EFFECT OF INTRAMUSCULAR ADMINISTRATION OF DEXAMETHASONE ON THE DURATION OF LABOUR

Thesis

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INTRODUCTION

Induction implies stimulation of contractions before the spontaneous onset of labor, with or without ruptured membranes ***(Cunningham et al., 2010).***

According to the National Center for Health Statistics, the incidence of labor induction in the United States more than doubled from 9.5 percent in 1991 to 22.5 percent in 2006 ***(Martin et al., 2009).***

About 10 percent of pregnancies may be prolonged. In general, the longer the truly postterm fetus stays in the uterus, the greater the risk of a severely compromised fetus and newborn infant. Therefore of major importance in handling compromised postdate pregnancies is the use of a suitable method of labor induction ***(Petraglia et al., 2003).***

A prolonged gestation is more likely to occur when the fetus has congenital adrenal hyperplasia caused by 21-hydroxylase deficiency, which may be due to an impaired cortisol production ***(O'Sullivan et al., 2007)***

Glucocorticoids are now known to play key roles in fetal maturation for example in maturation of the lung in anticipation of extra-uterine life and in several species appear to be mediators in the initiation of labor. In humans, the placenta synthesizes CRH, and the exponential rise of this hormone in

maternal plasma correlates with the timing of birth ***(Mclean et al., 1995).***

It is well known that glucocorticoids accelerate lung maturation by enhancing surfactant synthesis in the pulmonary alveolar cells. Evidence has been obtained from early studies that the phospholipid content of surfactant provides a source of arachidonic acid that can be used by the amnion for prostaglandin synthesis. Recently there is direct evidence pointing to surfactant protein A (SP-A) as the key link between the maturing fetus and the initiation of parturition in the mouse ***(Condon et al., 2004).***

Glucocorticoids derived from the maturing fetal hypothalamus-pituitary-adrenal axis play a crucial role in triggering parturition ***(Challis et al., 2005).***

Different studies have shown the paracrine and autocrine effects of corticosteroids on the human uterus, and receptors for these agents have been detected on the human amniotic membranes ***(Kavanagh et al., 2006).***

Several animal studies have shown the importance of corticosteroid secretion by the fetal adrenal glands on the beginning of labor, and infusing glucocorticoids in the lamb fetus was also shown to induce preterm labor. These findings have led to the hypothesis that corticosteroids also had an effect on the labor of women ***(Kavanagh et al., 2006).***

The corticotrophin releasing hormone (CRH), which has been identified in various organ systems, including the female reproductive system, is the principal regulator of the hypothalamic–pituitary–adrenal axis. Circulating placental CRH is responsible for the physiologic hypercortisolism of the latter half of pregnancy and plays a role in the onset of labor ***(Kalantaridou et al., 2007).***

During pregnancy, large amounts of Corticotrophin Releasing Hormone (CRH) are released from the placenta and fetal membranes. An increment in plasma CRH concentration occurs during spontaneous labor, with peak value at vaginal delivery ***(Riley & Challis, 2003).***

Placental CRH is also released into the fetal circulation, and in vitro CRH directly stimulates dehydroepiandrosterone sulfate (DHEAS) production from the fetal zone of the fetal adrenal ***(Sirianni et al., 2005).***

This increase in fetal zone activity correlates with rising levels of maternal estrogen levels through the conversion of DHEA-S to estrogens within the placenta. The increase in the maternal estrogen to progesterone ratio may promote the expression of contraction-associated proteins in the myometrium, thus facilitating the initiation of parturition ***(Mastorakos and Ilias., 2003).***

It has been very well recognized that increased prostaglandin (PGE2 and PGF2) biosynthesis as a result of

inflammation-like responses in intrauterine tissues is one of the key events leading to parturition in both term and preterm human labor because these compounds evoke uterine contractions as well as cervical softening and effacement ***(Kang et al., 2006).***

Human fetal membranes are generally regarded as the major sources of prostaglandins at the end of pregnancy. However, it is not clear whether SP-A affects prostaglandin synthesis in human fetal membranes ***(Kang et al., 2006).***

Cortisol increases the production of prostaglandins in the fetal membranes by either up regulating prostaglandin synthesis (PGHS-2) levels or down regulating 15-hydroxy prostaglandin dehydrogenase (PGDH) ***(Patel et al., 1999).***

Therefore, glucocorticoids also play an important role in human parturition.In the fetal membranes, the actions of glucocorticoids are amplifed by the actions of 11ß-Hydroxy steroid dehydrogenase type1 (11ß-HSD1), where 11ß-HSD1 converts biologically inert cortisone to active cortisol thereby increasing the local levels of biologically active glucocorticoids ***(Sun et al., 1997).***

This cascade of events initiated by glucocorticoids may play an important role in the positive feed-forward mechanisms.

AIM OF THE WORK

The aim of this work is to evaluate the effect of intramuscular dexamethasone administration on the duration of labor.

Chapter (1)

PARTURITION

The last few hours of human pregnancy are characterized by uterine contractions that effect cervical dilatation and cause the fetus to descend through the birth canal. Long before these forceful, painful contractions, there are extensive preparations in both the uterus and cervix, and these progress throughout gestation. During the first 36 to 38 weeks of normal gestation, the myometrium is in a preparatory yet unresponsive state. Concurrently, the cervix begins an early stage of remodeling termed softening, yet maintains structural integrity. Following this prolonged uterine quiescence, there is a transitional phase during which myometrial unresponsiveness is suspended, and the cervix undergoes ripening, effacement, and loss of structural integrity.

The physiological processes that regulate parturition and the onset of labor continue to be defined. It is clear, however, that labor onset represents the culmination of a series of biochemical changes in the uterus and cervix. These result from endocrine and paracrine signals emanating from both mother and fetus. Their relative contributions vary between species, and it is these differences that complicate elucidation of the exact factors that regulate human parturition. When parturition is abnormal, preterm labor, dystocia, or postterm pregnancy may result of these ***(Cunningham et al., 2010).***

Phases of Parturition

Parturition, the bringing forth of young, requires multiple transformations in both uterine and cervical function. As shown in Figure(1), parturition can be arbitrarily divided into four overlapping phases that correspond to the major physiological transitions of the myometrium and cervix during pregnancy ***(Word and colleagues, 2007).*** These phases of parturition include: (1) a prelude to—first phase; (2) the preparation for—second phase; (3) the process of—third phase; and (4) recovery from—fourth phase. Importantly, the phases of parturition should not be confused with the clinical stages of labor, that is, the first, second, and third stages—which comprise the third phase of parturition.

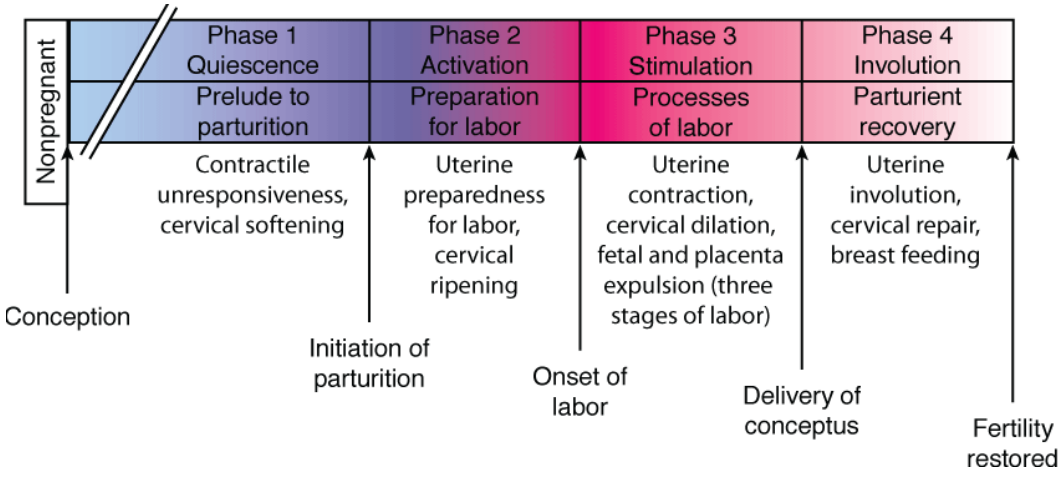

Fig. (1): The phases of parturition ***(Cunningham et al.,)***.

During pregnancy, the uterus is maintained in a state of functional quiescence (Phase 1) through the integrated action of one or more of a series of inhibitors, including progesterone, prostacyclin, relaxin, nitric oxide, parathyroid hormone-related peptide, calcitonin gene-related peptide, adrenomedullin, and vasoactive intestinal peptide. Before term, the uterus undergoes a process of activation (Phase 2) and stimulation (Phase 3). Activation is brought about in response to one or more uterotropins (such as estrogen) with increased expression of a series of contraction-associated proteins (including myometrial receptors for prostaglandins and oxytocin), functional activation of select ion channels, and an increase in connexin-43 (a key component of gap junctions). After activation, the ‘‘primed’’ uterus can be acted upon by uterotonins, such as oxytocin and the stimulatory prostaglandins (E2 and F2a), and stimulated to contract. Phase 4 events (uterine involution) occur after delivery and are mediated primarily by oxytocin and possibly thrombin ***(Liao et al., 2005)***.

The precise temporal control of uterine contractility is essential for the success of pregnancy. For most of pregnancy, progesterone acting through genomic and non-genomic mechanisms promotes myometrial relaxation. At parturition the relaxatory actions of progesterone are nullified and the combined stimulatory actions of estrogens and other factors such as myometrial distention and immune/inflammatory cytokines, transform the myometrium to a highly contractile

and excitable state leading to labor and delivery ***(Mesiano and Welsh, 2007).***

The uterine myometrium during labor

During labor, the uterine myometrium is converted from a tissue with relatively low connectivity between individual myocytes (Panel A) into a tissue with extensive physical connections (Panel B). The physical connections occur through pores formed by multimers of connexin 43. Connections between myocytes during labor are also formed by paracrine release of prostaglandin F2α and local release of calcium. This extensive physical and biochemical connectivity allows the depolarization in individual myocytes to be passed to neighboring cells and thus form extensive waves of depolarization and contraction over large areas of the uterus. This causes increased intrauterine pressure and progressive distention of the cervix, leading to expulsion of the fetus.

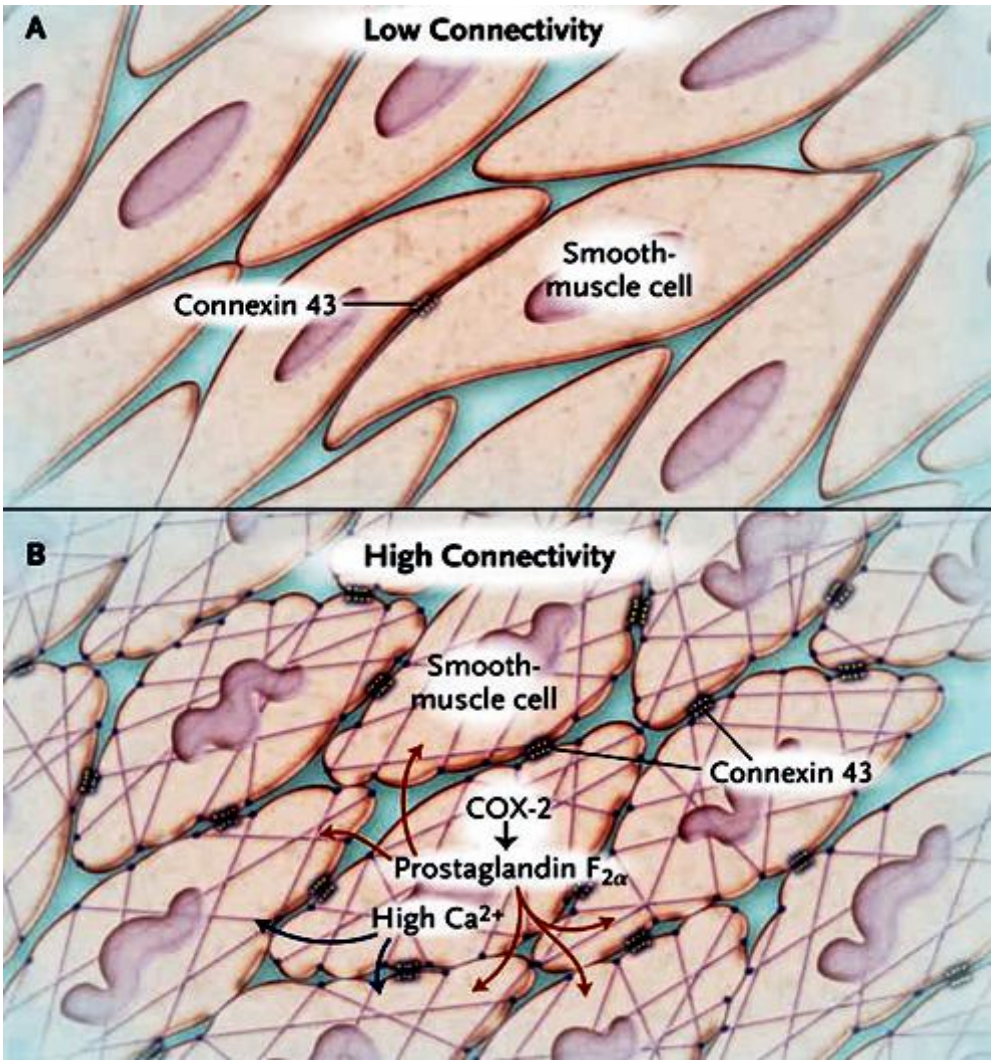

Fig. (2): The uterine myometrium during labor ***(Smith, 2007).***

Most parturition researchers have been struggling with two general theories, these are: (1) the retreat from pregnancy maintenance hypothesis and (2) the uterotonin induction of parturition theory. Some researchers speculate that the mature human foetus is the source of the initial signal for the commencement of the parturitional process; in this manner, the foetus could be in charge of its own destiny with respect to a

timely birth. Foetal induced retreat from continued pregnancy maintenance is a satisfactory theory but as yet has little direct experimental support in human parturition ***(Cunningham et al., 2005).***

Theories of the causes of labor

The exact mechanism, by which labor is initiated spontaneously, at either term or preterm, is not known. Many theories have been proposed.

A- Oxytocin stimulation:

Endogenously produced oxytocin, which causes uterine contractions, may play a role in the spontaneous onset of labor.

1. Levels of oxytocin in maternal blood in early labor are higher than before the onset of labor, but there is no evidence of a sudden surge.
2. Oxytocin influence must therefore rely on the presence of oxytocin receptors.

a. Receptors are found in the nonpregnant uterus.

b. There is a sixfold increase in receptors at 13 to 17 weeks' gestation and an 80-fold increase at term.

c. The increased number of oxytocin receptors amplifies the biologic effect of oxytocin, and contractions intensify.

B- Fetal cortisol levels:

Fetal cortisol levels may influence the spontaneous onset of labor.

1. Disruption of hypothalamic–pituitary–adrenal axis or the absence of adrenal gland or function results in prolonged gestation in humans and sheep. In sheep, infusion of cortisol or ACTH into a fetus with an intact adrenal gland causes premature labor.
2. However, in humans, there has been no documentation of prelabor surge in fetal cortisol secretion to completely support this theory.

C- Progesterone withdrawal:

1. In rabbits, the withdrawal of progesterone is followed by the prompt evacuation of the contents.
2. In humans, there is no obvious decrease in maternal blood levels of progesterone at term or in labor. However, the progesterone level at the placental site may decrease before the onset of labor.

This decrease in progesterone, in association with increased estrogen levels, is followed by increased formation of gap junctions, which permit coupling of the myometrial cells.

D- Prostaglandin release:

Prostaglandins, particularly PGF 2(alpha) and PGE 2, have long been believed to be involved in the spontaneous onset of labor. The normal processes of labor appear to result in inflammation, which results in increased prostaglandin synthesis. Prostaglandins produced in myometrial tissue may contribute to the effectiveness of myometrial contractions during labor, and may soften the cervix independent of uterine activity ***(YU-HSIN, 2012).***

Maternal–fetal interactions

In the intervillous space, the syncytiotrophoblasts release corticotropin-releasing hormone (CRH), progesterone, and estrogens into the maternal blood and into the fetal blood. Cortisol passes through a maternal artery and enters the intervillous space, where it stimulates the production of CRH by the syncytiotrophoblasts. A fetal umbilical vein carries CRH into the fetal circulation, stimulating the fetal pituitary to synthesize corticotrophin and drive fetal adrenal cortisol and dehydroepiandrosterone sulfate (DHEAS) synthesis. Cortisol and CRH stimulate the fetal lungs to produce surfactant protein A, which moves from the amniotic fluid to the amnion, where it stimulates the production of cyclooxygenase 2 (COX-2) and the synthesis of prostaglandin E2. They pass along the chorion and decidua and stimulate the underlying maternal myometrial cells to synthesize additional COX-2 and prostaglandin F2α ***(Smith, 2007).***

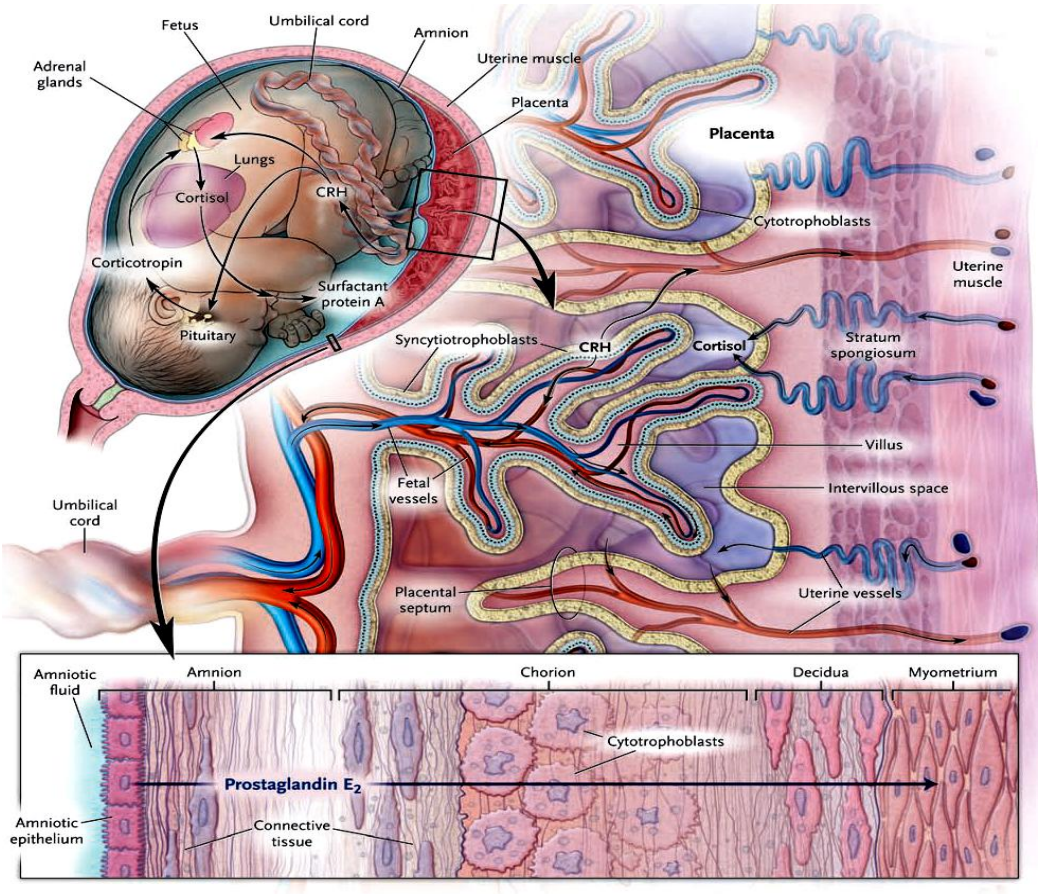

Fig. (3): Maternal–Fetal Interactions ***(Smith, 2007).***

The endocrine control of labour

Considerable evidence suggests that the foetus is in control of the timing of labour. Around the time of Hippocrates, it was believed that the reason the foetus presented head first was so that it could kick its legs up against the fundus of the uterus and propel itself through the birth canal. Although we have moved away from this simple and mechanical concept of labour, the idea that the foetus plays a central role in the initiation of labour remains and has been supported by