

**COMPARATIVE STUDY BETWEEN SUBLINGUAL AND
VAGINAL MISOPROSTOL FOR INDUCTION OF LABOR
IN POST TERM PREGNANT PATIENTS WITH
UNFAVOURABLE CERVIX**

Thesis
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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 metalloproteinases, 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

Our aim in this study was to compare the efficacy of a 25 mcg vaginal dose administered at 4-hour intervals with a 50 mcg dose regimen administered sublingually for induction of labor in post-term pregnancy. We also aim to assess safety and patient acceptability with the 2 modes of administration.

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 antiprogesterin, (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 myometrium and of the type-1 receptor in the amnion, chorion, and myometrium **(Jirecek, 2002)**.

Maternal cortisol levels also increase steadily during the second half of gestation; this suggests that placental CRH is driving a

“relative” hypercortisolism in the mother (**Mastorakos et al., 2003**).

Using data that were obtained from cordocenteses, they showed that fetal CRH and cortisol also increase during the second half of gestation and that fetal cortisol levels correlate most strongly with placental CRH secretion (**Lockwood, 1996**). This suggests that placental CRH expression drives fetal HPA activation. One explanation for this paradoxical cortisol stimulation of placental CRH expression may rest with the decreased levels of prostaglandins receptor expression in trophoblasts and progesterone’s weak antagonist effects on the Glucocorticoid Receptor (GR). Thus, before term, the increased relative amounts of progesterone compete with the decreased amounts of cortisol for binding to trophoplast (GR) binding sites (**Karalis et al., 1996**).

Increasing maternal and fetal cortisol levels at term progressively overcome progesterone’s tonic inhibition of cortisol/GR-mediated CRH expression, however. The resulting increase in placental-derived CRH “inappropriately” stimulates maternal and fetal pituitary corticotropin production, which normally would be suppressed significantly by the increasing cortisol levels. That this feed-forward loop is more pronounced in the fetus than in the mother, that maternal corticotropin concentrations decrease modestly, whereas fetal corticotropin

levels increase with increasing gestational age, despite increasing cortisol levels in both compartments. Thus, further maternal and, especially fetal, adrenal cortisol production is stimulated paradoxically to establish an endocrine or systemic feed-forward loop (**Lockwood, 1996**).

Because prostaglandins act as direct and indirect uterotonins and enhance fetal membrane and cervical protease production to promote cervical changes and fetal membrane rupture, the observation that CRH enhances prostanoid production by isolated amnion, chorion, and decidual cells directly implicates it in the onset of parturition. In addition, incubation of an amnion cell line with CRH results in a dose-dependent increase in EP-1 receptor protein (prostaglandin receptor isoform in the myometrium that regulate contractility) and mRNA levels further implicating CRH in the onset of parturition (**Spaziani et al., 2000**). Finally, prostaglandins seem to stimulate CRH production in the placenta and amnion which may create a paracrine feed-forward loop (**Jones et al., 1990**).

Cortisol:

Increasing fetal and amniotic fluid cortisol levels that result from progressive activation of the fetal HPA axis also may exert a direct effect on fetal membrane prostaglandin production.

There is evidence that cortisol and other corticosteroids increase the production of PgE_2 and the activity of PGHS-II/Cox-2 in cultured amnion fibroblast cells, although corticosteroids are considered to be potent anti-inflammatories and inhibit prostanoid synthesis in many other cell types **(Sun et al., 2003)**.

In addition, corticosteroids reduce prostaglandin degradation in the chorion by inhibiting NAD dependent 15-hydroxy-prostaglandin dehydrogenase (PGDH), the key enzyme that controls the metabolism of PgE_2 , $\text{PgF}_{2\alpha}$, and other prostanoids. The PGDH enzyme is localized to syncytiotrophoblasts in the placenta and to the extravillous cytotrophoblasts of the chorion. Labor is associated with decreased PGDH activity in placenta or chorion and cortisol exhibits a dose-dependent inhibitory effect on PGDH enzymatic activity and mRNA expression in placental and chorion trophoblasts cells in vitro; this effect is inhibited by progestins **(Patel et al., 1999)**.

Thus, cortisol can enhance amnion PgE_2 production and decrease its metabolism and decrease degradation of decidua-derived $\text{PgF}_{2\alpha}$. There is evidence that prostaglandins augment local concentrations of cortisol in the fetal membranes by enhancing expression of chorionic 11 β -hydroxy-steroid oxidase type 1 (11 β -HSD1) to convert biologically-inactive cortisone to cortisol **(Alfaidy et al., 2001)**.

Thus, decidual cell-derived $\text{PgF}_{2\alpha}$ rapidly increases 11 β -HSD1 reductase activity to increase local concentrations of amniochorion cortisol. This cortisol enhances amnionic PGDHS-II/Cox-2 activity and decreases chorionic PGDH expression to cause a net increase in amnion-derived PgE_2 and decidual-derived $\text{PgF}_{2\alpha}$ concentrations **(Patel et al., 1999)**.

Cortisol and, potentially, these prostaglandins also should drive additional decidual chorion or amnion CRH production which further amplifies amnion and decidual prostaglandin synthesis and activates the fetal HPA axis. Thus, progressive increase in decidual and fetal membrane prostanoid production may establish a third, combined paracrine-endocrine, feedforward loop to promote parturition **(Charles Lockwood, 2004)**.

Prostaglandins:

Among the various factors involved in parturition, prostaglandins appear to have an important role. They are synthesized within the human fetal membrane (amnion and chorion) and decidua and act to ripen the cervix, change membrane structure and contract the myometrium. Prostaglandin concentrations increase in amniotic fluid prior to myometrial contractions, and the activity of Prostaglandin H Synthase (PGHS) increases in the chorion laeve and amnion at labor. This increase is