PhD Thesis by Iben Sundtoft, MD

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Title:

Hydroxyproline in Cervical Biopsies from non-pregnant women as a Biomarker of Pregnancy Outcome

English summary:

Preterm birth (PTB) is a leading cause of perinatal morbidity and mortality with an estimated one million infant deaths a year on a global scale. Knowledge on the etiology is a prerequisite for prevention and treatment of factors leading to PTB. Cervical insufficiency (CI) is most probably an uncommon condition characterized by an inability of the uterine cervix to retain the pregnancy leading to PTB. Possible causes of CI include structural abnormalities, surgery or trauma, infection or inflammation, or a structural weakness of the cervix. A structural weakness may be caused either by a preterm ripening or a constitutional defect in the cervical collagen, as cervical resistance is determined primarily by the collagen.

The main purpose of this thesis was to study the hypothesis of CI being caused by a constitutional low cervical collagen concentration.

The first study describes the changes in cervical collagen concentration during 15 months following delivery. The collagen concentrations were determined in cervical biopsies obtained from 15 women at 3, 6, 9, 12, and 15 months after delivery. We found a steady increase in cervical collagen concentration until 9 to 12 months after a term birth. Based on the results of this study, we propose that the association between a short interpregnancy interval and PTB may be due to incomplete remodeling of the cervix as restoration of cervical composition is not achieved until 12 months after delivery. Especially when counseling women with a history of PTB, this information should be taken into account.

The second study evaluates a clinically applicable method for determining the cervical collagen concentration in non-pregnant women. In cervical biopsies from 182 women different aspects as handling of cervical biopsies, the distribution of collagen throughout the uterine cervix and the association to age and parity. With this study

we have demonstrated a clinically applicable method for the assessment of cervical collagen concentration. A weak correlation between collagen concentration, age and parity was found.

The third study investigates the cervical collagen concentration in 33 non-pregnant women with a history of CI compared to a control group of 95 normal non-pregnant women. CI women have a low mean collagen concentration compared to normal women; though a subgroup of women treated with vaginal cerclage in a previous pregnancy have a normal collagen concentration most probably caused by cicatricial tissue. These findings are promising for cervical collagen concentration as a biomarker of CI, thus further studies are needed.

The fourth study examine the association between CI and polymorphisms in cytokine genes, mannose- binding lectin (MBL) 2 gene, and genes related to the connective tissue metabolism in 30 women with a history of CI compared to a control group of 70 normal women. We found single nucleotide polymorphisms in the proinflammatory cytokine IL6, and MBL deficiency causing immunodeficiency to be associated with CI. We found no association between the mean cervical collagen concentration and genotypes of *COL1A1* and *TGF-B* in women with CI.

The conclusion of this thesis is that CI is associated with a constitutional low collagen concentration. A clinically applicable method has been demonstrated for the assessment of cervical collagen concentration. Biopsies must be obtained at least 12 months after completed pregnancy to ensure restoration of the cervix. The incomplete remodeling of the cervix until 12 months after delivery may also provide us with an explanation on the association between a short interpregnancy interval and PTB.