PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of xenobiotic substances in first-trimester blood samples from Danish pregnant women: a cross-sectional study
AUTHORS	Aagaard, Sissel; Larsen, Agnete; Andreasen, Mette; Lesnikova, Iana; Telving, Rasmus; Vestergaard, Anna Louise; Tørring, Niels; Uldbjerg, Niels; Bor, Pinar

VERSION 1 – REVIEW

REVIEWER	Mara G. Coyle, MD Women & Infants Hospital Providence RI, USA
REVIEW RETURNED	17-Jul-2017

GENERAL COMMENTS	Substance use, both licit and illicit, during pregnancy is an important topic. The authors aimed to better understand the prevalence of substance use in a cross-sectional population of pregnant Danish women in their first trimester. As they note, their data is derived from blood samples from an anonymous prenatal screening program, which is likely to have better accuracy than a questionnaire, the method employed by many previous studies aimed at understanding this issue. I have the following concerns regarding this manuscript that prohibits my supporting publication at this time: 1. There are MULTIPLE typographic/spelling errors throughout the manuscript. 2. The manuscript in its current form is not suitable English 3. The authors use adjectives such as “high” when describing prevalence despite the fact that their numbers are relatively low compared to other studies (eg: Acetaminophen) 4. An important finding is the percent of pregnant women exposed to any substance in the first trimester of pregnancy (82.6%), yet this is minimized as it is mentioned in the converse, in the final sentence of the result section 5. Inclusion/exclusion criteria are mentioned but not defined in the study design 6. When describing sample analysis, “500 different substances comprising toxic compounds, illegal and legal drugs….” is noted, yet common medications such as antibiotics and antiemetics were not assayed (p8 of discussion). This should be mentioned in the methods.

	Were common medications such as anithypertensives, thyroid medications assayed? The drugs listed in your table seem narrow in scope. 7. Table 1 notes number of women, yet when discussing data, the authors refer to number of samples. Presumably each women contributed one sample. If the illicit data is excluded, I count 90 women from column with a ”trace of medicine” not 78 as noted on p6. This should be more clear. Likewise, when I calculate the numbers for the other listed categories, the numbers do not add up. 8. I don’t think it is helpful to lump caffeine, nicotine, psychoactive prescription medications and illicit drugs into one category. 9. One of the issues not discussed in the manuscript is why women take medications during pregnancy. Were all women who come to pregnancy perfectly healthy, there would be no need. Obviously this is not the case as complex medical morbidities present for many pregnant women. Psychiatric illness is a major morbidity that can be exacerbated with pregnancy, and the drugs that presented with the most frequency were the antidepressants. The authors list multiple morbidities noted to be associated (not causal) with prenatal use. It is not appropriate in many clinical situations to recommend that a women refrain from use of this class of drug, as this itself has been associated with an increased risk of fetal loss. The message should be to minimize use when possible, avoid multiple medications for the same diagnosis, engage in thoughtful discussion with patients regarding risk/benefit, as data regarding causal morbidities is limited 10. While that authors suggest that their data notes a high prevalence of substance use during pregnancy, compared to the articles they reference, their prevalence figures appears to be less, which could make sense given that blood samples were analyzed, and data was not subject to recall as seen with questionaires.

REVIEWER	Carla Bouwmeester Northeastern University Bouve College of Health Sciences School of Pharmacy 360 Huntington Ave. 140 The Fenway (R218) Boston, MA 02115-5000 United States
REVIEW RETURNED	26-Jul-2017

GENERAL COMMENTS	It was a pleasure to review this article which represents a meaningful contribution in the area of drug use during pregnancy. Slight revisions are necessary for grammatical issues and typos. Consider what substances would be considered illegal/illicit in different countries and define what you considered illicit in this study (i.e. cannabis is used medically and recreationally in some states in the United States). Consider using the term xenobiotic in the title rather "medication and psychoactive substances" and define this term in the text.

	Specific comments: p3, line 16: readers may not be aware of the "thalidomide catastrophe" Consider expanding or rewording to be more precise. p4, lines 7-8: this study only demonstrated prevalence but not pattern of substance use given one-time screening p4, lines 18-20: it would be interesting to see if the results varied depending on the week that the samples were drawn (i.e. less substance use near 13 weeks compared to 8 weeks gestation). p4, lines 56-59: consider adding an appendix of the substances that are detectable via this process or specifically mention common psychoactive substances that cannot be detected via this method (i.e. alcohol). p5, line 18: consider using the term "prescription medication" in place of "medication" here and throughout the manuscript for consistency. p5, Table 1: very helpful table. Are the recommendations from Promedicine.dk considered a reliable resource? p6, Results: the information contained in this section is already communicated via the table. Consider consolidating the text and elaborating on other findings such as number/% patients using prescription medications that are in the "use if necessary", "only under certain conditions", and "should not be used" categories. p7, lines 27-40: What are the limitations of the screening based on dose of the substance? What is the lowest detectable dose? p8, lines 6-9: you mentioned that antibiotics and antiemetic drugs are not detected in the analysis. Please explain further. Is this a limitation? What other medications are not detectable? References: Overall some of the references can be consolidated when you summarize general findings (i.e. choose relevant citations among 17-23). p10, reference #15 Incomplete Overall, this paper adds important information to the field, given minor revisions.

VERSION 1 – AUTHOR RESPONSE

Answers for reviewer 1:

Reviewer Name: Mara G. Coyle, MD
Institution and Country: Women & Infants Hospital Providence RI, USA

Responses:

1.-2.

The reviewer suggests some language improvement and the manuscript has been carefully revised by professionals (American Journal Experts) and all the typographic and spelling errors have been corrected.

3. The reviewer rightly wonders why our exposure prevalence can be considered high? The use of medication in Denmark is generally very conservative and the access to several over-the-counter products is limited. As this is a cross-sectional study of women most likely having healthy and uncomplicated pregnancies we would respectfully argue that acetaminophen in 1 out every 10 samples constitute a high degree of use.

4. As suggested by reviewer the high number of women (82.6%) with traces of at least one xenobiotic substance has been highlighted in the results (p.5, l.24-25) and the discussion section (p.7, l.23-24).

5. As suggested by the reviewer clear descriptions of the inclusion and exclusion has been included in the method section in the revised manuscript (p.4, l.19-22)

6. As requested by the reviewer, more details on the strength and limitation of the analysis has been included in the method section (p.5, l.6-14).

7. The reviewer wonders why we state that 78 women have traces of medicine in their blood sample when a total of 90 traces have been found. This difference is caused by the fact that some of the women had traces of more than one substance in the sample. Thus, they figurate more than once in the table 1. This point has been made clearer in the revised manuscript (p.5, l.28-29)

8. We completely agree with the reviewer that the prevalence and consequences of each of this type of exposure needs individual concern. We aimed at investigating the prevalence of xenobiotic/psychoactive substances such as caffeine, nicotine and illicit drugs (e.g. cannabis and cocaine) use in pregnant women including the use of over-the-counter medications. These substances are therefore listed separately in both the result section and table 1 in the revised manuscript.

9. We agree with the reviewer that medical therapy during pregnancy is a complicated topic and avoiding all medication is not necessarily the safest way to proceed. We have included a paragraph on this is an important aspect in the revised manuscript as suggested (p.8, l.31 - p.9, l. 1).

10. The reviewer presents one of the advantage of our study compare to the others.

Answer for reviewer 2:

Reviewer Name: Carla Bouwmeester
Institution and Country: Northeastern University Bouve College of
Health Sciences School of Pharmacy, Boston, United States Competing

Responses:
We thank the reviewer for her encouraging comments.

The manuscript has been carefully revised by American Journal Experts and all the typographic and spelling errors have been corrected.

We agree with the reviewer that the fact that cannabis use is affected by the legal status of this product should be mentioned. Examples of illicit drugs has been added in the abstract (p.2, l.14) and explained further in the results section (p.7, l.12) and discussion (p.9, l.5-12)

As suggested by the reviewer the title of the manuscript has been changed and now includes the term xenobiotic. Furthermore, the term is explained in the introduction (p. 3, l.21-24).

As suggested by reviewer the mentioning of the thalidomide catastrophe has been slightly expanded in the introduction section in the revised manuscript (p.3, l.10-12).

The reviewer wonders why we refer to the pattern of exposure as only one sample is analyzed per women. This reflects the unique nature of the analyses which reveals the pattern of co-exposures in a given sample.
The reviewer wonders if the presence of xenobiotics vary with the gestational weeks during which the samples are taken. However, in our study it was not possible to look at the different gestational weeks separately due to the anonymization of all the blood samples. No data on the specific gestational weeks were disclosed to the research team.

As requested more information regarding the limitations of the analysis, and details on where to find more information has been included in the revised manuscript (p. 5, l. 6-14).

The reviewer asks for more details regarding the source Promedicin.dk. The page is published by Danish Medicine Information and contains information on all marked human medications written in technical terminology for medical doctors and other healthcare personnel. It is written by approximately 250 medical experts and edited by 4 clinical consultants. This information has been added to the food notes to the table (p. 6, l.1-3).

As suggested by reviewer details have been added regarding where to find the limitations of the screening based upon the dose of the substance. Furthermore, details regarding specific drugs not assayed in the analysis have been added in the method section in the revised manuscript (p. 5, l. 6-14).

As suggested by reviewer the references have been revised and some of the references have been deleted in the revised manuscript.

Some of the references has been consolidated as suggested by the reviewer (see the yellow highlights).

VERSION 2 – REVIEW

REVIEWER	Carla Bouwmeester Northeastern University, Bouve College of Health Sciences, School of Pharmacy Boston, MA, USA
REVIEW RETURNED	05-Sep-2017

GENERAL COMMENTS	Thank you for the opportunity to review your article revision. You have addressed all the reviewer comments from the previous draft and the current manuscript was a pleasure to read. I have a few minor comments: P18, L24: include OTC and prescription medications in the objective (ie …xenobiotic substances including prescription and nonprescription medications, caffeine, nicotine, and illicit drugs…) P19, L18-35: I appreciate the changes to the introduction and feel this provides a better stage for the reader to understand your research