

## Association between persistent HPV16 infection and salivary microbiome in pregnant women in a longitudinal 3-year follow-up

Tangtian He<sup>1</sup>, Vuokko Loimaranta<sup>2</sup>, Seija Grenman<sup>3</sup>, Stina Syrjänen<sup>2</sup>, Ville N. Pimenoff<sup>4</sup>, Karolina Louvanto<sup>1,5,\*</sup>

<sup>1</sup> Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

<sup>2</sup> Faculty of Dentistry, University of Turku, Finland

<sup>3</sup> Department of Obstetrics and Gynecology, Turku University Hospital, Turku, Finland

<sup>4</sup> Unit of Population Health, Faculty of Medicine, University of Oulu, Finland.

<sup>5</sup> Department of Obstetrics and Gynecology, Tampere University Hospital, Tampere, Finland

Human Papillomavirus (HPV) can infect human mucosa and cause severe oral and cervical diseases. Though the molecular mechanisms of HPV-induced oral/cervical diseases have been intensively investigated, the interaction between HPV infection and oral microbiome and their roles in disease development remains elusive. This study includes four independent groups: O-&G-, oral and genital HPV negative/fluctuate; O-&G+, genital HPV16 persistent (excluding oral HPV16 persistent cases); O-&G+(C), cervical intraepithelial neoplasia (CIN) cases; O+&G-/G+, oral HPV16 persistent. Saliva samples were collected at baseline (pregnancy), 12-, 24- and 36- month follow-up visits. A metagenomic approach was conducted to analyze the composition, diversity, and biomarker taxa of salivary microbiome. In the results, the diversity of the salivary microbiome in the O+&G-/G+ group was among the highest compared to the other groups. The beta diversity of salivary microbiome in women developed with a CIN was significantly different from that of the other groups, and significant variations in the fractions of *Haemophilus*, *Prevotella*, and *Schaalia* were observed. Moreover, the natural response of salivary microbiome to pregnancy that was observed in HPV negative group was largely reduced in HPV persistent groups. These results shown that the HPV infection and development of CIN can largely affect the diversity and composition of salivary microbiome and modify its natural response to pregnancy, implying the immunity and endocrine system of pregnant women may have been impacted. This study suggests that detecting longitudinal changes in salivary microbiome and status of HPV infection could potentially enhance the screening of HPV-induced premalignant and malignant lesions.

Keywords: human papillomavirus, salivary microbiome, pregnant women, cervical intraepithelial neoplasia, microbial change