

# Clinical, biochemical and morphological aspects of cervical ripening in the first trimester

## Akademisk avhandling

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- I. Gemeprost versus misoprostol for cervical priming before first-trimester abortion: a randomized controlled trial.  
Ekerhovd E, Radulovic N, Norström A.  
*Obstet Gynecol. 2003 Apr;101:722-5.*
- II. Outpatient cervical ripening before first-trimester surgical abortion: a comparison between misoprostol and isosorbide mononitrate.  
Radulovic N, Norström A, Ekerhovd E.  
*Acta Obstet Gynecol Scand. 2007;86:344-8.*
- III. Cervical priming in the first trimester: morphological and biochemical effects of misoprostol and isosorbide mononitrate.  
Vukas Radulovic N, Ekerhovd E, Abrahamsson G, Norström A.  
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- IV. Cervical tissue changes in women with miscarriage: a morphological and biochemical investigation.  
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## Abstract

**Background:** The uterine cervix has the ability to be transformed from being a rigid organ in non-pregnant women to become a loose structure that dilates and allows passage of the foetus at parturition. This process, cervical ripening, has been described similar to an inflammatory reaction of the extracellular matrix involving activation of inflammatory cytokines, matrix metalloproteinases and breakdown of the collagen framework. Cervical ripening can be induced prior to surgical termination of pregnancy by agents such as prostaglandins (PGs) and nitric oxide (NO). It appears reasonable that cervical ripening takes place as a spontaneous event in women with miscarriage before expulsion of gestational products.

**Aims:** The aims of the thesis were to investigate clinical, morphological and biochemical aspects of cervical ripening in the first trimester, both when induced by PGs or NO donors and when spontaneously occurring in women with symptomatic and silent miscarriage.

**Methods:** Nulliparous women admitted for surgical termination of pregnancies in the first trimester were randomized to cervical priming with either gemeprost or misoprostol (Study I), and to misoprostol or isosorbide mononitrate (IMN) (Study II). In Study I and II, the efficacy of cervical priming was measured by tonometry. Side effects were also estimated. In Study III cervical biopsies from women treated with misoprostol or IMN were analyzed using electron microscopy (EM). Inflammatory parameters were analyzed by ELISA (IL-8) and immunohistochemistry (IHC) (MMP-1, MMP-9). In Study IV biopsies were obtained from nulliparous women suffering symptomatic or silent miscarriage and from women undergoing surgical termination of pregnancy. Morphology was studied by EM and inflammatory parameters by ELISA (IL-8) and IHC (IL-8, MMP-1, MMP-8, MMP-9).

**Results:** There was no difference in baseline cervical dilation and cumulative force to dilate the cervix to 10 mm in women treated with misoprostol compared to gemeprost. Cervical resistance was higher in women treated with IMN compared to women treated with misoprostol. Abdominal pain and vaginal bleeding were frequent following cervical priming with misoprostol, while headache was common following IMN. In cervical specimens from women treated with misoprostol the collagen framework was disorganized and fibroblasts and mast cells appeared activated. Similar ultrastructural changes were observed in specimens from women treated with IMN, though less pronounced. Cervical tissue levels of IL-8 were higher in women treated with misoprostol compared to IMN and controls. Immunohistochemical staining for MMP-1 and MMP-9 was of higher intensity in women treated with IMN compared to misoprostol. In cervical tissue from women with miscarriage the organization of the collagen framework was deranged. Fibroblasts were reactive and mast cells were frequently observed and demonstrated secretory activity. Tissue levels of IL-8 were increased in women with miscarriage. Immunopositivity of MMP-1 and MMP-8 did not differ between women with miscarriage and control women. MMP-9 was lower in women with symptomatic miscarriage compared to women with silent miscarriage and controls.

**Conclusions:** Misoprostol is as effective as gemeprost for cervical priming in the first trimester. Misoprostol induces a more pronounced cervical ripening than IMN, but both treatments are associated with side effects when the treatment interval exceeds 4 hours. Both misoprostol and IMN induces a tissue response consistent with an inflammatory reaction. In women suffering either symptomatic or silent miscarriage an inflammatory response takes place, indicating an ongoing ripening process. Therefore, inadequate cervical remodelling does not seem to be the reason why some miscarriages remain silent.

Key words: cervical ripening, misoprostol, nitric oxide, IL-8, MMP-1, MMP-8, MMP-9, miscarriage, electron microscopy