COMPARATIVE STUDY BETWEEN SUBLINGUAL, ORAL AND VAGINAL MISOPROSTOL AS A METHOD OF LABOR INDUCTION

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Abbreviations

ARM	*Artificial rupture of membranes*
CS	*Cesarean section*
CTG	*Cardiotocogram*
DHEAS	*Dehydrorpiandrosterone sulfate*
EDTA	*Ethylene-diamine-tetra-acetate*
FAD	*Food and Drug Administration*
FHR	*Fetal Heart Rate*
GA	*Gestational Age*
GIT	*Gastrointestinal tract*
Gm	*Grams*
H	*Hours*
IV	*Intravenous*
IL-8	*Interleukin-8*
LMP	*Last Menstrual Period*
Mg	*Milligram*
NICU	*Neonatal Intensive care unite*
No.	*Number*
PG	*Prostaglandin*
PGE1	*Prostaglandin E1*
PGE2	*Prostaglandin E2*
PGF2α	*Prostaglandin F2 alpha*
S.D	*Standard Deviation*
U.S.	*United States*
U.S.A	*United States of America*

Abstract

This study was done to compare the safety and efficacy of 50µg Misoprostol sublingually, orally or vaginally 30 pregnant women were included in the study. Results show that 50µg of sublingual Misoprostol is effective as a method of induction of labor and more safe compared to vaginal route. Also it is more effective than 50µg of oral route with no statistically significant deference in safety profile.

Key words: Induction of labour, pharmacokinetics of prostaglandins, Misoprostol, Misoprostol controversy.

INTRODUCTION

Parturition is a multifactorial, physiological process involving numerous interrelated maternal and fetal pathways, which may be both positive feed-forward and negative feedback. The mechanisms that initiate human parturition are not yet fully understood, despite decades of clinical, physiological and biochemical research by many investigators **(Gelisen 2005).**

However, it has been proposed that there are a number of stages that promote the myometrium to a contractile state, including the upregulation of receptors, prostaglandin production, and increased formation of intracellular contraction-associated proteins. The exact trigger for uterine contractions and which pathway is pre-eminent is not yet clear. Cervical ripening is independent of the initiation of uterine contractions, although the pathways are not yet fully known, it does involve the release of proinflammntory cytokines, leukocyte infiltration into the cervix, the release and activation of extracellular matrix metalloproteinases, other proteins and glycoproteins **(Gelisen**, **2005).**

Drugs that act upon the pregnant uterus can be thought of as modifiers of these endogenous physiological

pathways controlling normal myometrial contractility and cervical ripening. They may be characterized by their sites of action into agents acting upon prostaglandin pathways, progesterone receptors, B-adrenergic receptors, calcium channels and the oxytocin receptor and via nitric oxide. Drugs may also be functionally classified into agents used for the induction and augmentation of labour, for the termination of pregnancy, to treat postpartum haemorrhage, and to treat threatened preterm labour **(Gelisen, 2005).**

One large survey study showed that the odds ratio for stillbirth increases at 41 completed weeks in nulliparas and, at 42 completed weeks in multiparas **(Ingemarsson and Kallen, 1997).** Also, compared with deliveries at 40 weeks of gestation, the risk of macrosomia, operative delivery, admission to neonatal intensive care units, and neonatal sepsis increases with every further gestational week. **(Alexander et al., 2000).** A comprehensive review of randomized controlled trials in 1994, before the era of misoprostol, concluded with the recommendation that labor should be routinely induced once pregnancy has continued beyond 41 full weeks of gestation **(Crowley, 2001).** Many clinicians adopted this practice, and the number of births at or beyond 42 weeks declined significantly **(Roberts et al., 1999).**

Induction of labor can be achieved by a variety of physical and chemical stimuli designed to affect change in uterine cervix and cause uterine contraction or both, these include; prostaglandins, oxytocin, amniotomy, antiprogesterone and others **(Michael S Rogers, 200l).**

Misoprostol which is a prostaglandin E1 analogue is widely used in U.S. and other countries for cervical ripening and labor induction. It is originally intended for prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs, misoprostol is not registered for use during pregnancy **(Collins, 1990).**

Misoprostol has number of advantages for clinical use (Khan et al., 2004):

1- It has long half life in plasma.

2- Unlike other prostaglandins used in obstetrics, it is significantly cheaper

3- It is easy to administer.

4- Does not require refrigeration.

Misoprostol is manufactured in two forms (Tang et al., 2002)

1- 25ug (scored tablet) contains Misoprostol 25ug.

2- 200ug (scored tablet) which can be broken to provide 100 ug 1/2 tab. and 50 ug 1/4 tab.

Although misoprostol is meant for oral administration, the tablets have also been administered vaginally, sublingually and rectally **(Zieman et al., 1997).**

No data are available about misoprostol pharmacokinetics during the 3rd trimester, but studies on the pharmacokinetics of misoprostol given by various routes for first trimester abortion have suggested that the sublingual and oral routes result in significantly higher serum peak concentrations of misoprostol acid compared with vaginal route, with significantly shorter times to peak concentration **(Tang et al., 2002).**

The area under the curve for plasma levels over 6h was significantly greater following sublingual administration than after oral treatment even vaginal application. (If tablets were not moistened before use) **(Bennett et al., 1998).**

Uterine hyperstimulation without fetal heart rate (FHR) changes may be occurring (i.e.) tachysystole (defined as more than five contractions in a 10-min period for two consecutive 10-min periods) or uterine hypersystole/hypertonus (defined as contraction lasting at

least two minutes), also uterine hyperstimulation syndrome (tachysystole or hypertonus with FHR changes such as persistent decelerations, tachycardia or decreased short term variability) may be occurring **(Tang et al., 1997).**

AIM OF THE WORK

This study is comparative study, aiming at comparing the efficiency and side effects of different routes of misoprostol administration including sublingual, oral and vaginal as a method of induction of labor.

INDUCTION OF LABOR

Definition

Induction of labor is the artificial initiation of uterine contraction prior to their spontaneous onset leading to progressive dilatation and effacement of the cervix and delivery of the baby. The term is usually restricted to pregnancies at gestations greater than the legal definition of fetal viability **(Mackenzie & Burns, 1997).**

Rate of induction of labor:

The rate of induction varies widely in different countries and units, and between individual obstetricians within the same unit.

Such variation may be due to differences in the incidence of the indications for induction, definition (e.g. of post-maturity or hypertension), availability of resources, as well as to unexplained differences in opinion and practice. According to the American National Center for Health Statistics, the overall rate of Induction of labor in the united state has increased from 90 per 1,000 live births in 1989 to 184 per 1,000 live births in 1997 **(Ventura et al., 1999)**, Labor is induced in more than 13 percent of deliveries in the United States. Postdate pregnancy is the

most common indication. Oxytocin is the drug of choice for labor Induction when the cervical examination shows that the cervix is favourable. In a patient hose cervix is unfavourable, the use of prostaglandin analogues for cervical ripening markedly enhances the success of induction. Rates between 10% and 25% are common in developed countries. There is no agreement or evidence to suggest an ideal rate **(Mackenzie & Burns, 1997).**

Temporal changes in rates and reasons for medical induction of term labor from 1980 to 1996 were studied by **(Yawn et al., 2001)**. They found that induction of term labor has almost doubled in prevalence during the past 15 years. The most common indications are elective induction and postdate pregnancy, often applied to gestations of 40 to 41 weeks duration. The rates of and indications for labor induction differ also according to hospitals.

Indications for labor induction:

The purpose of induction is to achieve benefit to the health of the mother and/or baby, greater than if the pregnancy continues. In the United Kingdom the commonest indication is prolonged pregnancy. There is good evidence that induction of labor should be offered routinely to all women whose pregnancies continue beyond

41 weeks gestation. Induction during this period is associated with beneficial outcome in terms of reduced cesarean section rate, reduced operative vaginal delivery, reduced chance of fetal distress, meconium staining, macrosomia, and, reduced risk of fetal and neonatal death. Induction must be justified according to the particular circumstances involved and any decision should be taken on an individual basis after fully informing the woman of any potential disadvantages **(Jarvelin et al., 1993).**

Methods of labor induction:

A) Striping (sweeping) of the membranes

Digital separation of the fetal membranes from the lower uterine segment has been used for many years to induce labor. There are good theoretical reasons to suggest that it may be effective, that it stimulates intrauterine prostaglandin synthesis **(EnKia et al., 2000).**

Stripping is an uncomfortable procedure for the patient, has questionable efficacy, and may generate some problems, but continues to be used frequently. It requires a cervix complaint enough to allow the introduction of one of the examining fingers, which is swept around the lower uterine segment attempting to strip or detach the amniotic membrane from the uterus, this maneuver causes the local