INTRODUCTION

Labor is a natural physiological process characterized by progressive increase in frequency, intensity and duration of uterine contractions, effacement and dilatation of cervix with descent of the fetus through the birth canal ***(Sachin et al., 2006).*** Obstetricians have divided labor into 3 stages that delineate milestones in a continuous process. The first stage begins with regular uterine contraction and end with complete cervical dilatation at 10 cm. This stage subdivided into early latent phase and ensuing active phase. Latent phase begins with mild, irregular uterine contractions that soften and shorten the cervix. The contractions become progressively more rhythmic and stronger. This followed by the active phase of labor, which usually at about 3-4 cm of cervical dilatation and characterized by rapid cervical dilatation and descent of the presenting fetal part. The second stage of labor begins with complete cervical dilatation and end with the delivery of the fetus. The third stage of labor defined by the period between the delivery of the fetus and the delivery of the placenta and fetal membranes ***(Cheng et al., 2008).***

In the 19th century, various methods developed that aid cervical dilatation to improve labor progress. Hence, the need of the hour was a pharmacological agent that would:

i. Help in dilatation and effacement of cervix and shorten the duration of first stage of labor.

ii. Not interfere with second and third stage of labor ***(Sachin et al., 2006).***

Metoclopramide hydrochloride is a derivative of p-aminobenzoic acid and structurally related to procainamide, but lacks local anesthetic and antiarrhythmic properties. It differs structurally from procainamide by the presence of 5-chloro and 2-methoxy aryl subsistent ***(Albibi et al., 1983).*** The pharmacology of metoclopramide is complex and its mechanism(s) of action has not been fully elucidated, with principal pharmacological effects involve primarily the GI tract and CNS ***(Schulze-Delrieu, 1981).*** The precise mechanism of action of metoclopramide is unclear, but the drug has been shown to directly affect the medullary chemoreceptor trigger zone (CTZ) in the area postrema, apparently by blocking dopamine (e.g., D_2) receptors in the CTZ. Also, it has been suggested that inhibition of serotonin (5-HT_3) receptors, at least when relatively high doses of metoclopramide are used, may contribute to the action of the drug ***(Freeman & Cullen, 1991).*** In addition, it seems to produce multiple endocrinal actions. It indirectly stimulates secretion of prolactin from the anterior pituitary gland by inhibition of dopamine receptors in the pituitary and hypothalamus. Moreover, it potentiates the

vasopressor response to dopamine ***(Lancashire et al., 1980).***

It has been obvious that metoclopramide is widely used among different hospitals in Egypt based on some believes that it accelerates the first stage of labor, owing to the effect on cervical effacement and dilation. Although such behavior supported by the successful acceleration of the first stage of labor in many pregnant women, who suffered from prolonged labor but such empirical treatment is still given on no clinical base. The precise mechanism of action of metoclopramide in the first stage of labor is unclear, however there are no solid evidence base studies proved such action. This study corroborates the role of metoclopramide in shorting the first stage during active management of labor.

AIM OF THE WORK

The aim of this work is to establish whether metoclopramide plays a role in shorting the first stage of labour as regard to cervical dilatation.

Chapter (1)

NORMAL LABOR

Labor refers to the chain of physiologic events that allows a term fetus to undertake its journey from the uterus to the outside world ***(Liao et al., 2005).*** It is achieved with changes in the biochemical 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 ***(Norwitz et al., 2003).*** 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 insufficiency, whereas uterine contraction without cervical change does not meet the definition of labor ***(Cheng et al., 2009).***

Uterine phases of parturition:

Parturition encompasses all physiological processes involved in birthing: the prelude to, the preparation for, the process of, and the parturient recovery from childbirth. Parturition can be divided into four uterine phases which correspond to the major physiological transitions of myometrium and cervix during pregnancy ***(MacDonald & Casey, 1996).***

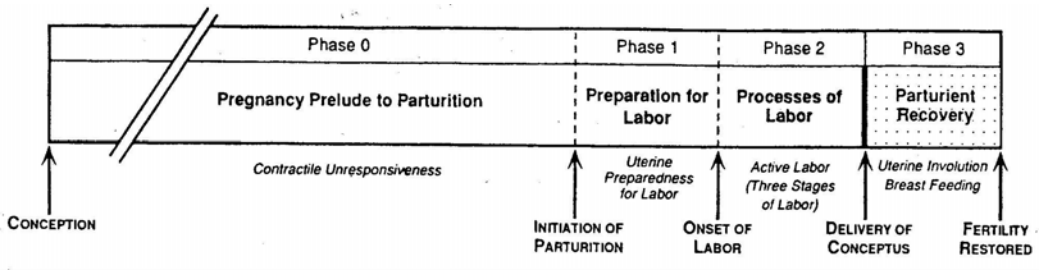

Fig. (1): Uterine phases of parturition ***(Cunningham et al., 2005 a).***

Phase (0): Uterine of quiescence:

It is a remarkably effective period of myometrial quiescence that is imposed on the uterus which is characterized by myometrial smooth muscle tranquility with maintenance of cervical structural integrity ***(MacDonald, 1993)***.

During this phase the myometrium 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 uterine contents while the cervix remains firm and unyielding which is essential to the success of phase 0 of parturition ***(Iams et al., 1996).***

Phase (1): Preparation of labor:

It is the time of uterine awakening in which the uterine tranquility of phase 0 of parturition must be suspended leading to morphological and functional changes

in myometrium and cervix to prepare the uterus for labor. Although the body of the uterus and cervix are parts of the same organ but must respond in quite different ways during pregnancy and parturition. On the one hand, it is essential that the myometrium be dilatable but remains quiescent. On the other hand, the cervix must remain unyielding and reasonably rigid. Coincident with the initiation of parturition, however, the cervix must soften, yield, and become more readily dilatable. The body must be transformed from the relatively, unresponsive organ characteristic of most of pregnancy to one that will produce effective contractions that drive the fetus through the yielding (dilatable) cervix ***(Challis & Lye, 1994).***

During this phase myometrium shows specific modification in uterine function with the suspension of the uterine phase 0 as:

1) A striking - 50 fold or more increase in the number of myometrial oxytocin receptors.
2) An increase in uterine contractile responsiveness to oxytocin and to other uterotonins.
3) An increase in gap junctions between myometrial cells before the onset of labor, continue to increase during labor, and then decrease quickly after delivery.

4) Transition from a contractile state characterized predominantly by occasional painless contractions to one in which more frequent contractions develop.
5) Formation of the lower uterine segment associated with descent of the fetal head to or even through the maternal inlet of the pelvis, a distinctive event referred to as lightening.

(Fuchs et al., 1982)

As regard the cervix, it shows cervical softening associated with two complementary changes which are collagen breakdown and rearrangement of the collagen fibers associated with alterations in the relative amounts of the various glycosaminoglycans. Near term, there is a striking increase in the relative amount of hyaluronic acid in cervix, with a concomitant decrease in dermatan sulfate. This hyaluronic acid is associated with the capacity of a tissue to retain water ***(Winkler & Rath, 1999).***

Biochemistry of uterine contractions:

The uterine smooth muscle cells contain bundles of filaments of actin and myosin. Myosin is made up of two heavy and four light polypeptide chains. The two heavy chains form the head of the protein that is the place of interaction with actin, whereas the light chains provide sites for phosphorylation and calcium binding. When a

contraction occurs, actin and myosin undergo conformational changes that allow them to slide over each other, causing shortening of the muscle cell. These conformational changes require energy in the form of Adenosine Triphosphate (ATP), which is generated in the heavy myosin chains. ATP generation is regulated by phosphorylation of the myosin light chains by the enzyme Myosin Light Chain Kinase (MLCK) ***(Kamm & Stull, 1985).***

The activity of this enzyme is central to the process of muscle contraction, and most of the stimulatory or inhibitory effects of drugs on uterine contraction occur through pathways that lead to this enzyme. Myosin light chain kinase activity is regulated by intracellular calcium, cyclic AMP, (cAMP) and cyclic GMP (cGMP). Uterotonic drugs act by increasing intracellular calcium concentration or by inhibiting the adenyl cyclase and guanylate cyclase systems, whereas tocolytic agents act by decreasing intracellular calcium concentration or by increasing the production of cAMP or cGMP ***(Word et al., 1991).*** Calcium has a stimulatory effect on Myosin Light Chain Kinase (MLCK) activity. It binds to and activates calmodulin, and the calcium-calmodulin complex binds to MLCK, enabling the enzyme to phosphorylate the short chains of myosin and causing formation of ATP and muscle contraction ***(Tansey et al., 1992).*** In contrast,

cAMP has an inhibitory effect on MLCK activity. This compound activates the enzyme protein kinase A that phosphorylates and eventually inactivates MLCK, causing inhibition of muscle contraction ***(Higashi et al., 1983).*** All myometrial contractions, independent of the pathway used to achieve high intracellular concentrations of calcium, are inhibited by activation of the cAMP system ***(Arias, 2000).*** The intracellular concentration of calcium increases as a result of calcium influx through calcium channels or by release from intracellular stores in the endoplasmic reticulum. The calcium channels are proteins that may be voltage-operated or agonist-operated. They are inhibited by magnesium and by calcium channel blockers such as nifedipine. Voltage-operated channels are activated by depolarization of the membrane potential. Agonist-operated channels are not well-defined and require further isolation and characterization ***(Sanborn, 1995).*** An increase in intracellular levels of cAMP or cGMP will inhibit the release of calcium from the endoplasmic reticulum, reduce MLCK activity, and cause cessation of myometrial contractions. The concentration of cAMP is modified through membrane receptors specific for β-adrenergic agents, relaxin, and prostacyclin, whereas the main stimulus for cGMP production is nitric oxide ***(Arias, 2000).***

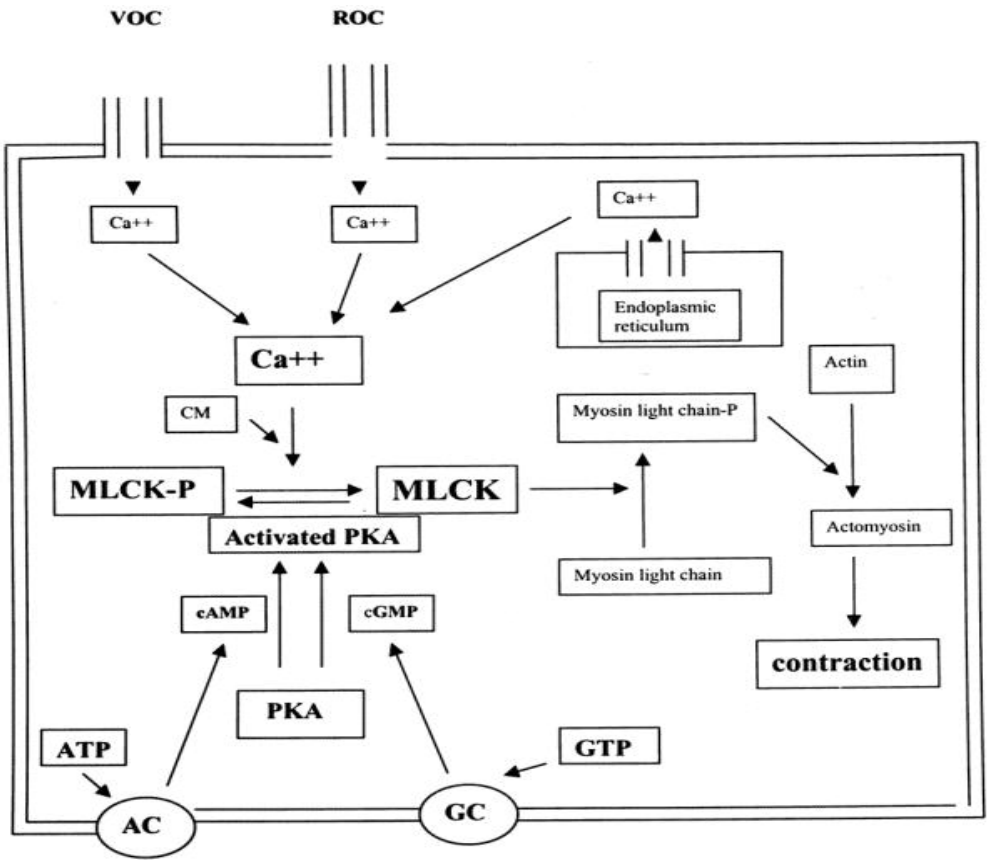

Fig. (2): Biochemistry of myometrial contraction and relaxation ***(Arias, 2000).***

Phase (2): The process of labor:

Phase 2 is synonymous with active labor, that is, the uterine contractions that resulting in progressive cervical dilatation and delivery of the fetus. Phase 2 parturition is customarily divided into three stages of labor:

1) First stage of labor **[**stage of cervical effacement and dilatation**].**

2) Second stage of labor **[**stage of expulsion of the fetus**]**.
3) Third stage of labor **[**stage of separation and expulsion of the placenta**]** ***(Cunningham et al., 2001).***

Factors affecting uterine phase 2 of parturition:

Once phase 0 is suspended and uterine phase 1 processes are implemented, a number of uterotonins may be important to the success of phase 2, active labor. Many uterotonoins known to cause myometrial contractions of smooth muscle in vitro have been proposed such as oxytocin, prostaglandins, angiotensin 2, and many others ***(Cunningham et al., 2001).***

The endothelins are very powerful inducer of myometrial smooth muscle contraction and their receptors are demonstrable in myometrial tissue. However, the researchers have found that the potential contribution of myometrial endothelin to phase 2 of parturition is not defined ***(Word et al., 1991).***

Serotonin and histamine are the secretary products of the mast cells and act in vitro as uterotonins; in which the mast cells concentration is very high in the myometrium and increased further during pregnancy. Moreover, serotonin acts uniquely in myometrial cells to induce the

expression of interstitial collagenase, membrane metalloproteinase-1, a major participant in post partum uterine involution. Consequently, these products of mast cells also, may promote the contractions of phase 2 of parturition ***(Jeffrey et al., 1991).***

Oxytocin means quick birth; however, it does not appear to cause the initiation of parturition. Once phase 1 of parturition is in place, oxyticin may be one of several participants in ensuring the effectiveness of active labor ***(Ku et al., 1995).***

As regard prostaglandins which are produced directly in myometrial tissue, they may contribute to the effectiveness of myometrial contractions of phase 2 (active labor) once parturition is initiated. In addition, possibilities of the inflammatory mediators produced in fore bag facilitate cervical dilatation ***(Winkler & Rath, 1999).*** The production of prostaglandin at time of labor within the myometruim could be seen as a most efficient mechanism of activating contractions. However, the fetal membranes and placenta also are able to produce prostaglandins. Indeed, prostaglandins primarily PGE2, are detected in amniotic fluid at all stages of gestation. As the fetus grows, the levels of prostaglandins in amniotic fluid increase gradually and the major increase in amniotic fluid occurs after labor begins, and is now believed to be the result of an

inflammatory response that signals the events leading to active labor ***(MacDonald & Casey, 1993).***

Phase (3) of parturition: The puerperium:

Phase 3 encompasses the events of the puerperium, maternal recovery from childbirth, maternal contributions to infant survival, and the restoration of fertility in the parturition ***(MacDonald, 1993).***

During this phase:

a) The myometrium must be held in a state of rigid and persistent contraction/ retraction leading to compression of large uterine vessels and thrombosis of their lumens, protecting against fatal postpartum hemorrhage.

b) Development of maternal-type behavior and maternal-infant bonding behavior.

c) Onset of lactogenesis and milk let-down in maternal mammary glands.

d) Involution of uterus which takes about four to six weeks to be completed. In this period, the uterus restores its size to the non pregnant state associated with resumption of ovulation.

(Chillis & Gibb, 1996)

Factors affecting uterine phase 3 of parturition:

There is a large evidence in support of an important role for oxytocin not only during the second stage of labor but also during the puerperium, phase 3 of parturition, causing firm and persistent contraction and retraction of the uterus for prevention of postpartum hemorrhage, and acting upon breast duct cells to effect milk let down. This evidence is based upon increased maternal plasma levels of oxytocin in the early postpartum period, and during breast feeding. This timing of increased oxytocin release is associated with increase in oxytocin receptor population in the myoepithelial cells of ducts of mammary tissue in a similar fashion to that in the myometrial smooth muscle cells late in pregnancy ***(Nissen et al., 1995).***

Stages of labor:

First stage:

The first stage begins with regular uterine contractions and ends with complete cervical dilatation at 10 cm. It is subdivides into an early latent phase and an ensuing active phase; the latent phase begins with mild, irregular uterine contractions that soften and shorten the cervix. The contractions become progressively more rhythmic and stronger. This is followed by the active phase of labor, which usually begins at about 3-4 cm of cervical dilation and is characterized by rapid cervical dilation and