Abstract Details

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Ovarian stimulation alters the cervical microbiota

Biography

SM graduated as a MD from the Free Brussels University, Belgium, in 2012. Afterwards, she started working at the Centre for Reproductive Medicine at the University Hospital Brussels, Belgium, as a PhD student/resident in OBGYN. She performed basic science and clinical research on endometrial receptivity and is currently preparing her PhD defence. She has authored several publications in peer-reviewed journals and lectured at international meetings. At present, she is associated to the Centre for Reproductive Medicine at the University Hospital Brussels, Belgium as a research fellow.

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Study question:

Does ovarian stimulation (OS) have an impact on cervical microbiota composition and diversity?

Summary answer:
OS significantly influences the cervical microbiota composition and increases its diversity.

What is known already:
Disturbances of the female genital microbiota are associated with female sexual health complications such as an increased risk for sexually transmitted infections and with obstetrical complications such as preterm delivery. Recently, it has been suggested that women undergoing IVF/ICSI are particularly prone to genital dysbiosis and that an abnormal microbiota composition and an increased species diversity might affect post-treatment pregnancy rates. However, before introducing reproductive tract microbiota analyses in clinical practice to predict IVF/ICSI outcome, confounders need to be investigated more thorough. For example, the impact of OS remains to be elucidated.

Study design, size, duration:
This analysis was part of a prospective observational cohort study investigating the potential effect of the female reproductive tract microbiota on IVF/ICSI outcomes and included 106 women each providing two samples between 2016 and 2019. Samples from the cervical microbiota were collected by swabbing at two different timepoints: prior to OS (baseline) and at the moment of oocyte retrieval (post-OS).

Participants/materials, setting, methods:
Caucasian women, aged <40y, planned for a first or second IVF/ICSI cycle performing OS in an antagonist protocol followed by fresh single blastocyst transfer were included. Cervical microbiota samples were retrieved by swabbing, flash-frozen in liquid nitrogen and stored at -80°C. Microbiota profiles were obtained by amplicon sequencing (16SrRNA V4) using the gold-standard DADA2 pipeline. Correlations to microbiota profiles were performed by constrained principal coordinates analysis at genus level (cPCoA with Aitchinson distance).

Main results and the role of chance:
OS led to a significant shift in cervical microbiota (n=106x2, paired cPCoA, R^2=0.006, p=0.016). Also, microbial diversity significantly increased during OS (n=106x2, paired t-test, t-ratio=4.80, p=5.4E-6). We evaluated whether the menstrual cycle phase at the moment of baseline sampling confounded this association between OS and the shift in diversity and observed that, in our dataset, this was not correlated (Kruskal-Wallis, p=0.72). The cervical microbiota profiles were typed into 4 different community-types (CTs), two of them having the characteristic dysbiotic high-species diversity. Focusing on 72 patients having achieved live birth (n=39) versus not having reached a +hCG (n=33) after a fresh embryo transfer, CTs were not significantly associated to outcome at both timepoints (Fisher's test, baseline p=0.63, post-OS p=0.27). However, CTs shifted significantly from baseline to post-OS (n=144, Fisher's test, p=0.03). In cervical microbial diversity, also no significant difference was observed between the two outcomes (live birth vs not pregnant), at baseline (n=72, Kruskal-Wallis, ES=0.16, p=0.18), nor after OS (n=72, Kruskal-Wallis, ES=0.13, p=0.28). However, an increase in diversity was confirmed for both outcome groups, with this increase being slightly higher for the negative outcome (n=33x2, paired t-test, t-Ratio=3.50, p=0.001) than for the live birth outcome (n=39x2, paired t-test, t-Ratio=3.11, p=0.004).

Limitations, reasons for caution:
Human-associated microbial communities have a high inter-person variability and even with a reasonably scaled study of 106 women, statistical significance is difficult to reach. Caution is warranted as non-significant associations do not prove non-correlations.

Wider implications of the findings:
Interest has increased in predicting IVF/ICSI outcome using reproductive tract microbiota analysis. The impact of potential confounders however needs to be assessed first. We found OS to be a significant driver of microbial compositional and diversity variation, labelling it as a potential confounder that deserves more attention in future research.

Keywords:
IVF/ICSI
ovarian stimulation
endometrial receptivity
cervical microbiota