

**MATRIX METALLOPROTEINASES (MMP) AND
TISSUE INHIBITORS OF METALLOPROTEINASES (TIMP)
IN THE CERVICAL MUCUS PLUG**

PhD dissertation
Naja Becher



FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY
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Author:

Naja Becher, MD
Research Laboratory of Obstetrics and Gynecology
Aarhus University Hospital, Skejby
nbecher@dadlnet.dk

Papers:

Paper 1

Becher N, Hein M, Danielsen CC, Uldbjerg N: Matrix metalloproteinases and their inhibitors in the cervical mucus plug at term of pregnancy. *Am J Obstet Gynecol* 2004, 191:1232-39.

Paper 2

Becher N, Hein M, Uldbjerg N, Danielsen CC: Balance between matrix metalloproteinases (MMP) and tissue inhibitors of metalloproteinases (TIMP) in the cervical mucus plug estimated by determination of free non-complexed TIMP. *Journal of Reproductive Biology and Endocrinology (RB&E)*. Sept. 30 2008

Paper 3

Becher N, Hein M, Danielsen CC, Uldbjerg N: In the cervical mucus plug, matrix metalloproteinase 8 (MMP-8) and MMP-9, but not MMP-2 and tissue inhibitor of metalloproteinase 1 (TIMP-1), reflect inflammation as indicated by interleukin 8 concentration.

Manuscript in preparation

Supervisors:

Carl Christian Danielsen, Associate Professor, Department of Connective Biology, Institute of Anatomy, University of Aarhus, Denmark (ccd@ana.au.dk)

Niels Uldbjerg, Professor, Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark (uldbjerg@dadlnet.dk)

Merete Hein, MD, PhD, Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark (merete.hein@dadlnet.dk)

Evaluation Committee:

Jan-Olof Winberg, Professor, Department of Medical Biochemistry, Institute of Medical Biology, University of Tromsø, Norway (jan.o.winberg@fagmed.uit.no)

Rikke Bek Helmig, Consultant, PhD, Department of Obstetrics and Gynecology, Aarhus University Hospital, Skejby, Denmark (rikke.bek.helmig@dadlnet.dk)

Thomas Ledet (chairman), Professor, Research Laboratory of Biochemical Pathology, Arhus university Hospital, Denmark (ledet@ki.au.dk)

Head of the defense:

Steffen Thiel, Associate Professor, PhD, Department of Medical Microbiology and Immunology, University of Aarhus, Denmark (st@microbiology.au.dk)

Summary in English

The cervical mucus plug (CMP) plays an important role in pregnancy by protecting the child and the mother from ascending infection. Ascending infection accounts for approximately one third of all cases of preterm delivery worldwide and represents a substantial socio-economic challenge.

From several studies performed on fetal membranes, amniotic fluid, and cervical tissue, it has become evident that specific proteolytic enzymes, the matrix metalloproteinases (MMPs), potentially can influence the degradation of connective tissue during pregnancy and term labor. These enzymes have also been implicated in the pathology of preterm labor caused by ascending infection.

The main purpose of the present thesis was to investigate whether MMPs in the CMP, situated in the cervical canal in close contact with the fetal membranes and with the cervical tissue, contribute to the labor process both in physiological and pathological situations.

On the basis of our results we conclude that cervical mucus plugs collected during active labor at term contain very high concentrations of specific MMPs (MMP-2, MMP-8 and MMP-9) together with their inhibitors, the tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2).

The potentially harmful CMP MMP activity is generally controlled by an excess of TIMP both within a molar and a functional range. A disturbance in this refined balance between TIMP and MMP may lead to preterm labor in the case of ascending infection.

Non-pregnant cervical mucus exhibits very low levels of inflammation compared to the CMP in accordance with the augmented immune functions of the CMP. A time course of MMP and TIMP in distal CMP samples throughout pregnancy shows a distinct pattern: pro-inflammatory components (MMP-8, MMP-9) are unchanged whereas anti-inflammatory components (TIMP-1, MMP-2) tend to decline.

Whole cervical mucus plugs from preterm deliveries are in general similar to term CMPs concerning MMP and TIMP. But there may be a connection between bacterial infection of the CMP and high MMP-8, MMP-9 and IL-8 concentrations. Analysis of CMP IL-8 makes it clear, that the content of neutrophil-derived MMPs in the CMP is highly related to inflammatory mechanisms.

Sammenfatning på dansk

Slimproppen spiller en vigtig rolle under graviditeten, hvor den beskytter kvinden og barnet mod ascenderende infektion. Ascenderende infektion er skyld i ca. en tredjedel af alle tilfælde af for tidlig fødsel og repræsenterer en stor socioøkonomisk udfordring.

Med flere studier foretaget på fosterhinder, fosterhals og på væv fra livmoderhalsen har man bevist, at specifikke enzymer, matrix metalloproteinaser (MMPs), potentielt kan påvirke nedbrydningen af netop disse væv under graviditet og fødsel. De samme enzymer kan også være involveret i mekanismen bag for tidlig fødsel forårsaget af ascenderende infektion.

Hovedformålet med denne Ph.D.-afhandling har været at undersøge om MMP i slimproppen, placeret tæt på livmoderhals og fosterhinder, bidrager til fødselsprocessen både i fysiologiske og patologiske situationer.

På basis af vores resultater konkluderer vi, at slimpropper, som indsamles under aktiv vaginal fødsel, indeholder meget høje koncentrationer af MMP (MMP-2, MMP-8 og MMP-9) og disse enzymers specifikke hæmmere, tissue inhibitors of metalloproteinases (TIMP-1 og TIMP-2).

Den potentiel skadelige virkning af MMP i slimproppen kontrolleres af netop TIMP, som både molært og funktionelt er i overskud. En forskydning i denne fine balance mellem TIMP og MMP i slimproppen kunne være medvirkende årsag til for tidlig fødsel i tilfælde af infektion.

Livmoderhalssekret fra ikke-gravide kvinder viser markant *færre* tegn på inflammation end slimproppen, som er stærkt inflammeret. Ved at skabe en ”tidslinje” igennem graviditeten med analyser foretaget på biopsier af slimproppens nederste del, har vi vist, at inflammatoriske komponenter (MMP-8 og MMP-9) er konstante igennem graviditeten, og at anti-inflammatoriske komponenter (TIMP-1 og MMP-2) falder hen imod terminstidspunktet.

Sammenligning af slimpropper fra hhv. for tidlig fødsel og fødsel til termin viser, at slimproppen generelt er ens mht. MMP og TIMP i de to situationer. Men der kan være en forbindelse imellem infektion i selve slimproppen, høje koncentrationer af interleukin 8 (IL-8), MMP-8 og MMP-9 og for tidlig fødsel. Analyser af slimproppens indhold af IL-8 viser, at der er en klar sammenhæng mellem inflammatoriske mekanismer og slimproppens indhold af MMP-8 og MMP-9.