# *THE EFFECT OF ORAL PROPRANOLOL ON CARDIOTOCOGRAPHY DURING LABOR: A RANDOMIZED CONTROLLED TRIAL*

**Thesis**

Submitted for partial fulfillment of the Master Degree
in Obstetrics and Gynecology

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**2016**

# Abstract

Investigation of newer methods to reduce prolonged labor and also to prevent cesarean sections, due to uterine dysfunction, has been requested; regarding no harm, neither to the parturient woman nor to her fetus because of the increased morbidity related to these problems.

In this study which included 103 primipara parturient women with spontaneous onset of labor admitted to Ain Shams Maternity University Hospital. The aim was to evaluate the effect of oral propranolol when administered in the active stage of labor on cardiotocography (CTG) to determine the role of the beta-blockers when received during labor on the uterine contractions and fetal CTG pattern.

# Key wards

Labor, beta blocker, fetal bradycardia, prolonged labor, cardiotocography, propranolol.

# Introduction

Labor is defined as the state of being in uterine contractions of adequate frequency, duration, and strength to cause effacement and dilation of the cervix **(ACOG, 2003).**

Labor duration has shown a wide variation in different women **(Neal et al., 2010)**, and slow labor progress is common in nulliparous women. Prolonged labor is associated with childbirth complications, concerns for fetal wellbeing, and negative birth experiences **(Waldenstrom et al., 2004)**, and is one of the main indications for unplanned caesarean section in labor **(Florica et al.,2006).**

Duration of labor varies widely depending on demographic, clinical, genetic factors, uterine activity, fetal lie or presentation and number of fetus **(Terkawi et al., 2012).**

Prolonged labor can lead to maternal and neonatal complications **(Cheng et al., 2009)** and These adverse labor outcomes increase in prolonged pregnancy in comparison with term gestational age **(Chantry and Lopez, 2011).** Prolonged pregnancies can result in development of oligohydramnios, macrosomia and intrauterine fetal demise at a later gestational age. Therefore, the factors affecting labor progression have been widely studied **(Hollis., 2002).**

Labor dystocia due to reduced uterine contractions is one of the main causes leading to cesarean section. In such conditions often oxytocin infusion is used for augmentation of the uterine contractions **(Coco et al., 2010).**

However, oxytocin is the best known and most widely used agent to induce and augment uterine contractions **(Hinshaw et al., 2008);** but the Institute for Safe Medication has termed oxytocin as a high-alert medication due to the risk of high dose or wrong prescription. This institute recommended many programs to minimize the maternal and neonatal risks of oxytocin administration **(Simpson and Knox, 2009).**

Propranolol is well established as a β adrenergic receptor–blocking drug that increases the uterine activity in pregnant and non-pregnant women by reversing the suppressive effect of the β agonist isoproterenol on human uterine motility **(Kashanian et al., 2008).** It is well known that the half-life of propranolol is 2-3 h and its peak effect is at 1 h.

The first uncontrolled study on the use of propranolol in dysfunctional labor was conducted about four decades ago. The results showed that administration of propranolol causes normal uterine activity and delivery without any significant maternal or fetal complications **(Mitrani et al., 1975).**

Recent studies have shown the effect of oxytocin to be associated with propranolol in decreasing the time of labor induction and the duration of active phase in labor dystocia **(DireKvand-Moghadam et al.,2013).**

# Aim of the Study

## Study hypothesis:

We suggest that oral propranolol when used during the process of active labor has no effect on fetal heart rate and may increase uterine contractions.

## Study question:

Does oral propranolol have any negative effect on fetal heart rate during the process of active labor?

## Outcome:

**Primary outcome**

- Effect of oral propranolol on fetal heart rate.
- Effect on uterine contractions during active labor..

**Secondary outcome**

- Labor outcome (duration and mode of delivery).
- Neonatal outcome (Apgar score at 1 and 5 mins and need for NICU admission).

# Chapter 1

# PHYSIOLOGY OF LABOR

Labor defined as a physiological process including a sequential, integrated set of changes within the myometrium, uterine cervix and decidua and that occur gradually over a period of days and may extend to weeks **(Errol et al., 2015).**

Labor and delivery both are not passive events by which uterine contractions push a solid object through a fixed aperture. The ability of the fetus to successfully manipulate 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 is a clinical diagnosis, it involves (1) the presence of regular phasic uterine contractions which increase in intensity and frequency, and (2) progressive cervical effacement and dilatation. A show (a bloody discharge) may or may not follow. 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 duration has shown a wide variation in different women **(Neal et al., 2010)**, and slow labor progress is common in nulliparous women. Duration of labor varies widely depending on demographic, clinical, genetic factors, uterine activity, fetal lie or presentation and number of fetus **(Terkawi et al., 2012).**

Prolonged labor may cause many maternal and neonatal adverse outcomes **(Cheng et al., 2009).** It is associated with childbirth complications, concerns for fetal wellbeing, and negative birth experiences, it is one of the solid indications for unplanned caesarean section during labor. These adverse labor

outcomes increase in prolonged pregnancy in comparison with term gestational age **(Chantry and Lopez, 2011).**

## LABOR AT TERM:

The mean duration of human singleton pregnancy is 280 days (40 weeks) calculated 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 (completed 37 to $41^{6/7ths}$ weeks) **(López et al., 1995).**

## MYOMETRIAL ACTIVITY PHASES:-

The physiological point of view. The regulation of myometrial activity during pregnancy can be divided into four distinct phases **(Challis et al., 1996):**

### *Phase 0: (inhibitors active)*

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

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

### *Phase 1: (myometrial activation)*

Near term, the myometrium becomes activated in response to uterotropins (eg: 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)***

After activation, the "primed" uterus can now be stimulated through the action of uterotonic agonists to contract, such as the stimulatory prostaglandins F2 alpha, estradiol (E2) and oxytocin.

***Phase 3: (involution)***

Finally involution of the uterus after delivery occurs during this phase and is mediated mainly by oxytocin.

**Parturition cascade**

It looks like that a "parturition cascade" exists at term that deactivate the mechanisms which maintain the uterine quiescence and stimulate factors which promote uterine activity **(Smith et al., 2007).**

The sequential activation of signals that serve to augment the labor process suggest that it cannot be possible to determine 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).**

I) **THE ROLE OF THE FETUS:-**

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

While we have moved away from this simple and mechanical explanation of labor, the factors responsible for the activation and maintenance of labor at term are not well recognized **(Huber et al., 2005)**.

Initial investigations focused on endocrine processes, such as changes in the level of circulating hormones in the maternal and fetal blood circulations. Other studies have concentrated on the dynamic biochemical interactions taking place between the fetus and mother (paracrine and autocrine events) in a trial to understand the molecular mechanisms that regulate such interactions. The genetic regulation of the molecular events that occur during labor are also being investigated **(Huber et al., 2005).**

The theory that the fetus takes the lead in determining the timing of labor was elegantly demonstrated in domestic ruminants. As an example, parturition in sheep is activated by a sudden rise in fetal adrenal cortisol secretion related to increased fetal concentrations of and response to corticotropin **(Liggins et al., 1973).**

Cortisol works on placental enzymes active in the biosynthesis of estrogens from progesterone which increase secretion of estrogen and decrease progesterone production. The outcome is increase in the ratio of estrogen to progesterone levels stimulates placental release of prostaglandin F2 alpha that enhances the myometrial response to oxytocin and stimulates contractions **(Matthews et al., 1996).**

However, the human placenta lacks the glucocorticoid-inducible 17-alpha-hydroxylase/17, 20-lyase enzyme that is necessary to this process. Therefore, activation of the

hypothalamic-pituitary-adrenal axis in humans could results in a different mechanism for initiation of labor **(Liggins et al., 1998).**

## II) MYOMETRIAL ACTIVATION

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

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

GTP-binding proteins play a vital role in myometrial contractility by coupling cell membrane receptors to ion channels and effector enzymes. 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, bind to Gaq/Gai/phospholipase C pathways leading to an increase in inositol-1,4,5-trisphosphate (that releases calcium from the sarcoplasmic reticulum) and 1,2-diacylglycerol (which activates protein kinase C). All of these cause an increase in intracellular calcium and myometrial contractions **(Phaneuf et al., 1995).**

Pregnancy not only affects cell surface receptor concentrations, but also the coupling and concentrations of the various G-proteins. Gai and Gaq are expressed at similar levels in non-pregnant and pregnant myometrium, both before and after the onset of labor. By comparison, Gas levels are higher in pregnant

as compared with non-pregnant myometrium, and levels have been shown to decrease before the process of labor, both at term and preterm **(Europe-Finner et al., 1994).**

Therefore, it has been concluded that labor results from a down-regulation of pathways that favor uterine quiescence leading to a relative dominance of stimulatory pathways that increase intracellular calcium bioavailability and promote myometrial contractility **(López et al., 1995).**

Other factors (eg, mechano-transduction via stretching or shortening) which could affect activation, frequency, or strength of contractions are under study **(Hurd et al., 2005).**

## III) HORMONES

Hormones involved in parturition cascade include:

### *1. Prostaglandins :*

Prostaglandins are mainly paracrine/autocrine hormones (ie, they act locally at their site of production on contiguous cells). An increase in uterine prostaglandin biosynthesis at term is a consistent promoter in the transition into labor **(Keirse et al., 1979).**

It looks likely that hormonal factors controlling the final pathway for the initiation of labor in women, both at term and near term, is an increased biosynthesis of prostaglandins of the E and F cascades within the uterine compartment, primarily from the decidua and fetal membranes **(Errol et al., 2015).**

The evidence can be summarized as:

●Human uterine tissues are selectively containing high levels of arachidonic acid, the primer precursor of prostaglandin biosynthesis **(Errol et al., 2015).**

●Concentrations of prostaglandins in amniotic fluid and in maternal plasma and urine are increased during labor **(Casey et al., 1988).**

Moreover, prostaglandin levels appear to increase before the onset of myometrial concentrations suggesting that they are a trigger, rather than a consequence, of labor **(Romero et al., 1996).**

●In a clinical trial of intravenous or vaginal administration of exogenous prostaglandins caused initiation of labor at any stage of gestation **(Casey et al., 1986).**

●Prostaglandins have been implicated in the three events most temporally related to the onset of labor:

The onset of synchronous uterine contractions, cervical ripening, and the increase in myometrial sensitivity to oxytocin due to an increase in myometrial gap junction formation and/or oxytocin receptor concentrations **(Karim et al., 1997).**

●Inhibitors of prostaglandin synthesis (including cyclooxygenase inhibitors such as indomethacin) are capable of suppressing myometrial contractility both in vitro and in vivo, and of prolonging the length of gestation **(Wigvist et al., 1975).**

These data summarize the critical role of prostaglandins in the process of labor. It seems that withdrawal of fetal-paracrine support of the quiescent uterus leads to decidual activation, followed by PGF2 alpha release and subsequent spontaneous labor **(Casey et al., 1988).**

PGE2 seems to play an essential role in cervical ripening (a remodeling process in which collagen is degraded leading to softening of the cervix) and rupture of the fetal membranes than in uterine contractility **(Keirse et al., 1979).**

### *2. Estrogen :*

The placenta is the major source of estrogen biosynthesis during pregnancy. Estrogens do not by themselves cause myometrial contractions, they act by increasing myometrial gap junctions and uterotonic receptors (including L-type calcium channels and oxytocin receptors), thereby enhancing the capacity of the myometrium to generate contractions **(Fuchs et al., 1986).**

### *3. Progesterone :-*

Progesterone is necessary for early pregnancy maintenance, administration of a progesterone receptor antagonist or removal of the corpus luteum readily induces abortion in early pregnancy (before seven weeks of gestation**) (Csapo et al., 1973).**

Administration of exogenous progesterone after early lutectomy prevents abortion, further supporting the hypothesis that ovarian progesterone production is essential in maintenance of early pregnancy **(Errol et al., 2015).**

Placental progesterone production increases between five and seven weeks, and the placenta is the dominant source of progesterone thereafter **(Errol et al., 2015).**

However, in late pregnancy the role of progesterone is not as well defined **(Zakar et al., 2011).**

Progesterone withdrawal does not occur in all women before labor, and mean circulating progesterone levels during

labor are similar to those measured one week prior **(Turnbull et al., 1989).**

Moreover, the administration of progesterone late in pregnancy does not delay the onset of labor in primates , and progesterone receptor antagonists are not an effective way of inducing labor at term (although they may promote cervical ripening) **( Elliott et al., 1998).**

These data suggest that systemic progesterone withdrawal is not a prerequisite for labor in humans. This is in contrast to most mammalian species in which systemic progesterone withdrawal is an essential component of parturition **(Zakar et al., 2007).**

However, circulating hormone concentrations do not necessarily reflect activity at the tissue level. The onset of labor in women does appear to be preceded by a physiologic withdrawal of progesterone activity ("functional progesterone withdrawal") at the level of the uterus **(Zakar et al., 2007).**

### *4. Oxytocin :*

Oxytocin is a peptide hormone synthesized in the hypothalamus and released from the posterior pituitary in a pulsatile fashion. It is also produced by the placenta. Its biologic half-life in the maternal circulation is approximately three to four minutes, but appears to be shorter when higher doses are infused. Oxytocin is inactivated in the liver and kidney, although during pregnancy it is primarily degraded by placental oxytocinase **(Errol et al., 2015).**

The evidence support a role for oxytocin in parturition can be summarized briefly as follows:

- Oxytocin is the most potent endogenous uterotonic agent, and is capable of inducing uterine contractions at intravenous infusion rates 1 to 2 mU/min at term **(Fuchs et al., 1984).**