Isosorbide Mononitrate Versus Misoprostol for Cervical Ripening and Induction of Labor

A Protocol of Thesis
Submitted for Partial Fulfillment of the Master Degree
In **Obstetrics and Gynecology**

Presented By
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Heba Fahmy Salim

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List of Abbreviations

ECM	Extracellular matrix
EDC	estimated date of confinement
CRF	corticotropin releasing factor
MMP	Matrix metaloprotienase
TNF	Tumer necrosis factor
IL8	interleukin 8
GAGs	glycosamioglycans
PAF	platlet activating factor
APH	Antepartum hemorrhage
PGE2	prostaglandin E2
PPROM	premature preterm rupture of membrane
FHR	Fetal heart rate
ISMP	institute for safe medication practices
MIU	mill international unit
Mcg - μg	Microgram
PGDH	Prostaglandin dehydrogenase
COX-2	cyclooxygenase-2
NO	Nitric oxide
NOS	Nitric oxide sysnthase
iNOS	inducible nitric oxide sysnthase
nNOS	Neuronal nitric oxide sysnthase
bNOS	Brain nitric oxide sysnthase
eNOS	Endothelial nitric oxide sysnthase
LPS	Lipopolysaccharides
IMN	Isosorbide mononitrate

List of Abbreviations (Cont.)

GTN	Glyceryl trinitrate
cGMP	Cyclic guanosine monophosphate
C.S	Cesarean section
U/S	Ultrasound scanning
LMP	Last menstrual period
CTG	Cardiotocography
AROM	Artificial rupture of membrane

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Introduction

Induction of labor is defined as the process of artificially initiating uterine contractions, prior to their spontaneous onset, with progressive effacement and diltation of the cervix and ultimately, the delivery of the baby ***(Martin et al, 2005).***

There are many indications for induction of labor in the obstetric practice, of which prolonged gestational age stands as the most common cause. It's well recognized that with an unripe cervix, induction may be difficult and often unsuccessful. The use of an agent to ripen the cervix prior to induction is acceptable in the modern practice ***(Josie, 2003).***

Cervical ripening is associated with an increase in cyclooxygenase enzyme, which leads to local increase of prostaglandin production in the cervix. This in turn leads to a subsequent series of important changes associated with progressive cervical ripening ***(Dede et al, 2004).***

Misoprostol, a prostaglandin E_1 analogue, is the most interesting alternative to Dinoprostone because of its effectiveness, low cost, and temperature stability. It ripens the cervix by inducing regular uterine contractions. However, it is associated with several adverse effects especially uterine hypertonicity which is painful and may result in fetal compromise. These adverse effects are infrequent, dose-dependent, and vary according to the route of administration ***(Hofmeyr et al, 2003).***

The ideal cervical ripening agent should produce a high degree of cervical ripeness without stimulating uterine activity and with minimal adverse effects to mother and fetus and nitric oxide (NO) donors are such agents e.g. Glyceryltrinitrate and isosorbide mononitrate ***(Nicoll et al, 2001).***

Aim of The Work

The aim of the work is to determine the effectiveness and adverse effects of isosorbide mononitrate versus the misoprostol in cervical ripening and labor induction.

Anatomy and Histology of the uterus and Cervix Female Genital Tract

A) Gross Anatomy The Uterus and Cervix :

Size and shape:

The uterus is a muscular organ in which the smooth muscle cells account for approximately 70% of tissue weight, they are oriented in an ordered fashion to promote effective contractions during labour. It's pear shaped, situated between the urinary bladder anteriorlly and the rectum posteriorly. It consists of two major unequal parts: an upper triangular portion, the body or the corpus and the lower 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's of a special obstetrical significance because it forms the lower uterine segment during pregnancy ***(Cunningham et al., 2005)***.

The cervix is the specialized portion of the uterus that is below the isthmus the whole cervical length is about 2.5-3 cm and its wall is about 1 cm thick throughout its length. The cervix is divided by the attachment of the vagina into vaginal and supravaginal portions, the supravaginal portion on its posterior surface is covered by a peritoneum. Laterally it's attached to the cardinal ligament, and anteriorly, it is separated from the overlying bladder by loose connective tissue ***(Cunningham et al., 2005)***.

B) Microscopic Anatomy (Histology):

(I) Cervix:

a- Cervical mucosa:

The mucosa of the cervical canal is composed of a single layer of high columnar epithelium that rests on a thin basement

membrane. The oval nuclei are situated near the base of the columnar cells, the upper portions of which appear to be clear because of contents of mucus. These cells are supplied abundantly with a cilia. There are numerous cervical glands that extent from the endocervical mucosa into the subjacent connective tissue; because there is no submucosa. These glands secrete the thick, tenacious mucus of the cervical canal. These glands end abruptly at the level of external os, giving way to the stratified squamous epithelium that covers the potiovaginalis and extends into the vagina ***(Cunningham et al., 2005)***.

b- Collagen:

The cervix in a fertile non pregnant women contains 80% water and 50% of its total dry weight is formed of collagen fibers, which represents 82% of total cervical proteins ***(Danforth, 1983).***

During parturition, the increased water content obviously helps to soften the cervix, but proper dilation is dependent on changes in the collagen containing fibers and in the other components of the extracellular matrix (ECM), so the connective tissue is the major component of the uterine cervix ***(Uldbjerg et al., 1983).***

c- Elastic tissue:

There is insignificant amount of the elastic fibers in the cervix. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. The ratio of elastin to collagen is higher at the area of internal os ***(Leppert and Yusy, 1991)***.

d- The fibromuscular junction:

The junction between the uterine corpus and its cervix is variable from one specimen to another and microscopic

examination is usually needed to determine the exact point of transition from predominantly muscle to predominantly collagen, in most cases transition occurs over the course of 2-3 ml and when line is drawn across the critical area of transition it appear in most of cases wavy line ***(Danforth, 1983).***

e- Muscle:

The muscle cells are scarce in the cervix comprising approximately 6% of the total number of the cells, in the distal part of the cervix. The Extracellular matrix performs an important function in holding the cervical cells together and has some appropriate combination of two basic attributes: an ability to withstand high tensile or compressional stresses and an ability to recover shape and form when these stresses are removed ***(Welsh and Nicolaides, 2002).***

Cervical ECM consists primarily of collagen fibrils the small proteoglycans decorin, influence the organization of ECM and also contains binding sites for growth factors cytokines and other regulatory molecules ***(Kjellen and Lindah, 1994).***

Histological changes during pregnancy:

The collagen fibers are loosened and the loosening process consists of three components namely:

1. Separation of individual fibers into a number of very fine fibrils.
2. Actual fiber reabsorption.
3. Replacement by fluid with increasing the vascularity of the cervix as pregnancy advances.

(Granstrom et al., 1989).