Introduction

Induction of labor is an increasingly common obstetric procedure. Recent data demonstrates that over 40% of primiparous women, and over 30% of multiparous women, undergo labor induction ***(Laughon et al., 2012).***

Methods for labor induction include both mechanical and pharmacological options. Pharmacological interventions to ripen the cervix as part of labor induction include administration of oxytocin, and prostaglandins delivered p.o. or vaginally. However, when induction of labor is attempted for a woman with an unfavorable cervix, other interventions used to assist the induction process, such as oxytocin or rupture of membranes, are connected with reduced effectiveness and high failure rates ***(Crane et al, 2006).***

The portion of pregnancies undergoing induction varies widely between countries, but it is estimated that approximately 20% of labors in the UK and USA are induced ***(Calder et al., 2008).***

Labor induction involves stimulation of uterine contractions to produce delivery before the onset of spontaneous labor, this procedure has been commonly used

since the synthesis of oxytocin in the 1950s ***(Saeed et al., 2011).***

Induction of labor is an integral part of obstetric practice. In modern obstetrics, it is mainly attempted when continuation of pregnancy may harm either mother or foetus or both. Induction of labor has been traditionally done by oxytocin infusion but numerous studies have shown that it is unable to achieve equally gratifying results in un-favourable cervix ***(Kulshreshtha et al., 2007).***

Prostaglandins are frequently used for labor induction in pregnant women with postdate pregnancies or in complicated pregnancies such as preeclampsia, diabetes mellitus, intra-uterine fetal growth retardation and fetal distress. The presence of cervical immaturity indicates the use of prostaglandin compounds, frequently followed by oxytocin infusion, prostaglandins are received orally or applied locally to the cervix or the vagina, to promote both cervical ripening and myometrial contractility ***(Sifakis et al., 2007).***

Various prostaglandins preparations including misoprostol vaginal tablets, dinoprostone vaginal gel and vaginal insert are commercially available to be used in labor

induction. Misoprostol is a synthetic prostaglandin El analogue and has been reported to be a considerably safe and efficacious cervical ripener. It's inexpensive, easy to administer, stable at room temperature, does not require refrigeration. It acts as an effective myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostaglandin receptors. In spite of different doses and routes of administration (sublingual, oral, vaginal), ideal dosage and mode of administration still remain to be controversial. Potential complications such as uterine rupture, tachysystole and uterine hyperstimulation should be emphasized with respect to adverse maternal-neonatal outcome ***(Ozkan et al., 2009).***

Dinoprostone or Prostaglandin E2 is a naturally occurring bimolecule found in low concentrations in most body tissues. In pregnancy, prostaglandin E2 is secreted continuously by fetal membranes and placenta. It is known that prostaglandin E2 stimulates the production of prostaglandin $F_{2\alpha}$, which in turn sensitizes the myometrium to endogenous or exogenously administered oxytocin. Although capable of initiating contractions and interacting with oxytocin to increase uterine contractility, prostaglandin E2 plays an important role in the complex set of biochemical

and structural alterations involved in cervical ripening, this process involves activation of the enzyme collagenase, which is responsible for the partial degradation of collagen, leading to a softening or ripening of the cervix ***(Brennan et al., 2011).***

Dinoprostone (prostaglandin E2) vaginal inserts have traditionally been used for cervical priming and has been approved by the US Food and Drug Administration for cervical ripening in women at term ***(Tan et al., 2010).***

Dinoprostone is expensive, requires refrigeration, needs to be instilled in the cervix and many patients require additional oxytocin augmentation during induction of labor ***(Saxena et al., 2011).***

Aim of work

Research hypothesis:

In women undergoing induction of labor at term:

Vaginal misoprostol may be equally effective as intracervical dinoprostone in successful induction.

Research question:

In women undergoing induction of labor at term:

Does vaginal misoprostol have equal efficacy as intracervical dinoprostone?

Aim of the study:

The aim of this study is to compare the efficacy and safety of vaginal misoprostol versus dinoprostone intracervical insertion for induction of labor at term.

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 the uterus after the age of fetal viability. 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 ***(ACOG, 2013).***

Labor is a clinical diagnosis. The onset of labor is defined as regular, painful uterine contractions resulting in progressive cervical effacement and dilatation ***(Chong et al., 2004).***

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-pituitaryadrenal (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 ***(Lockwood, 2004).***

Initiation of parturition:

In most mammalian species, including humans, estrogen levels increase in the amniotic fluid and plasma before the onset of term parturition ***(Chaim and mazor., 1998; Challis et al., 2000).***

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 ***(Lockwood, 2004).***

Fetal control of human parturition:

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

Many lines of evidence suggest that development and maturation of the fetal HPA axis are the primary regulators of the onset of parturition ***(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. (1999) 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).***

Using data that were obtained from cordocentesis, 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. This suggests that placental CRH expression drives fetal HPA activation. One explanation for this paradoxic 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 ***(Lockwood 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. 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 ***(Lockwood et al., 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 dosedependent 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).***

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-inflammatants 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-hydroxyprostaglandin dehydrogenase (PGDH), the key enzyme that controls the metabolism of PGE_2, $PGF_{2\alpha}$, 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 choriontrophoblasts 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 decidualderived $PGF_{2\alpha}$. 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 $PGF_{2\alpha}$ rapidly increases 11 β-HSD1 reductase activity to increase local concentrations of amniochorion cortisol. This cortisol enhances amnionic PGDHSII/ Cox-2 activity and decreases chorionic PGDH expression to cause a net increase in amnion-derived PGE_2 and decidual-derived $PGF_{2\alpha}$ concentrations ***(Patel et al., 1999).***

Prostaglandins:

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 due to increased expression of the PGHS-2 isoenzyme rather than the PGHS-1 isoenzyme ***(Gribb, 1998).***

Prostaglandin metabolism also plays an important role in altering prostaglandin output by the human fetal membranes. Prostaglandin dehydrogenase (PGDH) activity

decreases in certain cases of preterm labor, and at term it decreases in the area of the chorion laeve covering the cervix. This may allow active prostaglandins produced by the amnion and chorion to access the cervix and myometrium. Many studies have indicated that glucocorticoids may be important in regulating prostaglandin formation within the human fetal membranes by increasing expression of PGHS-2 in the amnion and decreasing PGDH activity in the chorion ***(Gribb, 1998).***

Prostaglandin formation is also important in infection induced preterm labor and both phospholipase and PGHS-2 activities can be increased by various cytokines ***(Gribb, 1998).***

Estrogen:

Estrogens facilitate parturition by enhancing transcription of a variety of uterine activation protein genes ***(Di et al., 2001).***

Estradiol seems to augment connexin 43 gene transcriptions by increasing levels of the estrogen-responsive transcription factor, cjun. Increases in gap junctions facilitate cell-cell communication in the myometrium and efficient transmission of contractions ***(Lockwood, 2004).***

Other fetal-triggers of parturition:

It is well-established that a variety of pathologic mechanisms can trigger preterm parturition, including ascending genital tract infections. The leading theory behind infectionassociated prematurity is that activation of the maternal and fetal immune system leads to increased decidual and fetal membrane macrophage activation. The latter causes the release of tumor necrosis factor-a and IL-1β which activates the NF-kB transcription factor in decidual, amnion, chorion, myometrial, and cervical cells to promote the release of decidual and amnion prostaglandins, the inhibition of chorionic prostaglandin dehydrogenase enzyme (PGDH), and increases in matrix metalloprotienases (MMP) and IL-8 release in the cervix, decidua, and fetal membranes ***(Wickelgren, 2004; Condon et al., 2004).***

Phases of parturition:

Phases of parturition should not be confused with the clinical stages of labor (first, second, third stages), which comprise phase 2 of parturition ***(Cunningham et al., 2001).***

Phase 0: Uterine quiescence:

This phase is characterized by smooth muscle tranquility with maintenance of cervical structural integrity. Thus the uterine myometrial smooth muscle is rendered unresponsive to natural stimuli, and relative contractile paralysis is imposed against a host of mechanical and chemical challenges that otherwise would promote emptying of the uterine contents. As the myometrium is maintained in a quiescent state, the cervix must remain firm and unyielding ***(Cunningham et al., 2001).***

Phase 1: Preparation for labor:

To prepare the uterus for labor, the myometrial tranquility of phase 0 of parturition must be suspended through what has been called uterine awakening or activation. This process is termed phase 1 and represents a progression of changes in the uterus during the last 6 to 8 weeks of pregnancy ***(Cunningham et al., 2001).***

Cervical changes:

With initiation of parturition, the cervix must soften, yield, and become more readily dilatable. The cervical modifications during phase 1 of parturition principally