Göteborg, 2022

Human papillomavirus infection and preterm delivery

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Jubileumsaulan, Gula stråket 2A, Göteborg, den 6e maj, klockan 09.00.

av Johanna Wiik

Fakultetsopponent: Peter Sasieni, Professor, King´s College, London, UK

Avhandlingen baseras på följande delarbeten

I. Wiik J, Nilsson S, Kärrberg C, Strander B, Jacobsson B, Sengpiel V. Associations of treated and untreated human papillomavirus infection with preterm delivery and neonatal mortality: A Swedish population-based study. PLoS Med. 2021;18(5):e1003641. doi: 10.1371/journal.pmed.1003641

II. Wiik J, Kärrberg C, Nilsson S, Strander B, Jacobsson B, Sengpiel V. Associations between cervical intraepithelial neoplasia during pregnancy, previous excisional treatment, cone-length and preterm delivery: a register-based study from western Sweden. BMC Medicine. 2022;20(1):61. doi: 10.1186/s12916-022-02276-6

III. Wiik J, Værnesbranden MR, Jonassen CM, Staff AC, Carlsen KCL, Granum B, Haugen G, Hedlin G, Hilde K, Jacobsson B, Nilsson S, Nordlund B, Rangberg A, Rehbinder EM, Sengpiel V, Skjerven H, Sundet B, Söderhäll C, Vettukattil R, Sjøborg K. Maternal human papillomavirus infection during pregnancy and preterm delivery, a mother-child cohort study in Norway and Sweden. Manuscript

IV. Wiik J, Sengpiel V, Kyrgiou M, Nilsson S, Mitra A, Tanbo T, Jonassen CM, Møller Tannæs T, Sjøborg K. Cervical microbiota in women with cervical intra-epithelial neoplasia, prior to and after local excisional treatment, a Norwegian cohort study, BMC women's health. 2019;19(1):30. doi: 10.1186/s12905-019-0727-0

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Human papillomavirus infection and preterm delivery

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Abstract

Background: Persistent human papillomavirus (HPV) infection causes cervical intraepithelial neoplasia (CIN). Excisional treatment of CIN has been linked to increased risk of preterm delivery (PTD). The specific mechanism behind is however unclear. Also untreated CIN has been associated with an increased risk of PTD. It is unknown whether this is attributable to the HPV infection itself or other causes.

Aims: To examine whether HPV infection, untreated CIN and/or previous treatment for CIN is associated with PTD and other adverse obstetric outcomes. To study possible causal pathways for an association, including cone length of treatment, changes in cervical microbiota and infectious complications.

Material and methods: *Paper I*; a Swedish register-based study (1999-2016), studying obstetric outcomes in women with normal cervical cytology (NCC) (n=338,109), abnormal cytology (n=11,727) or positive HPV test (n=2,550) - in conjunction with pregnancy, previously treated women (n=23,185), and women with CIN2+ diagnosed after pregnancy (n=33,760). *Paper II;* a register-based study from western Sweden (2008-2016), comparing obstetric outcomes in women with NCC (n=42,398), women with CIN during pregnancy (n=1,380) and previously treated women (n=3,250) including a subgroup with cone length measured at treatment (n=2,408). *Paper III;* a prospective observational study in Sweden/Norway (n=950) comparing obstetric outcomes in women with or without HPV infection detected in urine at mid-pregnancy and at delivery. *Paper IV;* a prospective observational study in Norway with culture and PCR of cervical microbiota in women with CIN (n=89) before and six and 12 months after LEEP and also compared to women with NCC (n=100).

Results:

Paper I; HPV infection (HPVtest) compared to NCC was associated with PTD (aOR 1.2, 95% CI 1.0-1.4), and preterm prelabor rupture of membranes (pPROM) (aOR 1.5, 1.2-2.0), but treated women had higher risk compared to women with HPV infection; PTD (aOR 1.7, 1.4-2.0), pPROM (aOR 1.6, 1.2-2.0). Treatment but also HPV infection were associated with increased risk of neonatal mortality and PROM at term and treatment also with chorioamnionitis and neonatal sepsis.

Paper II; Treatment was associated with an increased risk of PTD (aOR 1.6, 1.2-2.1), pPROM (aOR 2.7, 1.7-4.5), and PROM at term compared to women with CIN, and risks increased with cone length. Small treatments (≤10 mm) were also associated with increased risk for PTD and pPROM.

Paper III; Women positive for high-risk-HPV genotypes at mid-pregnancy had a higher frequency of PTD compared to those negative for high-risk-HPV, but comparisons were non-significant.

Paper IV; Treatment resulted in a reduction of non-*Lactobacillus* bacterial species. More types of bacterial species were detected in women planned for LEEP than in women with NCC.

Conclusion: Women with HPV infection have increased risk of PTD, pPROM and neonatal mortality. Excisional treatment for CIN, also minor excisions, increases the risks for PTD and pPROM further compared to having untreated CIN/HPV infection. The risks increase with cone length. Previous treatment is also associated with increased risk of PROM at term and maternal and neonatal infectious complications. Treatment appears not to result in a more diverse or dysbiotic cervical microbiota while CIN is associated with increased bacterial diversity.

Keywords: CIN, HPV, LEEP, pPROM, PROM, PTD

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