



NITRIC OXIDE DONORS IN LABOR MANAGEMENT

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av

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- I.** Ekerhovd E, Bullarbo M, Andersch B, Norström A. Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term: A randomized controlled study. *Am J Obstet Gynecol* 2003; 189: 1692-1697
- II.** Bullarbo M, Eriksson-Orrskog M, Andersch B, Granström L, Norström A, Ekerhovd E. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: A randomized controlled study. *Am J Obstet Gynecol* 2007; 196: 50.e1-e5
- III.** Bullarbo M, Norström A, Andersch B, Ekerhovd E. Isosorbide mononitrate induces increased cervical expression of cyclooxygenase-2, but not of cyclooxygenase-1, at term. *Eur J Obstet Gynecol* 2007; 130: 160-164
- IV.** Bullarbo M, Tjugum J, Ekerhovd E. Sublingual nitroglycerin for management of retained placenta. *Int J Gynecol Obstet* 2005; 91: 228-232

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ABSTRACT

Nitric oxide donors in labor management

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Background: Nitric oxide (NO), a free radical with ultra-short half-life synthesized from L-arginine by the enzyme nitric oxide synthase (NOS), is in the human involved in many physiological and pathophysiological processes, including different reproductive processes. During pregnancy NO is produced endogenously in the human uterine cervix and placenta. Different effects of NO can be studied by administering NO donors.

Aims and methods: The aims of the thesis were to perform experimental and clinical studies on late pregnant women to examine the effects of NO donors on cervical ripening and labor induction and to evaluate possible effects of NO on the management of retained placenta. In Paper I the effects of the NO donor isosorbide mononitrate (IMN) administered vaginally were examined by measuring cervical distensibility using a cervical tonometer. In addition, maternal and fetal side effects of the medication were evaluated. In Paper II the efficiency of vaginally administered IMN to induce cervical ripening and labor induction in an outpatient setting was examined. The safety and side effects of this treatment were also evaluated.

In Paper III cervical biopsies were obtained prior to elective caesarean section following vaginal administration of IMN. Western blotting was used for semiquantitative measurements of cyclooxygenase-1 and -2 (COX-1 and COX-2), enzymes involved in prostaglandin synthesis as well as cervical ripening. Immunohistochemistry was used for localizing these enzymes within the cervical tissue. Paper IV describes the efficiency of sequential treatment with oxytocin and nitroglycerin for management of retained placenta.

Results: Treatment with IMN resulted in a significantly increased cervical distensibility. Headache and palpitations of little to moderate intensity were common maternal side effects. A significant decrease in maternal blood pressure and increase in pulse rate were registered. However, the effects were modest and not of clinical importance. No fetal side effects were observed according to CTG, Doppler ultrasound, Apgar score and umbilical pH. Vaginally administered IMN seemed to be effective in promoting labor induction within 24 hours (22 patients compared to 8 in the placebo group). There were no differences in fetal side effects and the rate of caesarean section between women treated with IMN and women in the placebo group. Semiquantitative measurements by immunoblotting revealed increased expression of COX-2, but not of COX-1 in the NO donor group compared to placebo group. Immunohistochemistry showed similar localizations of COX-1 and COX-2 in the two groups. Sublingually administered nitroglycerin in combination with oxytocin resulted in successfully delivered placenta among all 12 women compared to only 1 woman in the control group. Maternal hemodynamic effects were mild to moderate. Blood loss was increased in women who needed manual removal of placenta.

Conclusion: The data suggest that IMN administered vaginally at term and postterm for cervical ripening and labor induction seems to be effective and safe. Combined treatment with oxytocin and nitroglycerin seems to promote detachment of retained placenta.

Key Words: cervical ripening, labor induction, nitric oxide donor, retained placenta.

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