

Careful management of severe dysmenorrhea, using analgesics and amenorrhea obtained with continuous low-dosage contraceptive pills, is possible. If the goal is to prevent a spontaneous worsening of the disease, prevention of menstruation is enough.<sup>4</sup> Finally, the absence of a noninvasive diagnostic test does not demonstrate that the cause of endometriosis is permanent, that the number of lesions is constantly increasing, or that recurrences are unavoidable thus implying that deep hypoestrogenism may be indicated when endometriosis is “suspected” on clinical symptoms. ■

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#### REFERENCES

1. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol* 2019;220:354–64.
2. Evers JL. Is adolescent endometriosis a progressive disease that needs to be diagnosed and treated? *Hum Reprod* 2013;28:2023.
3. Parker MA, Sneddon AE, Arbon P. The menstrual disorder of teenagers (MDOT) study: determining typical menstrual patterns and menstrual disturbance in a large population-based study of Australian teenagers. *BJOG* 2010;117:185–92.
4. Brosens IA. Endometriosis—a disease because it is characterized by bleeding. *Am J Obstet Gynecol* 1997;176:263–7.

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#### REPLY



Thank you for your letter entitled “Years of unjustified hypoestrogenism, fear, and stress will not improve the management of chronic pelvic pain!” The goal of our manuscript entitled “Clinical diagnosis of endometriosis: a call to action”<sup>1</sup> was to highlight the current unacceptable delay in diagnosis and to encourage a focus on pain, functioning, and quality of life, with or without a previous surgical diagnosis of endometriosis. We agree with your statement “Even

minimally invasive surgery is too invasive to manage minimal endometriosis, which is not always progressive and may heal during medical treatment or even spontaneously.”

You mention that as a result of an empiric diagnosis of endometriosis, “young patients will experience years of unjustified fear and anxiety about probable infertility induced by a possible mysterious chronic disease which cannot be cured.” We contend that years of pelvic pain without answers or a diagnosis is a far greater tragedy—one that leads to women seeking multiple medical opinions and tests often without diagnosis and effective improvement in pain, functioning, and quality of life. Such an existence has substantial negative psychological and other consequences.

We are not proposing a paradigm in which women will have to endure “years of unnecessary hypoestrogenism.” On the contrary, we propose trying effective endometriosis medical therapy and, if it does not work, to consider more extensive and possibly more invasive investigation and management. As highlighted in our manuscript, by excluding common confounding diagnoses before making the clinical diagnosis of endometriosis and initiating therapy, one has a high likelihood of improving the patient’s pain, functioning, and quality of life in an expeditious and relatively noninvasive manner. ■

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#### REFERENCE

1. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol* 2019;220:354–64.

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## Bacterial vaginosis and the risk of human papillomavirus and cervical cancer



**TO THE EDITORS:** In response to the article titled “Vaginal dysbiosis and the risk of human papillomavirus and cervical cancer: systematic review and metaanalysis,”

we the authors believe that the findings of Brusselaers et al<sup>1</sup> potentially could support the theory that there is a causal link between vaginal dysbiosis and cervical cancer.

However, before this theory can be fully supported, issues of ambiguity that were identified in this systematic review should be addressed. Brusselaers et al aimed to assess the association between vaginal dysbiosis and cervical cancer. Concerns arise with respect to the definition of vaginal dysbiosis that was used and the study selection criteria.

First, vaginal dysbiosis was defined as a deviation from a *Lactobacillus*-dominant microbiota. However, a definitive cut off point for *Lactobacillus* dominance was never identified, and this may vary from study to study. Further confusion occurs because the definition that was used by Brusselaers et al uses microscopy-based assessment of *Lactobacillus* dominance, but the authors included studies that used Amsel's criteria. Amsel's criteria does not directly assess *Lactobacillus* dominance, rather it assesses the presence or absence of clue cells via microscopy.<sup>2</sup> Additionally, the presence of clue cells is not required for the diagnosis of vaginal dysbiosis. Three of the 4 Amsel's criteria are required to be diagnosed with vaginal dysbiosis, of which presence of clue cells is only 1.<sup>2</sup> This may have resulted in an overestimation of results because of misclassification. It should also be noted that it is possible to have a *Lactobacillus*-dominant vaginal microbiota and be classified as unhealthy or exhibit characteristics that are similar to that of a vaginal microbiota that has deviated from *Lactobacillus* dominance.<sup>3</sup>

Second, we are concerned that Brusselaers et al<sup>1</sup> acknowledge that vaginal dysbiosis commonly is also referred to as bacterial vaginosis; however, this term was not included in the search strategy. Furthermore, although the authors used MESH and Emtree terms, CINAHL headings were not included in the search strategy for the CINAHL database. Further clarity is also needed with respect to the inclusion of grey literature. Conference abstracts were cross checked for relevant full text papers; the time frame and conferences that were searched were not included. We acknowledge the efforts of Brusselaers et al to assess bias; however, a customized tool was used for assessment of risk of bias, and the validity of the tool could not be verified. It was not expressed clearly whether this tool was validated or piloted before its use. Additionally, the authors failed to assess publication bias. Funnel plots could have been used to assess publication bias graphically. Brusselaers et al amply highlight the need for further investigation into the association between vaginal dysbiosis and the risk of human papillomavirus and cervical cancer. ■

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## REFERENCES

1. Brusselaers N, Shrestha S, van de Wijgert J, Verstraelen H. Vaginal dysbiosis and the risk of human papillomavirus and cervical cancer: systematic review and meta-analysis. *Am J Obstet Gynecol* 2019;221:9–18.e8.
2. Onderdonk AB, Delaney ML, Fichorova RN. The human microbiome during bacterial vaginosis. *Clin Microbiol Rev* 2016;29:223–38.
3. Petrova MI, Reid G, Vaneechoutte M, Lebeer S. *Lactobacillus iners*: friend or foe? *Trends Microbiol* 2017;25:182–91.

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## REPLY



We thank Drs Coudray and Kiplagat for their interest in our work and agree that our study has limitations, as described earlier.<sup>1</sup>

There is an important debate ongoing considering the vaginal microbiome, in particular how to categorize this, for example to use community state types or not.<sup>2</sup> Yet, because of the almost discrete distribution of community state types, there is a clear distinction between *lactobacilli*-dominated vaginal microbiota compositions, and those not dominated by *lactobacilli*, which makes cut-offs redundant. Beside the difficulties in categorising, it remains to be established which microbiome composition is to be considered healthy, which does not necessarily equal asymptomatic. To date, it remains to be established firmly which vaginal microbiota composition (ie, which specific *lactobacilli spp*) should be preferred and how a dysbiotic state can be restored from an “unhealthy” microbiome composition.

There is increasing evidence that the vaginal microbiome plays an important role in many outcomes, including HPV acquisition and persistence, yet many subquestions remain to be answered. What came first? The vaginal dysbiosis or the human papillomavirus? Therefore, longitudinal data are required to assess changes over time in the same individuals. Until the present, most published microbiome studies that have assessed the vaginal microbiota composition are relatively small and cross-sectional; to date, longitudinal data based on molecular studies remain too scarce to be implemented in a metaanalysis.

We also would like to point out that, although the Amsel criteria do not measure the presence of *lactobacilli* directly, individuals with a positive result will not present with a large abundance of *lactobacilli*. The presence of clue cells and positive Amsel tests have shown to be highly specific for bacterial vaginosis (98% and 99%, respectively), although sensitivity is suboptimal.<sup>3</sup>

Considering the literature search: The conference abstracts were those retrieved through the Web of Science, which also indexes abstracts of major conferences. No additional hand searching was conducted, because we aimed to include