ABSTRACT

Cervical dysplasia and cervical cancer in pregnancy: diagnosis and outcome

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Cervical cancer is one of the most common types of cancer that is diagnosed during pregnancy. The primary aim in investigation of atypical cervical cytology during pregnancy is to exclude cancer so that further treatment of the lesion can be postponed until after delivery**.** However, there are difficulties in colposcopic evaluation of cervix due to specific changes and cancer can be overlooked if not multiple biopsies are obtained, but these invasive interventions may increase the risk of bleeding from the vascularized cervix and further obstetrical complications. Thus, there is need for means to reduce the number of biopsies and to find biomarkers that can exclude cervical cancer among pregnant women with atypical cervical cytology.

In this thesis, pregnant women were evaluated with the Swede score colposcopic scoring system, due to atypical cervical cytology, dysplasia in biopsy or signs of malignancy in a prospective clinical study. Five colposcopic variables, acetowhiteness, margins plus surface, vessel patterns, lesion size and iodine staining were scored. Colposcopically directed biopsies were taken from all lesions and histology was compared with the Swede score sum. All CIN2+ lesions and cancers had total scores of ≥5and ≥8, respectively. All variables except iodine staining were found significant predictors of CIN2+. In prediction of CIN3+, lesion size, vessel patterns and margins plus surface were significant factors.

In a prospective clinical study, surgical/obstetric complications due to colposcopically directed cervical biopsies, loop-biopsies, or LEEP-cones were evaluated. The histology results during pregnancy were compared to that after delivery to evaluate the natural course of dysplastic lesions. Obstetric outcome was recorded and compared to the 54919 other births in the same geographical area during the study period. Only a minor part (12.3%) of the dysplastic lesions showed progression during pregnancy with 54.6% and 33.1% showing persistence and regression, respectively. No surgically-related postoperative bleeding that needed surgical (diathermy/suture) treatment occurred. The miscarriage rate was low (0.8%). There were no differences in mode of delivery, rate of premature birth or other obstetrical variables between the study group and the control cohort.

In a retrospective clinical study, medical records were evaluated of all women with cervical cancer diagnosed during pregnancy or within 6 months after parturition between 1993 and 2008 in the Western region of Sweden. Cervical cancer was diagnosed in 47 women (15.6/100 000 deliveries). Sixteen women were diagnosed after abnormal vaginal bleeding and/or discharge. The other women were asymptomatic and diagnosed by abnormal cervical smear or clinical signs at vaginal examination. Nine women had ASCUS as presenting cervical atypia. Cancer was diagnosed in the 1st trimester in 2 women, in the 2nd trimester in 14, in the 3rd trimester in 5 and post-partum in 26 women. Twenty women underwent cesarean section due to cancer, combined with the Wertheim-Meigs procedure in six women. Sixteen women having stage IA1 cancer underwent conization as final treatment. Six women died of the disease.

Liquid-based cytology samples were analysed for high-risk-HPV DNA genotype (an In-house real-time DNA PCR assay and the commercial Linear Array®), high-risk-HPV E6/E7 mRNA (a recently developed In-house real-time mRNA PCR assay and the commercial PreTect^{TM} HPV-Proofer) and p16^{INK4a} immunocytochemistry in pregnant women with normal cytology and atypical cytology. This study followed an initial study of different HR-HPV tests in mainly non-pregnant populations. In pregnant women stepwise logistic regression analysis showed that the p16 ^{INK4a} test and the In-house real-time mRNA PCR test were the most suitable tests in detecting high-grade lesions.

In summary, the Swede score seems to be a useful tool in evaluating atypical cervical cytology in pregnant women and may reduce the need for diagnostic biopsies and analysis of p16 ^{INK4a} positivity and HR-HPV mRNA may be useful supplementary tests in pregnant populations with atypical cytology to accurately detect high-grade lesions. Investigation of atypical cytology during pregnancy with biopsy including large loop excisions is a safe procedure in regards to surgical complications and obstetrical outcome. There is a high rate of persistence and regression of dysplasia during pregnancy. Early detection of cervical cytological atypia and proper follow-up during pregnancy may lead to the detection of an increased proportion of stage I cancer, thereby avoiding radical operative procedures.

Keywords: Cervical dysplasia, cervical cancer, pregnancy, colposcopic scoring system, regression, persistence, progression, HPV DNA test, HPV mRNA E6/E7 test, p16^{INK4a}

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This thesis is based on the following papers:

I. **Histological diagnosis and evaluation of the Swede score colposcopic system in a large cohort of pregnant women with atypical cervical cytology or cervical malignancy signs**
Kärrberg C, Ryd W, Strander B, Brännström M, Rådberg T
Acta Ob Gyn Scand, 2012;91:952-8.

II. **Colposcopically directed cervical biopsy during pregnancy; minor surgical and obstetrical complications and high rate of persistence/regression**
Kärrberg C, Brännström M, Strander B, Ladfors L, Rådberg T
Submitted.

III. **Incidence and treatment of cancer of the uterine cervix in pregnancy, including all cases in the Western region of Sweden 1993-2008**
Kärrberg C, Rådberg T, Holmberg E, Norström A
Submitted.

IV. **Type-specific human papillomavirus E6/E7 mRNA detection by real-time PCR improves identification of cervical neoplasia**
Andersson E, Kärrberg C, Rådberg T, Blomqvist L, Zetterqvist B-M, Ryd W, Lindh M, Horal P
J Clin Microbiol, 2011;49:3794-9.

V. **Could p16 ^{INK4a} and high-risk HPV mRNA analysis of liquid-based cytology identify pregnant women at risk for cervical carcinoma?**
Kärrberg C, Andersson E, Ryd W, Dohse M, Brännström M, Rådberg T
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