

Nitric Oxide Donors for Pre-induction Cervical Ripening

A Thesis

Submitted for Partial Fulfillment of Master Degree
in Obstetrics and Gynecology

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2013

Acknowledgment

*My deepest gratitude and thanks to **ALLAH** the most Merciful for guiding me through and giving me the strength to complete this work the way it is.*

*I wish to express my deepest thanks and gratitude to **Prof. Dr. Abdel Megeed Ismail Abdel Megeed**, Professor of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University, who gave me the honor of working under his supervision, continuous guidance and valuable advice throughout the work. He offered me his support and patience, enriching me with his vast experience and continuous advices which helped me to overcome any difficulty.*

*I would like to express my deepest gratitude and special thanks to **Dr. HayamFathy Mohammed**, Lecturer of Obstetrics & Gynecology, Faculty of Medicine, Ain Shams University, for her close observation, generous guidance, effective help, and valuable supervision.*

Finally, it is a great honor to me to express my deepest gratitude, extreme thankfulness and deep appreciation to my Family who helped me a lot to complete this work.

✍️ Ahmed Samir Eid Mohamed

LIST OF CONTENTS

Title Page No.	
List of Abbreviations	<i>i</i>
List of Tables	<i>iii</i>
List of Figures	<i>v</i>
Introduction	1
Aim of the Work	3
Review of Literature	
- Morphology of Human Cervix	4
- Induction of Labor	14
- Cervical Ripening	32
- Nitric Oxide	51
Patients and Methods	103
Results	111
Discussion	127
Summary	134
Conclusion	135
Recommendations	138
References	139
Arabic Summary	

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- α : 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

LIST OF TABLES

Table (1): Bishop Scoring System Used for Assessment of Inducibility, Quoted from Williams Obstetrics, 2005..... 39

Table (2): Properties of NOS 55

Table (3): Postulated roles of endogenous NO: 59

Table (4): Comparison between the two studied groups regarding age and gestational age 111

Table (5): Comparison between the two studied groups regarding indications for induction of labor..... 111

Table (6): Comparison between the two studied groups regarding duration of first, second and third stage of labor. 113

Table (7): Comparison between the two studied groups regarding Time from drug administration till end of latent phases and time from drug administration till vaginal delivery..... 115

Table (8): Comparison between the two studied groups regarding changes in modified bishop's score after 2 hours, 4hours, 6hours and 8 hours. 117

Table (9): Comparison between the two studied groups regarding mode of delivery..... 118

Table (10): Comparison between the two studied groups regarding causes of cesarean sections. 119

Table (11): Comparison between the two studied groups regarding fetal weight..... 120

Table (12): Comparison between the two studied groups regarding Apgar score at 1 min and 5 min..... 121

Table (13): Comparison between the two studied groups regarding maternal complications. 122

Table (14): Comparison between the two studied groups regarding fetal complications. 123

Table (15): Comparison between the two groups regarding total number of tab. Used, MABP, and pulse at admission and after treatment. 124

Table (16): Comparison between the two studied groups regarding MABP and pulse at admission and after treatment. 125

LIST OF FIGURES

Figure (1): A cross-sectional view of the cervix.	6
Figure (2): Different cut sections and the E/M view of the cervix	9
Figure (3): A: Schematic diagram showing how the tropocollagens are composed of 3- α chains, cross-linked and staggered to give rise to light and dark bands on electron microscopy.	11
Figure (4): Cervidil vaginal insert contains 10 mg of dinoprostone.....	25
Figure (5): A major source of collagenase is the neutrophil which contains MMP-8 (neutrophil collagenase) in specific granules.	34
Figure (6): The internal os of the cervix, where ripening starts, lies in close proximity to the fetal membranes.....	35
Figure (7): Changes in the cervical stroma and epithelia during the remodeling process.	37
Figure (8): Proposed model for the functions of hyaluronan in cervical remodeling.	38
Figure (9): Electron micrographs of the cervix illustrating the changes in morphology resulting in cervical ripening with the onset of parturition.....	40
Figure (10): Extra-amnionic saline infusion (EASI) through 26F Foley catheter is placed through the cervix.	45
Figure (11): Cervical ripening using balloncatheter	46

Figure (12): The synthesis of nitric oxide (NO) from L-arginine.	53
Figure (13): Scheme showing constitutive release of NO. ...	55
Figure (14): Effect of no. on vascular smooth muscle cells.	60
Figure (15): Metabolic pathway of ISMN.	62
Figure (16): Comparison between the two studied groups regarding age of patients.	112
Figure (17): Comparison between the two studied groups regarding gestational age.	112
Figure (18): Comparison between the two studied groups regarding indications for induction of labor.....	113
Figure (19): Comparison between the two studied groups regarding the time of 1st stage of labor.	114
Figure (20): Comparison between the two studied groups regarding the time of 2nd. and 3rd. stage of labor.	114
Figure (21): Comparison between the two studied groups regarding the time interval from drug administration till vaginal delivery.	116
Figure (22): Comparison between the two studied groups regarding the time from drug administration till end of latent phase.	116
Figure (23): Comparison between the two studied groups regarding the changes in the modified bishop's score after 2 hours, 4 hours, 6 hours and 8 hours.	117

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*).

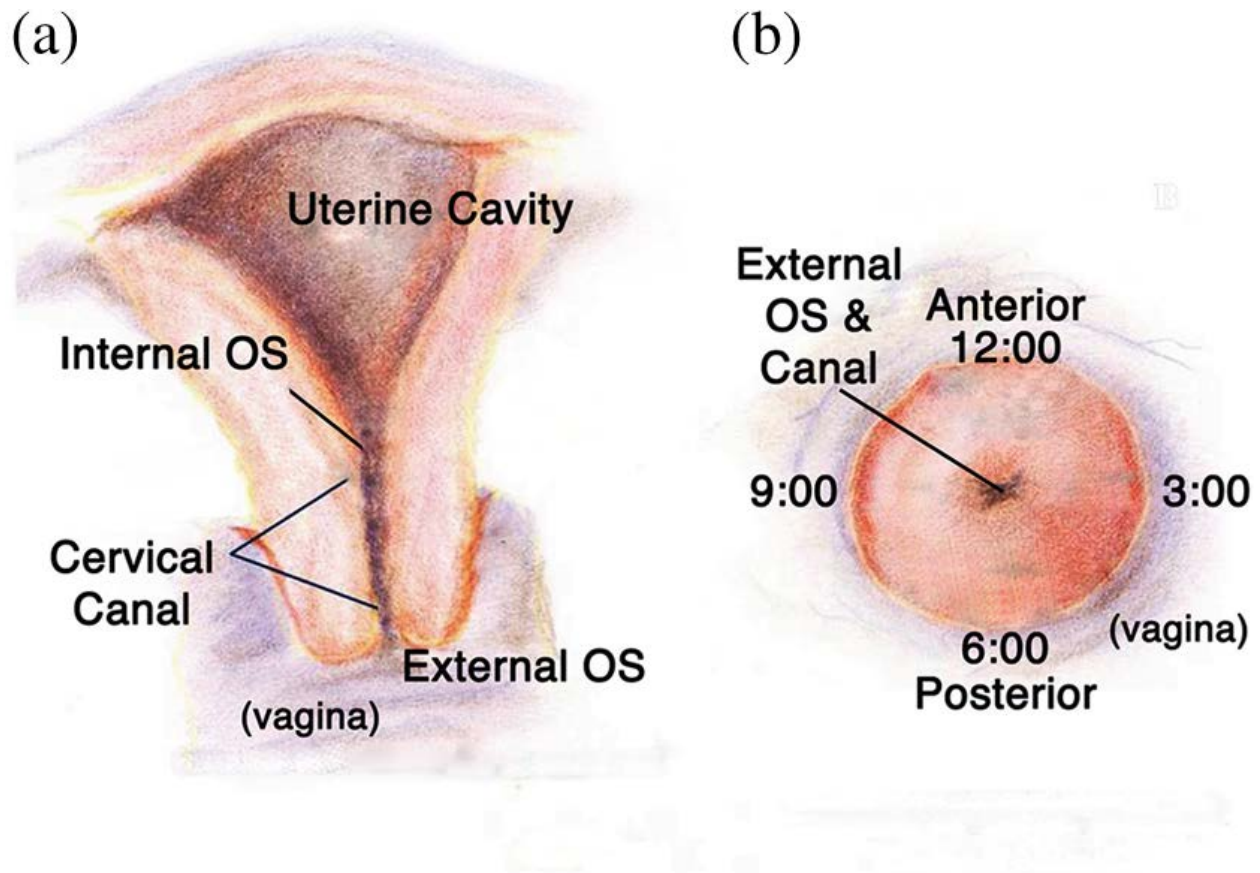


Figure 1: A cross-sectional view of the cervix. The uterus is above the internal os, and the cervix below. The proximal portion of the cervix (closest to the uterus) resides in the pelvis, and the distal portion protrudes into the vagina. The inner cavity is called the endocervical canal and is contiguous 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*).