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.

Major compulsory revisions:
The addition of vaginal bleeding findings in the abstract and conclusion. Further discussion of 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”.
2. Please rephrase “No studies are found that specifically address the safety of use of cranberry during pregnancy.” See comment #2 under the introduction.
3. Please state the dates of the Norwegian Mother and Child Cohort Study.
4. Present your results on vaginal bleeding in the 1st, 2nd and 3rd trimesters.
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.”

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”.
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
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.

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

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 “,”.

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

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

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 13 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.

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.

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.

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.

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.

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.

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.

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.

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.”

Conclusion
1. Include vaginal bleeding conclusions.

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

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