Effect of Oxytocin Discontinuation during the Active Phase of Labor on the Duration of Labor and the Maternal & Fetal Outcomes in Primi-gravida

Thesis

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By

Raghda Mohamed Rashed
M.B,B.Ch, 2011 - Ain Shams University
Resident of Obstetrics and Gynecology at Ain Shams University

Under Supervision of

Prof. Dr. Shereif Mohamed Abdel Hameed
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr. Noha Abd El-Sattar Afify Sakna
Lecturer of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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Raghda Mohamed Rashed

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APM	:	Arrector pili muscle
CMC	:	Cell membrane complex
Cr	:	Cellular remanants

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Introduction

Labor is defined as the presence of regular uterine contractions with progressive cervical dilation and effacement ***(O'Driscoll et al., 1969).***

There are three stages of labour that delineate milestones in a continuous process. The First stage which is the Time from onset of labor to complete cervical dilation. The Second stage which is the time from complete cervical dilation to fetal delivery. And the third stage of labour which is the Time between fetal delivery and placental delivery ***(Robert et al., 2015).***

The first stage consists of a latent phase and an active phase. The latent phase is characterized by gradual cervical change and the active phase is characterized by rapid cervical change. The labor curve may show an inflection point between the latent and active phases; this point occurs at about 5 cm dilation ***(Zhang et al., 2010).***

Dystocia is defined as Abnormal labor resulting from abnormalities of "power, passenger, or passage" that results in slower than normal (protraction disorders) or complete cessation of progress (arrest disorders) ***(Nnepqin, 2012).*** It is commonly diagnosed by observing the rate of cervical dilatation once a woman has been confirmed to be in the first stage of active labour. A woman's labour progress can be pictorially represented on a partograms and alert lines can be used to highlight a woman who is progressing slowly ***(Lavender, 2008).***

The actual definition, however, remains controversial. Initially, it was suggested that any nulliparous woman with a rate of cervical dilatation less than 1cm/hr required treatment

for slow progress. ***(O'Driscoll, et al., 1969).*** However, more recently a rate below 0.5 cm/hr is now taken as the threshold for treatment ***(NICE, 2008).***

Slow progress is commonly treated with an intravenous oxytocin infusion to increase the frequency,duration and strength of uterine contractions. This use of oxytocin for the augmentation of labour in nulliparous women was first popularised over 40 years ago as part of a package of care termed 'active management of labour' ***(Sadler, 2000).***

Since oxytocin was first synthesised in 1953, it has become one of the most widely used medications in obstetrics to induce and augment labour. In many delivery units, oxytocin is used in more than 50% of deliveries ***(Simpson, 2009).***

Oxytocin, whether endogenous or exogenous, works within the myometrium to stimulate oxytocin receptor cells that in turn stimulate contractions of the uterine muscle. Oxytocin receptor cells, similar to other receptor cells, once saturated are unable to absorb any more of the drug, thus increasing the potential for undesirable effects ***(Mahlmeister, 2008).***

With increasing levels of exogenous oxytocin, the receptor sites become desensitized and are unable to initiate a myometrial contraction. If the oxytocin receptor sites are not saturated, they continue to absorb oxytocin and to signal the myometrium to contract.The half-life of oxytocin is brief, between 10 and 12 minutes. Three to 5 half-lives are required to achieve steady state concentration and uterine response would be notable within 30 to 60 minutes after the steady state of oxytocin is achieved ***(Simpson, 2008).***

Although various oxytocin regimens for the induction or augmentation of labour have been described, ***(Kenyon et al., 2013)*** relatively few studies have focused on the duration of oxytocin administration in labour ***(Diven et al., 2012).***

The use of oxytocin during labour may result in a number of maternal adverse effects including hypotension, tachycardia, arrhythmias, nausea, vomiting, headache and flushing ***(Dansereau et al., 1999).*** Rarely, large doses of oxytocin may cause water retention, hyponatraemia, myocardial ischaemia, seizures and coma ***(Begum et al., 2009).***

Furthermore, a long duration of labour induction or augmentation due to use of oxytocin decreases the efficacy of labour induction and increases complication rates. Thus, there is growing concern about the use of non-standardised oxytocin infusion for labour augmentation or induction ***(Oscarsson et al., 2006).***

Recently, oxytocin was added to the list of high-alert medications designated by the Institute for Safe Medication Practices (ISMP), a distinction reserved to only 11 other specific drugs. Such drugs are defined as those "bearing a heightened risk of harm when they are used in error" and that may "require special safeguards to reduce the risk of error. To reduce rates of maternal and fetal adverse events due to inappropriate, excessive or unnecessary oxytocin administration, a standard and specific protocol is needed ***(Institute for Safe Medical Practices, 2008).***

Aim of the Study

The aim of this study is to investigate whether discontinuation of oxytocin infusion could affect the duration of the active phase of labour compared with continuation of oxytocin until delivery, and to compare maternal and neonatal outcomes.

Research question:

In primigravida women that is subjected to labour augmentation by oxytocin infusion, Is there a benefit from the discontinuation of the oxytocin infusion during the active phase of labour over the continuation of the oxytocin as regards duration of the active phase of labour and maternal and fetal outcomes?

Research hypothesis:

The discontinuation of the oxytocin during active phase of labour enhances the maternal and fetal outcomes although it may prolong the duration of labour.

Physiology of Labor

Labor is a physiological event involving a sequential, integrated set of changes within the myometrium, decidua, and uterine cervix that occur gradually over a period of days to weeks ***(Errol et al., 2015).***

Labor is a clinical diagnosis, which includes (i) the presence of regular phasic uterine contractions increasing in frequency and intensity, and (ii) progressive cervical effacement and dilatation. A show (bloody discharge) may or may not be present. The myometrial contractility pattern changes in labor from "contractures" (long-lasting, low frequency activity) to "contractions" (high intensity, high frequency activity) ***(Nathanielsz et al., 1997).***

Labor and delivery are not passive processes by which uterine contractions push a rigid object through a fixed aperture. The ability of the fetus to successfully negotiate the pelvis during labor and delivery depends upon a complex interaction of three variables: power (uterine contractions), passenger (fetus), and passage (both bony pelvis and pelvic soft tissues) ***(Norwitz et al., 2001).***

LABOR AT TERM:-

The mean duration of human singleton pregnancy is 280 days (40 weeks) from the first day of the last menstrual period. A term pregnancy is defined as the period from 259 to 293 days after the first day of the last menstrual period ($37^{0/7ths}$ to $41^{6/7ths}$ weeks) ***(López et al., 1995).***

Term labor may be regarded physiologically as a release from the inhibitory effects of pregnancy on the myometrium, rather than as an active process mediated by

uterine stimulants. Nevertheless, both inhibitory and stimulatory mechanisms likely play a role in uterine activity ***(Garrioch et al., 1978).***

PHYSIOLOGICAL PHASES OF MYOMETRIAL ACTIVITY:-

The regulation of uterine activity during pregnancy can be divided into four distinct physiologic phases ***(Challis et al., 1996):***

Phase 0: inhibitors active:-

Throughout most of pregnancy the uterus is maintained in a state of functional quiescence through the action of various putative inhibitors including, but not limited to:

- Progesterone
- Prostacyclin (prostaglandin I-2)
- Relaxin
- Parathyroid hormone-related peptide
- Nitric oxide
- Calcitonin gene-related peptide
- Adrenomedullin
- Vasoactive intestinal peptide.

Phase 1: myometrial activation:

As term approaches, the uterus becomes activated in response to uterotropins, such as estrogen. This phase is characterized by increased expression of a series of contraction-associated proteins (CAPs) (including myometrial receptors for prostaglandins and oxytocin), activation of specific ion channels, and an increase in connexin-43 (a key component of gap junctions). An increase in gap junction formation between adjacent myometrial cells leads to electrical synchrony within the myometrium and allows for effective coordination of contractions.

Phase 2: stimulatory phase:

Following activation, the "primed" uterus can be stimulated to contract by the action of uterotonic agonists, such as the stimulatory prostaglandins E2 and F2 alpha and oxytocin.

Phase 3: involution:

Involution of the uterus after delivery occurs during phase 3 and is mediated primarily by oxytocin.

Parturition cascade:

It is likely that a "parturition cascade" exists at term which removes the mechanisms maintaining uterine quiescence and recruits factors promoting uterine activity ***(Smith et al., 2007).***

The sequential recruitment of signals that serve to augment the labor process suggest that it may not be possible to single out any one signaling mechanism as being responsible for the initiation of labor. Therefore, it is prudent to describe such mechanisms as being responsible for "promoting," rather than "initiating," the process of labor ***(Myers et al., 1993).***

THE ROLE OF THE FETUS:

During the Hippocratic period, the fetus was thought to be positioned head down at term so it could kick its legs up against the fundus of the uterus, thereby propelling itself through the birth canal ***(Duff et al., 1984).***

While we have moved away from this simple and mechanical view of labor, the factors responsible for the initiation and maintenance of labor at term are not well defined. Initial investigations focused on endocrine events, such as changes in the profile of circulating hormone levels

in the maternal and fetal circulations. Subsequent studies have concentrated on the dynamic biochemical dialogue between the fetus and mother (paracrine/autocrine events) in an attempt to understand the molecular mechanisms that regulate such interactions. The genetic regulation of the molecular events that occur during parturition are also being investigated ***(Huber et al., 2005).***

MYOMETRIAL ACTIVATION:

Regardless of whether the trigger originates within or outside the fetus, the final common pathway for labor ends in the maternal tissues of the uterus and is characterized by the development of regular phasic uterine contractions ***(Garfield et al., 1988).***

As in other smooth muscles, myometrial contractions are mediated through ATP-dependent binding of myosin to actin. This interaction is dependent upon the phosphorylation of myosin light chain by a calcium/calmodulin-dependent enzyme, myosin light chain kinase. The availability of free intracellular calcium is thus a key modulator of myometrial contractility ***(Garfield et al., 1988)***

GTP-binding proteins (G-proteins) play a pivotal role in myometrial contractility by coupling cell membrane receptors to effector enzymes and ion channels. As an example, activation of beta-adrenergic and/or PGE2 receptors promote myometrial relaxation via the Gas/ adenyl cyclase/cAMP signal transduction pathway ***(Garfield et al., 1988)***

Oxytocin receptors, on the other hand, couple to Gaq/Gai/phospholipase C pathways leading to an increase in inositol-1,4,5-trisphosphate (which releases calcium from the sarcoplasmic reticulum) and 1,2-diacylglycerol (which activates protein kinase C). The end result is an increase in