# Lipid metabolism in the cervicovaginal space during pregnancy

We appreciate the interest in our original article examining cervicovaginal metabolites and short cervix in pregnancy and welcome the opportunity to clarify details. The key findings include associations between a second trimester short cervix and (1) a decreased abundance of cervicovaginal lipid metabolites, specifically sphingolipids and (2) an increased abundance of immunostimulatory xenobiotics.

As noted by Lin and Li[1] in their Letter to the Editor, consistent with our previous work,[2] we detected an association between *Lactobacillus*-deficient cervicovaginal microbiota and a short cervix. They also point out that in a secondary analysis of participants with *Lactobacillus*-deficient microbiota, we did not detect significant differences in cervicovaginal lipid metabolites between cases of short cervix and normal cervical length controls. Given the small sample size and a conservative Bonferroni correction for multiple comparisons, the lack of statistical significance does not exclude the possibility of associations. In addition, substantial overlap was noted when comparing the results of this secondary analysis to the primary analysis, with sphingolipid metabolites appearing among the top hits. These findings suggest that the association between a sphingolipid-depleted microenvironment and a short cervix cannot be explained solely by the cervicovaginal microbiota. Similarly, in an additional secondary analysis of the 27 participants with a short cervix, we did not detect significant metabolite differences between those with spontaneous preterm birth (sPTB) and term birth. However, we could not rule out associations that may be detectable in larger samples. In addition, the sphingolipid metabolites identified in the primary analysis appeared among the top hits in this analysis, suggesting that alterations in lipid metabolism observed in association with a short cervix may play a role in the pathophysiology of sPTB, which is an active area of ongoing inquiry.

The molecular events underlying cervical remodeling and sPTB are complex and multifactorial,[3] and alterations in lipid metabolism are not solely responsible for the initiation or progression of these processes. Findings from our study, though hypothesis-generating with respect to mechanism, are associations only and cannot establish causation. The lack of samples from nonpregnant individuals precludes determining whether lipid metabolism in the cervicovaginal space before pregnancy may offer an insight into underlying biology. Although lipid metabolism in association with cervicovaginal microbiota has been preliminarily investigated,[4] the extent to which individual microbial species contribute to select lipid profiles remains unknown. Through ongoing and future translational research, we will leverage this work to understand metabolism in the cervicovaginal space to improve pregnancy outcomes and promote reproductive health. ■

Kristin D. Gerson, MD, PhD
Michal A. Elovitz, MD
Center for Research on Reproduction and Women's Health
Department of Obstetrics and Gynecology
Biomedical Research Bldg. II/III
Perelman School of Medicine
University of Pennsylvania
1351 421 Curie Blvd.
Philadelphia, PA 19104-6160
Department of Microbiology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA
kristin.gerson@pennmedicine.upenn.edu

Heather H. Burris, MD, MPH
Center for Research on Reproduction and Women's Health
Department of Obstetrics and Gynecology
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA
Children's Hospital of Philadelphia
Department of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

M.A.E. receives salary support from the National Institutes of Health (NIH) (The National Institute of Nursing Research [NINR], National Institute of Allergy and Infectious Diseases [NIAID], and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD]). She is also a consultant for Mirvie. The other authors report no conflict of interest.

Society of Maternal-Fetal Medicine (SMFM)/American Association of Obstetricians and Gynecologists Foundation Award (K.D.G.); NIH R01NR014784 (M.A.E.). The funding sources had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication.

## REFERENCES

1. Lin X-M, Li D-Z. Second trimester short cervix and decreased abundance of cervicovaginal lipid metabolites. Am J Obstet Gynecol 2022.
2. Gerson KD, McCarthy C, Elovitz MA, Ravel J, Sammel MD, Burris HH. Cervicovaginal microbial communities deficient in Lactobacillus species are associated with second trimester short cervix. Am J Obstet Gynecol 2020;222:491.e1–8.
3. Nallasamy S, Mahendroo M. Distinct roles of cervical epithelia and stroma in pregnancy and parturition. Semin Reprod Med 2017;35:190–200.
4. Baldewijns S, Sillen M, Palmans I, Vandecruys P, Van Dijck P, Demuyser L. The role of fatty acid metabolites in vaginal health and disease: application to candidiasis. Front Microbiol 2021;12:705779.

 https://doi.org/10.1016/j.ajog.2022.05.067