Reviewer’s report

Title: Tampon Use, Environmental Chemicals and Oxidative Stress in the BioCycle Study

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Reviewer: Robin Dodson

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ENHE-D-18-00339
This paper summarizes an exploratory analysis of tampon use, metal biomonitoring data, and biomarkers of inflammation and oxidative stress among healthy women. This analysis is based on data from an existing prospective cohort study on menstrual cycling, reproductive hormone levels, and oxidative stress. While the analysis is based on a very interesting hypothesis - tampon use can lead chemical exposures and subsequent inflammation and oxidative stress - it is not currently presented in a way that helps to explore that hypothesis fully.

Background:
While the authors present a lot of important background literature, I think the organization of several of the introductory paragraphs could be improved. For example, I suggest the authors consider a more informative first sentence like, "The vaginal route is a potentially important yet understudied route of chemical exposure."

Page 3, Line 12: instead of 'compounds' should be 'drugs', right?

Also, I suggest a stronger topic sentence for the second paragraph. Perhaps, "Tampons are a potential source of chemical exposure." And then follow with how cotton can be contaminated because of where it is grown, chlorine bleaching may introduce dioxins, and fragrances may also be present.

The current topic sentence of the third paragraph is almost circular in logic. I suggest rewriting.

What is the background literature on inflammation and oxidative stress during the menstrual cycle? Presumably there are other influences besides chemical exposures.

Have there been any studies on the cyclical nature of chemical concentrations in blood during the menstrual cycle? If yes, please reference.

Page 3 Line 60: references for "has been documented"

It's a little strange to talk about pesticides so much and then drop them in the final paragraph. I suggest mentioning them in the background but focus only on the metals. Pesticides can be further discussed in the Discussion section.
Methods:
Page 4 Line 42: "were planned to be collected" or "were collected"? Or is it that the study was designed to collect blood samples at certain times during the menstrual cycle and you used historic data on cycling to estimate the blood draw times?

A very large limitation to this analysis is that the metal concentrations in blood were collected before the reported tampon use and biomarkers of effect.

It is hard to determine whether the authors have captured a reasonable list of confounders without knowing more about the association between menstrual cycle and inflammation and oxidative stress. I understand this is partly the point of this paper but are there endogenous changes that could explain the relationships and should these be considered in the model?

Have tampons ever been tested for metals? Just curious.

Are the biomarkers of effect temporally correlated? Was that accounted for in the modeling?

Discussion:
Can the authors provide more biological context for the various biomarkers of effect? What is the significance of higher TBARS and lower PON1P levels?

Page 8 Line 24: "daily intake of dioxins" from what?

The phthalates discussion is interesting. These should be mentioned in the Background.

Conclusion:
The authors may be overstating their findings of suggestive evidence without further convincing the reader of the plausibly and relevance of the metal exposures (measured before the "exposure") and inflammatory markers and oxidative stress. This is a unique study and it raises some interesting questions that need to be explored further.

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