COMPARATIVE STUDY BETWEEN ORAL MISOPROSTOL AND VAGINAL MISOPROSTOL FOR INDUCTION OF SECOND TRIMESTER ABORTION ON PATIENTS PRIMED BY VAGINAL NITRIC OXIDE DONORS

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Abstract

Induction of lab our can be achieved b a variety of physical and biochemical stimuli designed to effect changes in the uterine cervix cause the myometrimn to contract or both the favorability of successful induction (especially in nulliparae) and should be assessed prior to induction by means of the bishop score.

Key word:

Misoprostol trimester abortion oxide donors

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LIST OF ABBREVIATIONS

°C	**Degree Centigrade**
cAMP	**Cyclic Adenosine Monophosphate**
cGMP	**cyclic Gunanosine MonoPhoshpate**
D&E	**Dilation and Evacuation**
D&X	**Dilatation and Extraction**
ECM	**Extra Cellular Matrix**
EDTA	**Ethyl Diamin Tetra Acitic acid**
EDRF	**Endothlial Derived Relaxing Factor**
eNOS	**Endothelial nitric oxide synthase**
F	**Phosphat buffer**
GTN	**glyceryl trinitrate**
hrs	**Hours**
HETE	**Hydroxy Eicosatetraenoic acid**
IUP	**Intra Uterine Pressure**
IUFD	**Intrauterine Fetal Death**
mg	**Milligram**
µg	**Microgram**
MMPs	**Matrix metalloproteinases**
mRNA	**Messenger ribonucleotide acid**
NO	**Nitric Oxide**
NOS	**Nitric Oxide Synthase**
PG	**Prostaglandins**
PROM	**premature rupture of the membranes**
S.D	**Standard Deviation**
TX	**Thromboxane**

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INTRODUCTION

Termination of pregnancy is one of the most common procedures in gynecological practice ***(Nagai et al.,2000).*** Access to safe second trimester abortion services is poor in many countries ***(Turner et** al, **2008).***

Outdated second trimester abortion methods are still being used and very few studies have compared them to currently recommended methods ***(Boza et al. ,2008).***

Various management protocols have been used for second trimester pregnancy termination. These include surgical techniques (dilation and evacuation) and medical approaches such as intra-amniotic prostaglandins $F_{2\alpha}$ instillation, prostaglandin E2 vaginal suppostiories, prostaglandin EI and high does oxytocin ***(Behrashi andMahdian 2008).***

Although dilation and evacuation had been used for second trimester pregnancy termination, it was an invasive method and lead to possible complications such as cervical trauma, cervical or uterine perforation, cervicovaginal fistula, sepsis and bleeding. Surgical method also needed the availability of adequately trained individuals and equipments ***(Behrashi and Mahdian 2008).***

Many uterotonic drugs traditionally used to induce labor, prevent or manage postpartum hemorrhage such as oxytocin or other prostaglandins have been used for second trimester pregnancy termination. ***(Cristina Herman, 2005).*** In these settings, increasing access to misoprostola synthetic prostaglandin El analog that is used for a range of obstetric and gynecologic indications-could play an important role ***(Cristina Herdman,2005).***

Misoprostol is a synthetic 15-deoxy-16-hydroxy-16-methyl analog of naturally occurring PGE_1. It is a viscous oil susceptible to the same types of chemical degradation as natural PGE_1 but stable at room temperature. This means that the drug is easily stored and transported. Misoprostol exhibits a wide range of biologic activities. It is protective of the gastric mucosa, and has vasodilator, immunosuppressive, and uterotonic effects. The uterotonic features of misoprostol are of value in pregnancy termination and in the medical management of miscarriage. Vaginal misoprostol provides safe and effective preoperative preparation for surgical dilation ***(Apuzzio et al., 2006).***

Intravaginal administration of misoprostol tablets can terminate first-trimester and second-trimester pregnancies. A large number of published controlled trials have shown that misoprostol, administered either vaginally or via the oral route, is an effective agent for cervical ripening and labor induction in patients with viable pregnancies. ***(James et al., 2005).***

Nitric oxide (NO) is a free radical that plays a fundamental role in human physiology, being involved in the homeostasis of different functions. In obstetrics this molecule is determinant in the physiology of labor and cervical ripening ***(Pace et al.,2007).***

Prostaglandin (PG)-induced cervical ripening is associated with local NO release. NO plays an active role in cervical remodeling since it positively correlates with both cervical shortening and Bishop score increase. NO oxide and PG are the two pathways that, cross activating each other, trigger the cascade of events responsible of cervical ripening ***(Chiossi et al., 2006).***

AIM OF THE WORK

Our purpose is to compare safety, efficacy and effectiveness of oral versus vaginal prosataglandin E1 analogue (Misoprostol) as an oxytocic agent used for pre induction cervical ripening and induction of abortion during the second trimester of pregnancy.

Our aim in this study is to compare the efficacy of a 100 micro-gram oral misoprostol every 4 hours with a maximum dose 500 micro-grams versus the same dose of vaginal misoprostol and the all patients under the study are primed by vaginal nitric oxide donor in a dose of 20 milligrams glyceryl trinitrates, 24 hours before the administration of misoprostol. We also wanted to assess safety and patient acceptability with the 2 modes of administration.

Chapter 1

Review of literature

Review of Literature

MORPHOLOGY OF NON PREGNANT CERVIX

A- Characteristics and attachment:

The uterus consists of two basic parts the body and its endometrium ard the uterine cervix. The uterus is primarily muscular organ, is located in the pelvic cavity of non pregnant women and of women during first trimester of pregnancy ***(Leppert,1998)***.

The uterus is usually described in terms of cervix. body and fundus. In the nulliparous woman it is pear-shaped and measures about 7.5 x 5 x 2.5 cm. There is a cavity which communicatcs witn peritoneal cavity via the fallopian tubes and with the cavity of the vagina via the cervical canal. The fundus is that part of the uterus which lies above the openings of the tubes, while the tapering body lies below the fundus. It is somewhat flattened anteroposteriorly and is continuous with the cervix below. The cervix protrudes into the vault of the vagina. The gap between the cervix and the vaginal wall is called the fornix of the vagina: it is deepest posteriorly ***(Chamberlain and steer 2001).***

later stages of gestation, it becomes an abdominal organ. It is situated between the bladder on its anterior surface and the rectum on its posterior surface. The whole of the non pregnant uterus appears as a flattened pear. The caudal inferior portion of the uterus protrudes into the vagina and is approximately 2cm long, 0.5-1 cm wide and cylindrical in shape. It is called the cervix ***(Leppert 1992, McMinn 1999)***.

The uterus in the non-pregnant state weighs about 60 g and its cavity holds about 6 mL; at term, the weight has increased to 1,000 g and

the volume to 5,000 mL. There is an increase in muscle fibre size (hypertrophy) and number (hyperplasia), with an increased total amount of the contractile protein (actomyosin). Late in pregnancy, there is a marked increase in the number of gap junctions between muscle cells ***(Norman et al ., 1997)***.

Early in pregnancy, the lower uterine segment becomes softened such that the cervix can be readily distinguished from the body of the uterus on bimanual exam (Hegar 's sign). The surface of the cervix along with the vaginal walls appears more blue secondary to increased vascularity (Chadwick's sign) ***(Gilstrap et al ., 2002)***.

The uterus is described as having four layers. First, there is an outer peritoneal or serous coat, below which is a subserous connective tissue layer that is most dense where the various ligaments attach to the cervix. Third is the myometrium, the muscle layer of the uterus; it is the thickest layer, made up of interlacing bundles of smooth muscle fibres separated by connective tissue sheds containing blood vessels. This layer is about 15 mm thick in the nulliparous uterus of the adult The fourth innermost layer is the endometrium surrounding the cavity of the uterus, the endometrium undergoes considerable changes during the menstrual cycle ***(Chamberlain and steer 2001)***.

In pregnancy, the smooth muscle of the uterine myometrium undergoes important alterations that are critical to the uterus's role in providing a chamber in which the developing fetus can grow and mature. In the nonpregnant state, distention of the uterus leads to reflex contractions as it does in most smooth muscle. In normal pregnancies,

however, the uterus distends and grows to accommodate the enlarging conceptus, yet remains relatively quiescent until term ***(Bansal et al., 1997)***.

The cervix has a central canal that extends from the internal os, where it becomes continuous with the cavity of the uterus, to the external os, where it becomes continuous with the cavity of the vagina. It forms a narrow bottleneck betwern these two organs. The cervix is divided from the corpus by a fibromuscular junction, the internal os, which acts as a sphincter: its competence is important, especially during the second trimester of pregnancy ***(Chamberlain and steer 2001)***.

The cervix projects into the vagina, surrounded by a gutter like fornix. The vaginal cervix has a short anterior lip and a longer posterior lip. It is penetrated by the endocervical canal, which joins the uterine cavity to the vagina. The canal is fusiform in shapes is flattened from front to back, measures 7 mm across at its widest part and is about 3 cm long ***(Chamberlain and Steer 2001)***.

Anteriorly the supravaginal part is separated from the bladder by the connective tissue layer, the parametrium. The uterine arteries run in this tissue while the ureter runs down-wards and forwards within the parametrium about 2 mm from the cervix ***(Chamberlain and Steer 2001)***.

Posteriorly the supravaginal cervix is covered with the peritoneum lining the rectouterine pouch of Douglas. The cervix is supported posteriorly by the uterosacral ligaments, which extend from this part of the cervix to the second, third and fourth sacral vertebrac. The cardinal ligaments support the cervix laterally and are the major support of the cervix and uterus ***(Chamberlain and steer 2001)***.

The role of the cervix in pregnnncy has been often oversimplified. It was thought that it simply acts as a sphincter in pregnancy which relaxed during delivery. In fact, although in early pregnancy the cervix is long and tight, it begins to shorten, open, and relax by midgestation, a process termed 'ripening' ***(Apuzzio et al ., 2006)***.

B-Composition of non pregnant cervix:

Like the uterine corpus, the cervix is formed as the para-mesonephric ducts fuse beginning around 6 weeks' gestation. By 11 weeks, the cervix can be seen as a fusiform thickening of mesenchyme at the junctune of the upper vagina and uterine corpus. While the exact source of the ectocervical and endocervical epithelium has been debated, most believe this to be of müllerian origin ***(Gilstrap et al ., 2002)***.

The uterine cervix is derived from the fusion of the distal müllerian ducts and subsequent central atrophy. The cervix consists primarily (>70%) of fibrous connective tissue, mostly collagen types I and III, with most of the remainder consisting of smooth muscles. The percentage of smooth muscle is more prominent in the upper (29%) than in the lower (6%) parts of the cervix. Only about 1% of cervical tissue is made of elastin ***(Gilstrap et al ., 2002)***.

The cervix is very important in the development of a pregnancy. The non-pregnant cervix is normally composed of a dense collagenous fibroconnective tissue with small amounts of smooth muscles to give it a tough texture. In pregnancy, the increased water content and vascularity in the cervix leads to a softening and a blue coloration. Throughout pregnancy the cervix and lower utrine segment change but maintain a "functionally intact" internal OS ***(Mala Arora 2007)***.