SUBLINGUAL MISOPROSTOL FOR INDUCTION OF LABOUR IN POST TERM PREGNANT PATIENTS WITH SATISFACTORY DOPPLER

Thesis

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BY

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ABSTRACT

Our aim of this study was to detect the effect of administration of 50 mcg of sub-lingual misoprostol at 6 hours interval for 4 doses in post-date pregnant women with satisfactory Doppler on fetal outcome. This study was carried out in El-Galaa teaching hospital on40 post term pregnant females who were divided into two groups as follows :

1. Group A :- will include 20 pregnant females beyond 41 weeks gestation who will receive sublingual misoprostol.
2. Group B :- will include 20 pregnant females beyond 41 weeks gestation who came in labour.

There was no statisticallly significant difference between the two groups .

Key Words : Sublingual Misoprostol - Induction of Labour - Post Term Pregnantpatients

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ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
ARM	Artificial rupture of membranes
CRH	Corticotropin Releasing Hormone
Cs	Cesarean section
CTG	Cardiotocogram
^{o}C	Degree Centigrade
EDD	Expected delivery date
EFW	Estimated fetal weight
FDA	Food and Drug Administration
FHR	Fetal heart rate
GA	Gestational age
GIT	Gastrointestinal tract
gm	Gram
GR	Glucocorticoid Receptor
HETEs	hydroeicosatetraenoic acids
HPETEs	hydroperoxyeicosatetraenoic acids
HPA	Hypothalamic pituitary adrenal axis
IV	Intravenous
Kg	Kilogram
LMP	Last Menstrual Period

LT	Leukotrienes
µg	Microgram
mg	Milligram
mmHg	Millimeter mercury
MMP	Matrix metallo proteinases
NICU	Neonatal Intensive Care Unit
NST	Non Stress Test
No.	Number
NVD	Normal vaginal delivery
P	P value
PGS	Prostaglandins
PGDH	Prostaglandin dehydrogenase enzyme
PGE_1	Prostaglandin E_1
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PGHS	Prostaglandin H Synthase
RD	Respiratory distress
SD	Standard Deviation
U/S	Ultra sound
U.S	United States
U.S.A	United States of America

INTRODUCTION

Parturition is a multifactorial, physiological process involving numerous interrelated maternal and fetal pathways. It has been proposed that there are several 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 proinflammatory cytokines, leukocyte infiltration into the cervix, the release and activation of extracellular matrix metalloprotienases, and other proteins and glycoproteins **(Gelisen O., 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. These drugs may be functionally classified into agents used for the induction and augmentation of labor, for the termination of pregnancy, to treat postpartum haemorrhage, and to treat threatened preterm labor. **(Gelisen O., 2005).**

Post-term pregnancy is defined as gestation lasting beyond 42 full weeks (>294 days). Diagnosis of every pathological risk that might delay labor is not yet possible, but delay in this physiological event can cause serious fetal and maternal problems. Large surveys have shown that 1.86 and 2.26 per 1000 deliveries are stillbirths at 41 and 42 completed weeks of gestation, respectively **(Ingemarsson and Kallen, 1997).**

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, concluded 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].**

After induction at 41 weeks there was a lower incidence of neonatal morbidity without any significant change in abdominal delivery rates or duration of hospital stay. **(Parry et al., 1998 – Seyb et al., 1999 – Maslow and Sweeny, 2000).**

On the other hand, elective induction of labor at or beyond term has been blamed for the increased costs of cesarean delivery and labor in retrospective studies in which oxytocin, misoprostol, or other prostaglandins were used for labor induction **[Parry et al., 1998 – Seyb et al., 1999 – Maslow and Sweeny, 2000].**

Induction of labor using medication involves the stimulation of uterine contractions to produce delivery before the onset of spontaneous labor. Two most common prostaglandins analogues (PGs) currently utilized as cervical ripening and labor inducing agents are misoprostol (PGE1) and dinoprostone (PGE2). Misoprostol is an effective agent for cervical ripening and labor induction in mother with viable pregnancies **[Blanchard et al., 2002].**

Labor induction with misoprostol has become an intensely investigated topic. Various authors have reported that the use of misoprostol has an excellent efficacy, minimal side effects and cost saving benefits. **[Blanchard et al., 2002].** They mentioned five primary outcome of ineffectiveness and complication of use of misoprostol such as uterine hyperstimulation with fetal heart rate changes, increased incidence of cesarean section, serious neonatal morbidity (seizures, birth asphyxia) or perinatal death, serious maternal morbidity or death and vaginal delivery not achieved within 24 hours **[Blanchard et al., 2002].**

The use of misoprostol for labor induction with a living fetus was first described in 1992, in the pioneering study by Margulies et al., 1992. Since then, decreasing doses have been proposed and labor induction with misoprostol has been favourably compared with other methods. . There has, however, been the worry of excessive uterine contractility with vaginal doses of 50 mcg or higher **[ACOG committee opinion no. 248, 2000& no.228, 1999].**

Rayburn, 1993, said that to reduce the incidence of contractility disturbances and neonatal complications, 25 mcg is the recommended dose of vaginal misoprostol for induction of labor **[Rayburn, 1993].** Many studies have suggested the possibility of sublingual administration of misoprostol for labor induction **[Hofmeyr and Gulmezoglu , 2002, Kelly et al., 2001 and Fletcher et al., 1993].**

The route of administration of misoprostol was noted to be a significant factor, whereas multiple studies indicated that vaginal misoprostol was more effective than oral misoprostol even with equivalent doses. There has, however, been the worry of excessive uterine contractility with vaginal doses of 50 mcg or higher **[ACOG committee opinion no. 248, 2000 & no. 228, 1999].**

Partly because of issues relating to patient preference, we will investigate the sublingual route of administration of misoprostol. This route of administration has been reported previously in the literature. We speculated that sublingual misoprostol could combine the higher efficacy of the vaginal route by avoiding gastrointestinal and hepatic metabolism, but it could have a more restrained effect on uterine contractility by avoiding direct effects on the uterus and cervix.

Aim of the work

The aim of this work is to evaluate the efficacy of misoprostol usage for induction of labor in postdate female with a satisfactory Doppler and its effect on the fetal outcome using a dose of 50ug administered sublingually every 6 hours for a maximum 4 doses.

CHAPTER 1
PHYSIOLOGY OF LABOR

Labor is a physiologic process during which the products of conception (i.e., the fetus, membranes, umbilical cord, and placenta) are expelled outside of the uterus. Labor is achieved with biochemical changes in the connective tissue and with gradual effacement and dilatation of the uterine cervix as a result of rhythmic uterine contractions of sufficient frequency, intensity, and duration **(American college of obstetricians and gynecologists, 2003).**

Labor is a clinical diagnosis. The onset of labor is defined as regular, painful uterine contractions resulting in progressive cervical effacement and dilatation. Cervical dilatation in the absence of uterine contraction suggests cervical incompetence whereas uterine contraction without cervical change does not meet the definition of labor **(Yvonne Cheng, et al., 2006).**

Parturition:

Although the precise mechanisms that underlie the initiation of parturition in humans remain to be elucidated, a series of natural experiments and clinical observations provide valuable insights. Conditions that disrupt the fetal hypothalamic-pituitary-adrenal (HPA) axis (e.g., anencephaly in the absence of polyhydramnios) or the synthesis of estrogen by the placenta (e.g., placental sulfatase deficiency) lead to prolonged gestation. That prostaglandins play a crucial role is suggested by the finding that prostaglandin synthetase inhibitors delay parturition, whereas administration of prostaglandins initiates parturition. Thus, theories of the initiation of parturition in humans must reconcile the need for an intact fetal HPA axis, increasing placental estrogen synthesis, and enhanced reproductive tract prostaglandin activity **(Charles Lockwood, 2004).**

Initiation of parturition:

Human parturition is similar yet different from that of other species. The initiation of parturition in humans shares many features with that of other non-primate and primate species. For example, in the sheep, pig, horse, and many other mammalian species, fetal plasma cortisol levels increase rapidly in the last 14 to 17 days before labor begins **(Magyar et al., 1980; McNellis et al., 1988).**

In most mammalian species, including humans, estrogen levels increase in the amniotic fluid and plasma before the onset of term parturition. Finally,

in virtually all mammalian species, prostaglandins play a pivotal role in the onset of parturition **(Chaim et al., 1998; Challis et al., 2000).**

The initiation of parturition in humans and higher-order primates also has one major difference when compared with other species; it is not associated with obvious reductions in circulating progesterone levels **(Turnbull, 1989).**

Administration of the antiprogestin, (RU486) although it enhances cervical ripening, it does not induce parturition in humans **(Frydman et al., 1992).**

In most mammals, maturation of the fetal HPA axis and development of the transient "fetal inner zone" of the fetal adrenal gland cause an abrupt increase in circulating cortisol levels that activate the placental 17 α-hydroxylase-17,20-lyase enzyme to shunt steroid precursors away from the progesterone to the estradiol synthetic pathway. Parturition in humans and higher primates cannot result from such direct progesterone withdrawal, however, because of the absence of the glucocorticoid-inducible form of this enzyme in the placenta. However, activation of the fetal HPA axis does seem to play a crucial role in the onset of human parturition **(Charles lockwood, 2004).**

Fetal control of human parturition:

The role of the fetal hypothalamic-pituitary-adrenal axis:

Our species can ensure that the labor will be delayed until vital fetal organs (e.g., lungs) are biochemically and anatomically mature enough to sustain extrauterine survival. Many lines of evidence suggest that development and maturation of the fetal HPA axis are the primary regulators of the onset of parturition **(Charles Lockwood, 2004).**

Corticotropin Releasing Hormone (CRH):

Plasma CRH levels increase dramatically during the second half of pregnancy, peak during labor, and rapidly decline in the postpartum period, whereas levels of its inactivating binding protein decrease in the third trimester **(Mastorakos et al., 2003).**

Mclean et al. (1995), conducted a prospective study of 485 pregnant women. They reported an increase in placental-derived maternal plasma CRH concentrations with advancing pregnancy that was associated with a concomitant decrease in concentrations of its binding protein in late pregnancy. This combination results in a rapid increase in circulating levels of bioavailable CRH that coincides with the onset of parturition.

Although CRH levels increase sharply at term, labor also is associated with increased expression of the CRH receptor-2 in the chorion and