# Nitric Oxide Donors for Pre-induction Cervical Ripening

## A Thesis

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*Ahmed Samir Eid Mohamed*

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# List of Abbreviations

**CS** : Cesarean section
**cGMP**: Cyclic guanosine monophosphate
**FAP** : Fetal arterial perfusion pressure
**FHR** : Fetal heart rate
**GTN** :Glyceryltrinitrate
**GAGs** :Glycosaminoglycans
**HA** :Hyaluronan
**HAase**:Hyaluronidase
**HPV** : Hypoxic pulmonary vasoconstriction
**IVF** : In vitro fertilization
**IOL** : Induction of labor
**IL** : Interleukin
**ISDN** :Isosorbiddinitrate
**ISMO** :Isosorbidemononitrate
**IMN** :Isosorbidemononitrate
**ISMN** :Iso-sorbidemononitrate
**ISTN** :Iso-sorbidetrinitrate
**IUD** : Intrauterine device
**LPS** : Lipopolysaccharide
**mU**:Milliunit
**ml** : Milliliter
**TNF-** $\alpha$ : Necrosis factor-alpha
**Neu**: neutrophils

**NO** : Nitric oxide
**NOS** : Nitric oxide synthase
**NTG** : Nitroglycerine
**NMDA** : N-methyl-D-aspartate
**OT** : Peptide Oxytocin

**PG** : Prostaglandins

**PGE2** : Prostaglandins E2
**PI** :Pulsatility index
**PCT** : Randomized controlled trial
**RCOG** : Royal college of Obstetricians and Gynecologists
**SNAP** : S nitroso-N-acetyl-penicillamine
**SNP** : Sodium nitroprusside
**SOD** : Superoxide dismutase
**TENS** : Transcutaneous nerve stimulation
**TGF-**β : Transforming growth factor-β

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# INTRODUCTION

# Introduction

Artificial cervical ripening is a component part of induction of labor that is used when the cervix is unfavorable to facilitate cervical dilation when labor is established. Because the success of induction is related to cervical ripening, artificial cervical ripening before labor induction is used to reduce the associated risk of cesarean delivery ***(Osman et al., 2006).***

Induction of labor (IOL) in the presence of an unripe cervix is associated with failed induction, failure to progress in labor, and an increased risk of chorioamnionitis and cesarean section (CS) ***(Furukan et al., 2007).***

The drugs commonly used in hospital settings, such as prostaglandins E2 (PGE2, dinoprostone) and prostaglandin E1 (PGE1, misoprostol), are effective for cervical ripening. However, the high incidence rates of myometrial hyperstimulation, uterine hypertonus, tachysystole, and fetal distress associated with their use ***(Agarwal et al., 2012).***

In contrast to prostaglandins, nitric oxide donors such as isosorbide mononitrate (IMN) and glyceryl trinitrate inhibit rather than stimulate uterine contractions, and promote rather than restrict uterine blood flow. Therefore, nitric oxide donors appear to be the ideal cervical ripening agent for outpatient use ***(Ekerhovd et al., 2003).***

Isosorbide mononitrate 40 mg is originally an orally administered medicine, marketed and registered for use in the prevention and treatment of angina pectoris. However, its observed uterine tocolytic and cervical ripening effects suggest its possible role in pre-induction cervical ripening ***(Habib et al. 2008).***

The major physiological effect of nitric oxide (a free radical gas with a half-life of less than four seconds) is the relaxation of smooth muscle. Nitric oxide itself is endogenously supplied from L-arginine through the action of the nitric oxide synthase (NOS), which has been identified as being present in the human cervix. This NO product reacts with soluble guanylate cyclase, the product of which raises the concentration of intracellular cyclic guanosine monophosphate (cGMP). cGMP causes the dephosphorylation of myosin light chains within the smooth muscle structure leading to its relaxation. Significantly, the cervix is largely composed of connective tissue, including smooth muscle. Previous studies have confirmed that this smooth muscle component of the cervix has a functional role in cervical ripening ***(Kelly et al., 2011).***

# Review of Literature

# Morphology of human cervix

## *Anatomy and* Embryology of the cervix:

The human female reproductive tract is a complex multifunction organ system that passes through its most critical developmental stages in the first 12 weeks of gestation **(McFadden et al., 1992).**

The formation of the urorectal septum subdivides the primitive cloaca and distinguishes the anorectal and urogenital sinus **(Paidas et al.,1999).**

Development begins between the third and fifth gestational weeks, when the metanephric ducts emerge and connect with the cloaca. Between the fourth and fifth weeks, two ureteric buds develop distally from the mesonephric ducts and begin to grow cephalad toward the mesonephros. Mullerian (paramesonephric) ducts form bilaterally between the developing gonad and the mesonephros. The mullerian ducts extend downward and laterally to the mesonephric ducts, and they finally turn medially to meet and fuse together in the midline. The fused mullerian duct descends to the urogenital sinus to join the mullerian tubercle.
The uterus is formed by the union of the two mullerian ducts at about the 10th week.The vagina forms between the urogenital sinus and the mullerian tubercle by a dissolution of the cell cord between the two structures. It is believed that this dissolution starts at the hymen and moves upward toward the cervix.
***( Cunningham et al., 2005).***

## Anatomy

***Size and shape:***

The uterus is located in the pelvic cavity in non-pregnant women and also during first trimester of pregnancy, the later with advancement of pregnancy, it becomes an abdominal organ. It is situated between the bladder on its anterior surface and the rectum on its posterior surface. The uterus resembles a flattened pear in shape. It consists of two major but unequal parts: an upper triangular portion, the body, or corpus; and a lower, cylindrical, or fusiform portion, the cervix, which projects into the vagina. The isthmus is that portion of the uterus between the internal cervical os and the endometrial cavity. It is of special obstetrical significance

because it forms the lower uterine segment during pregnancy ***(Leppert, 1995; Cunningham et al., 2005)***.

In the premenarchal girl, the body of the uterus is only half as long as the cervix. In nulliparous women, the cervix is only a little more than a third of the total length of the organ. After menopause, uterine size decreases as a consequence of atrophy of both myometrium and endometrium ***(Cunningham et al., 2005).***

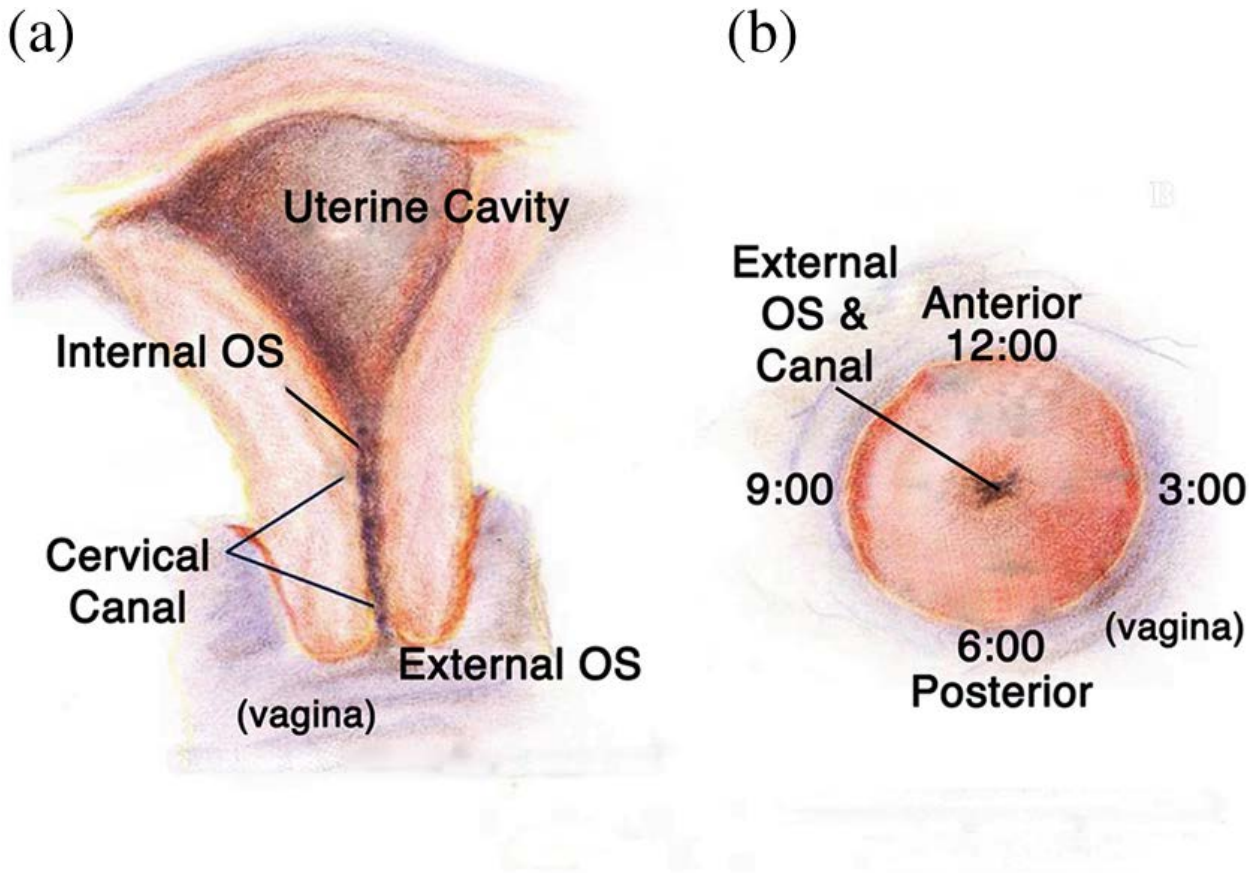


***Figure 1***: A cross-sectional view of the cervix. The uterus is above the internal os, and the cervix below. The proximal portion of the cervix (closest to the uterus) resides in the pelvis, and the distal portion protrudes into the vagina. The inner cavity is called the endocervical canal and is contiguous with the uterine cavity. (b) Distal portion of the cervix as seen through a speculum. Locations on the cervix are conventionally labeled as if the distal end were the face of a clock***(Reusch et.al.,2013).***