First Trimester Pre-abortion Cervical Priming: A Pilot Randomized Study Comparing Misoprostol and Vaginal Acidity Enhancement with 3% Acetic Acid Gel

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Contents

Page

List of Abbreviations I

List of Tables..... II

List of Figures ……..... III

Introduction 1

Aim of the Work.....3

Review of Literature

Chapter (1): ***Uterine Cervix*** **4**

Chapter (2): ***Misoprostol*** **34**

Chapter (3): ***Collagen and Acidity*** **56**

Chapter (4): ***Induction of Abortion*** **83**

Patients and Methods.....99

Results 114

Discussion.....124

Summary.....136

Conclusion and Recommendations 142

References 143

Arabic Summary .....

List of Abbreviations

Abbreviation	Meaning
BV	Bacterial Vaginosis
cAMP	Adenosine 29, 59-Cyclic Monophosphate
CDC	Centers for Disease Control and Prevention
D & C	Dilation and Curettage
D&E	Dilatation and Evacuation
ECM	Extra Cellular Matrix
ER	Endoplasmic Reticulum
ERPC	Evacuation of the Retained Products of Conception
EVA	Electric Vacuum Aspiration
GAG	Glycosaminoglycans
IUFD	Intrauterine Fetal Death
LBW	Low Birt weight
Mg	Milligram
Ml	Milliliter
MMPs	Matrix metalloproteinases
MVA	Manual Vacuum Aspiration
NSAID	Non Steroidal Anti-Inflammatory Drugs
PG	Prostaglandin
PKA	Protein kinase A
PTD	Preterm Delivery
TJs	Tight junctions
TNF	Tumor necrosis factor
VEGF	Vascular Endothelial Growth Factor
µg	Microgram
Ml	Milliliter

List of Tables

Table No. ***Page***

(1) Overview of possible factors influencing the vaginal pH cause effect Microbial factors 74

(2) Demographic data 115

(3) Force needed to dilate the cervix 116

(4) Outcome measures in both groups 118

(5) Correalations 118

(6) Pre-Post-operative complications between 2 study groups 121

List of Figures

Figure No. ***Page***

(1) Misoprostol structure 35

(2) Mean plasma concentrations of misoprostol acid over time 42

(3) Flow diagram of the study population..... 114

(4) Force needed to dilate the cervix..... 117

(5) Pre-Post-operative complications between 2 study groups..... 121

(6) The effect of vaginal Ph on cervical ripening in Group I (misoprostol) 122

(7) The effect of vaginal Ph on cervical ripening in group II (A.A. Jel). 123

Introduction

Surgical termination of pregnancy is associated with complications such as uterine perforation, cervical laceration and incomplete evacuation of the uterus ***(Beric and Kuperesanin, 1972; Wright et al., 1972).*** Vacuum aspiration is considered to be a safe and effective method of surgical abortion, but has been associated with major morbidity in up to 1% of women and minor morbidity in 10% ***(Anonymous, 1985),*** the major determinants of morbidity being gestational age and the procedure used to terminate the pregnancy In the first trimester, the complication rate is lowest at 7-8 weeks of gestation (0.26 per 100 abortions) and increases progressively to 1.37 per 100 abortions at 13 weeks ***(Grimes and Cates, 1979).*** The incidence of cervical trauma and uterine perforation is related to the degree of forcible mechanical dilatation required ***(Schultz et al., 1983; Grimes et al., 1984).*** Traumatic complications may jeopardize future fertility, and have been associated with increased risk of miscarriage and preterm labour in subsequent pregnancies ***(Harlap et al., 1979).*** Difficult or inadequate cervical dilatation may increase the risk of hemorrhage and incomplete uterine evacuation ***(Mackenzie and Fry, 1981).***

As first trimester vacuum aspiration is widely performed on an outpatient or day surgery basis, there has been considerable interest in establishing the optimal dosage and administration route for rapid and effective cervical priming with minimum side effects. Pre-operative treatment with a priming agent, to ripen i.e. soften and dilate the cervix, has been shown to decrease the morbidity associated with pregnancy termination by vacuum aspiration ***(Mackenzie and Fry, 1981; Schultz et al., 1983; Grimes et al., 1984).*** The use of preoperative cervical preparation agent prior to termination of pregnancy by vacuum aspiration has been well established in gynecological practice as it reduces the risk of cervical injury and uterine perforation ***(Schultz et al., 1983; Grimes et al., 1984).***

Agents commonly employed for pre-operative cervical ripening include mifepristone ***(Henshaw and Templeton, 1991),*** laminaria and prostaglandin analogues. The efficacy of prostaglandins for such purposes has been clearly demonstrated ***(Christensen and Bygdeman, 1984; Fisher and Taylor, 1984).*** Prostaglandins produce more effective cervical ripening than laminaria ***(Helm et al., 1988)***, but are associated with several side effects such as abdominal pain, gastrointestinal upset and vaginal bleeding ***(Anonymous, 1981).***

Misoprostol, a synthetic 15-deoxy-16-hydroxy-16methyl analogue of naturally occurring prostaglandin E1 (PGE1) has been shown to represent a stable, easily stored, inexpensive and effective alternative, being comparable with gemeprost in terms of efficacy ***(El-Refaey et al., 1994; Baird et al., 1995).*** Furthermore, misoprostol is associated with fewer side effects than gemeprost ***(Henry and Haukkamaa, 1999).*** Randomized controlled trials have shown different results as to whether the oral or the vaginal administration route is most effective and what is the optimal dose ***(El-Refaey et al., 1995; Lawrie et al., 1996; Singh et al., 1998; Saxena et al., 2004; Oppegaard et al., 2004).*** It is suggested to be administered vaginally at least 3 hours prior to operation ***(Singh et al., 1999a).*** The efficacy of vaginal misopristol for cervical priming is both dose and time dependent, however, with increasing the dose from 400 µgm to 600 µgm more side effects –fever, abdominal pain, and vaginal bleeding- were noted ***(Singh et al., 1999b).*** Misoprostol binds to myometrial cells causing strong myometrial contractions leading to softening and dilation of the cervix. This results in separation of the conceptus from the uterine wall, thereby initiating the abortion process before surgical evacuation ***(Saxena et al., 2004).*** Though the occurrence of gastro-intestinal upset seems less, misopristol use still appears to be associated with abdominal pain, above-average vaginal

bleeding ***(Henry and Haukkamaa, 1999; Ngai et al., 1999)*** and fever ***(Saxena et al., 2004).***

The human cervix, in contrast to the uterine corpus, is essentially a fibrous connective tissue organ, mainly composed of collagen and proteoglycans. The connective tissue content is ~90-95% in the lower part of the human cervix and ~75% in the isthmic region of the uterus ***(Granström et al., 1989).*** In obstetric practice, it is well known that an extensive remodeling of the connective tissue prior to parturition, i.e., cervical ripening, is necessary for a harmless and successful delivery of the fetus. The idea of the cervix as a passive, inert, connective tissue structure is no longer tenable. The cervix is in fact a dynamic structure, the control of which we still do not fully understand. During ripening, marked biochemical changes take place in the cervix, causing it to become soft and dilatable at the time of parturition ***(Uldbjerg et al., 1983b; Leppert, 1995).*** The most striking changes are the decreases in concentrations of collagen and glycosaminoglycans, estimated to be about 50-70%, concomitantly with an increase in collagen synthesis. This higher proteolytic activity coincides with an increase in the solubility of collagen. This change in turnover of matrix components results in a reorganization of the collagen fibrillar network ***(Uldbjerg et al., 1983a; Granström et al., 1989).*** Also, there is a marked increase in hyaluronic acid concentrations

(von Maillot et al., 1979; El-Maradny et al., 1997). The final ripening is characterized by an influx of neutrophils capable of secreting collagenase and elastase ***(Junqueria et al., 1980).*** It is suggested that decreased expression of type I collagen, the main macromolecular component of the ECM of the cervix, might be a key event in cervical dilatation at parturition. The reduced cervical levels of type I collagen in the process of cervical softening suggest at least two possible mechanisms for regulation of the turnover of this collagen. First, the synthesis of type I collagen by cervical stromal cells might be reduced at the gene level in the process of cervical softening, Second, the degradation of cervical type I collagen might be intensified in the process of cervical softening ***(Iwahashi et al., 2003).***

The effect of acidity on connective tissue remodelling and softening of the cervix needs consideration. It has been shown that acidity enhances bone resorption by decreasing the collagen through suppressing the osteoblastic activity along with stimulating the osteoclastic activity ***(Krieger et al., 1992; Bushinsky, 1995; Bushinsky and Nilsson, 1995; Krieger et al., 2000)***, an effect that appears to be mediated by prostaglandins (PGE2) synthesis ***(Krieger et al., 2000).*** In a recent study, it was shown that both the increased acidity and the elevated lactate concentration act, independently, to depress osteoblast elaboration of vascular endothelial growth factor (VEGF)

(Spector et al., 2000). Moreover, pH is suggested to play a role in modulating the function of matrix metalloproteinases (MMPs) ***(Davis, 1991; Dung et al., 1995; Fasciglione et al., 2000; Johnson et al., 2000; Murphy et al., 2004; Zhang et al., 2004).***

In normal pregnancy vaginal pH (using a pH meter with connected glass electrode) was found to be between 3.8 and 4.0 at the introitus, mid-vaginal, and at the anterior and posterior fornices; while cervical pH ranged between 6.5 and 7.0 ***(Riedewald et al., 1990).*** During pregnancy, the systemic concentrations of oestrogens and progesterone increase up to 100-fold until parturition ***(Speroff et al., 1989).*** However, in contrast to other species the serum concentrations of neither oestrogen nor progesterone are abruptly changed immediately before parturition in humans ***(Csapo et al., 1971; Turnbull et al., 1974).*** So, there has been some debate about whether or not oestrogens stimulate cervical ripening. It has been recently shown that the levels of both the oestrogen receptor alpha (ERα) and the progesterone receptor (PR) in the cervix are significantly lower in term pregnant in comparison with non-pregnant women ***(Stjernholm et al., 1996; Stjernholm et al., 1997).*** On the other hand, other investigators reported an increased level of ERβ in the myometrium of term pregnant women, and a down-regulation in the expression of labour-

associated genes in the uterine smooth muscle cells, suggesting that ERβ may play an important biological role during term pregnancy ***(Wu et al., 2000).*** Also, it was reported that ERβ concentrations were significantly increased in term pregnancy ***(Wang et al., 2001).*** This might be associated with increased glycogen deposition in epithelium, lactic acid concentration and vaginal acidity that might pay a role in cervical ripening. The reported increased efficacy of misoprostol in induction of labour in the presence of a moderately acidic vaginal pH ***(Gunalp and Bildirici, 2000)*** concurs with this assumption.

Based on the aforementioned facts, one may hypothesize that acidity is important in the modulation of ripening process, and may be active in the connective tissue remodeling. It was reported that the solubility of collagen undergoes a huge increase at full dilatation with no significant change in the water content ***(von Maillot and Zimmermann, 1976).*** The same author demonstrated in the course of pregnancy that the fractions of collagen which are acid-soluble increased in relation to the total collagen content and dry weight, with the highest value found during labour at full cervical dilatation and also immediately postpartum. In fact, acids have been used in other in vitro studies to extract the newly cross-linked collagen ***(Bank et al., 1999; Zhao et al., 2000).*** Based on this observation, a pilot in vitro study was performed to examine the

effect of acids on the collagen fibers of the cervix. Following exposure to acids, the collagen fibers appeared to be cleaved longitudinally and randomly dispersed within the cervical stroma, with more fragmentation and dissolution on prolonged exposure. These changes are quite similar to that of maturation of cervix during pregnancy and labour ***(Ghazy and Tawab, unpublished).***

A lower initial vaginal pH has been shown to highly increase the rate of success of vaginally appliedmisoprostol formidtrimester abortion ***(Abd-El-Maeboud et al., 2008)*** and labor induction ***(Gunalp & Bildirici, 2000)***. Misoprostol tablets sometimes dissolve incompletely in the vagina ***(Zieman et al., 1997)***, which led to the suggestion of moistening them with water or a saline solution ***(Mishell et al., 1998; Wiebe, 2001)***. Yet, a recent randomized trial did not show improved efficacy in terminating second-trimester pregnancies ***(Yilmaz et al., 2007)***. Although misoprostol tablets are known to liquefy more easily in an acidic medium ***(Karim et al., 1989)***, there are conflicting reports on the value of the use of acetic acid to dissolve them for vaginal application ***(Yilmaz et al., 2005; Pongsatha & Tongsong, 2011)***. A study of the effects of vaginal misoprostol in the second trimester was recently carried out with women with missed abortions ***(Abd-El-Maeboud et al., 2008)***. Even though all participants received misoprostol