these references. If a link is provided, the date accessed should be stated.
• Same comment for references: 35, 37-19, 41-43
Response:
We have included the authors of the different websites and information of when it was accessed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I declare that I have no competing interests
Reviewer's report:

The authors studied whether use of cranberry during pregnancy was associated with an increased risk of malformations or with selected pregnancy outcomes such as stillbirth/neonatal death, low birth weight, preterm birth, low Apgar score, neonatal infections and maternal vaginal bleeding. This is a well written and interesting paper, which according to the authors is the first to specifically address the safety of use of cranberry during pregnancy. This is an important study as the use of dietary supplements and herbs is increasingly popular during in pregnant women. Of particular interest is the possible use of cranberries as replacement for antibiotics.

The results showed that women who reported use of cranberry during pregnancy did not have increased risk neither of malformation nor any other of the pregnancy outcomes studied. The questions posed by the authors are well defined, the methods are appropriate, the data sound, the discussion and conclusion is balanced and supported by the data.

I would like to commend the authors for the particular interesting stratification of cranberry use, UTI and use of antibiotics in Table 4.

Response:
We thank you for the review of our manuscript, and hope we have addresses your questions and comments in an adequate manner.

I only have a few points that I the authors need to clarify.

Major Compulsory Revisions:
None

Minor Essential Revisions:
1) Page 6, Exposure variable. Information on cranberry use was retrieved from the three MoBa questionnaires. How was this information on cranberry use extracted from other herbs and supplements reported as text by the women and how did you handle the huge amount of text information originating from three questionnaires and a very large study sample? Was it done by visual inspection of thousands of questionnaires, was it done by more than one person? etc etc. This process needs to be described in more detail.

Response:
We have added further information with regards to how this work was done. The text now reads: “All medicine text fields and text fields for dietary supplements/herbal remedies in the three questionnaires were systematically reviewed for herbal products by the research team (see also acknowledgement). Whenever a herbal product was identified, the herbal ingredient(s) was systematically coded according to a pre-determined herbal classification list. This classification system had been developed by the
research team and included the common name of the herb and a seven character specific code as a means to standardize the coding in the questionnaire database. Cranberry was defined as any herbal coded with the assigned herbal code.

This work took us over a year and was facilitated 1) by sorting each text field by product/herbal names in descending order to make sure no herbal product was missed and 2) the classification list making sure the four individuals coded the herbals in the same way.

2) For the outcomes reported in Tables 3 and 4 it is not clear from what is written in the methods section whether the same babies might be included as a case in more than one of these outcomes? This is not likely to influence the results, but should be clarified in the methods.

Response:
Thank you for pointing this out. We have included the following sentence under “outcome variables” in the Methods section and as a footnote under table 3 and 4: “The outcomes were not mutually exclusive.”

3) In Table 1 the differences in proportions which reached statistical significance is difficult to read. I suggest placing the * and the # symbols by the numbers in the columns depicting “use of cranberry” for the stars and by the numbers in the columns depicting “Exposed to cranberry, UTI and no antibiotics against UTI during pregnancy”.

Response:
We agree. To enhance readability we have introduced two additional columns and added the actual p-values from the Pearson’s chi-square tests. Significant findings are now in bold.

No further comments.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** I declare that I have no competing interests.