Title: PROBIOTICS AND VAGINAL MICROECOLOGY: FACT OR FANCY?

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Author’s response to reviews:

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Dear Editor,

Thank you for your e-mail of 14 June 2018 in which you inform us that our manuscript No. BMWH-D-18-00112 entitled:

“PROBIOTICS AND VAGINAL MICROECOLOGY: FACT OR FANCY?”

needs major revision.

All the reviewers’ comments have been addressed point by point, and the relative modifications made are indicated in the revision notes and highlighted in yellow in the revised text.

We believe that, thanks to the particularly useful reviewers' comments and suggestions, the manuscript has been improved. We hope that our debate can now be considered for publication in BMC Women’s Health and look forward to hearing your decision.

Yours sincerely,

Laura Buggio

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Reviewers’ comments:

Reviewer #1:
David Fredricks (Reviewer 1): This is a valuable review and my suggestions are minor:

1. Line 177: rational, not rationale
   Modified.

2. Please check all genus and species names; Gardnerella vaginalis, not Gardnerella Vaginalis in capital.
   Checked and modified where needed.

Reviewer #2:
Francesco De Seta (Reviewer 2):

1) the authors ignored to differentiate oral and vaginal route in the introduction

We have now specified that probiotics were administered either orally or vaginally (line 57). A brief distinction between the two mechanisms of action have been added in the introduction section (lines 58-62). In addition, in the conclusion section the practical issue of the two different routes of administration is commented (lines 210-214).

2) In the Cochrane Database Syst Rev. 2017 (Probiotics for vulvovaginal candidiasis in non-pregnant women. Probiotics for vulvovaginal candidiasis in non-pregnant women) the data show the beneficial effects of probiotics in short term follow up not confirmed in long term cure, but we know that also with traditional/conventional treatment (azoles) the recurrences represent a sort of not solved issue.

A phrase and three references to underline this issue have been added in the text (lines 108-112; references 21,22 and 23).

3) Regarding BV and probiotics the authors considered only data from Tan H, Fu Y, Yang C, Ma J. and they completely neither cited nor mentioned other trial or cochrane with results not

A paragraph citing these two trials have been added (lines 119-128; references 24 and 25)

4) the authors dont differentiate between acute and recurrent form of infections (candidiasis or vaginosis) and relative therapeutic implications. In fact in complicated forms (recurrent infections) all treatments (also antymicotic or antibiotic) are not supportive, until today ,of long term beneficial results

Two phrases have been added specifying the definition of recurrent VVC and the difficulty in eradicating these infections also with conventional antimicrobial treatments (lines 110-113). Moreover, the potential beneficial role of Lactobacillus plantarum P17630 in the treatment of recurrent infections has been underlined (lines 114-117).

5) in the obstetric population data showed in the paper are only related to the negative studies, instead other data reported beneficial effects in case of pPROM (Daskalakis et al) . Also the norvegian protocol showed beneficial effects when administrating in the early gestational age. At the end we know how far we are to having significant results in Ob patients but the sensation is that the authors have considered only a negative data of the literature to stress the incocnclusive effects of probiotics

We have now added a paragraph presenting the results of the study by Daskalakis et al. (lines 162-167). In the subsequent paragraph of the original version, we had already reported the outcomes of the Norwegian study (Nordqvist et al. 2018) including the protective effect of probiotic ingestion in early pregnancy for the prevention of preterm delivery (lines 174-176).

6) in the text there is a big confusion related to the endpoints considered in obstetric patients : prematurity? pPROM? Metabolic outcomes? Preeclampsia ?

Our aim is to provide a global view of the potential role of probiotics in the management of different obstetrical and gynaecological conditions. In addition, we believe it would be useful for readers and patients to raise awareness also on the economic aspects of probiotics, and thus on the cost-benefits ratio of their use in a specific area of application.

This is a debate and not a systematic literature review. We have selected the most recent evidence, giving priority to Cochrane reviews, international guidelines, and meta-analyses. Given the nature of our article, not all the available evidence was reviewed. However, the reviewer correctly suggested the inclusion of some additional publications. Therefore, seven more references are now cited (9,21,22,23,24,25,33) and the relative studies are mentioned in the
text. We believe that, thanks to the reviewers’ suggestions our article is now more comprehensive and descriptive of the outcomes of probiotic use.