Propranolol and Misoprostol versus Misoprostol Only for Induction of Abortion during Second Trimester of Pregnancy: Randomized Controlled Trial

Thesis

Submitted for Partial Fulfillment of Master Degree in Obstetrics & Gynecology

By

Nada Alaa Eid

M.B.B.Ch – Ain Shams University (2013)

Visitor Resident of Ob / Gyn, Ain Shams University Maternity Hospital

Under Supervision of

Prof. Waleed Hitler Ahmed

Professor of Obstetrics and Gynecology

Faculty of Medicine - Ain Shams University

Dr. Kareem Mohamed Labib

Assistant Professor of Obstetrics and Gynecology

Faculty of Medicine - Ain Shams University

Dr. Maii Medhat Nawara

Lecturer of Obstetrics and Gynecology

Faculty of Medicine - Ain Shams University

Faculty of Medicine - Ain Shams University

2017

Acknowledgements

I'd like to express my respectful thanks and profound gratitude to ***Prof. Waleed Hitler Ahmed,*** *Professor of Obstetrics and Gynecology - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to ***Dr. Kareem Mohamed Labib,*** *Assistant Professor in Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Dr. Maii Medhat Nawara,*** *Lecturer in Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Last but not least my sincere thanks and appreciation to all patients participated in this study.

Nada Alaa

List of Contents

List of Tables

List of Figures

INTRODUCTION

Abortion-related morbidity and mortality increase significantly as gestation advances. Abortions after 14 weeks of pregnancy constitute 10-15% of all abortions; however, they are responsible for two-thirds of all abortion-related complications and 50% of abortion related deaths ***(Dilek et al., 2011).***

The development of safe and effective abortion techniques for second trimester pregnancy terminations and fetal demise is a major clinical challenge. The main aim of abortion induction is rapid, uneventful, and complete expulsion or delivery of the products of conception. Termination of second trimester pregnancies can be achieved by various techniques, including prostaglandin analogues, hygroscopic dilatators, and Foley balloon traction. Time period between beginning of induction to abortion or delivery of products of conception can be prolonged in the second trimester of pregnancy due to uterine unresponsiveness and unfavorable cervix ***(Dilek et al., 2011).***

Prolonged administration of various methods and lower response rate to oxytocin infusion results in discomfort and increased anxiety for the woman. Therefore, cervical priming is the major step of second trimester pregnancy termination. The most employed method of termination of pregnancy (TOP) is

the application of the prostaglandin analogue (misoprostol), RU486 and Methotrexate ***(Ngai et al., 2003).***

Misoprostol in an initial dose of 800 mcg followed by 400 mcg every 4 hours is the recommended dose in induction of abortion in the second trimester ***(Danielsson, 2007).***

The last 20 years scarce evidence have been reported regarding propranolol mode of action during the latent and active phases of labor. Propranolol is a sympatholytic nonselective beta blocker. Twenty-five years ago, ***Peiker et al. (1990)*** suggested that it causes contractions of uterine muscle stripes in pregnant rats and eventually leads to induction of labor. Since then various molecular pathways which involve the adrenergic system have been implicated in the regulation of uterine contractility, despite this evidence, however, the interest on propranolol use as a pharmaceutical mean to induce and/or enhance contractions is very limited ***(Bardou et al., 2000; Rouget et al., 2005; Tanaka et al., 2005).***

Propranolol is one of these agents which have been suggested for assisting labor induction ***(Kashanian et al., 2008).*** In several studies, it was seen that propranolol could induce contractions in the pregnant uterine musculature ***(Peiker et al., 1990; Kitazawa et al., 2001).***

Propranolol, as a Beta- adrenergic receptor blocking drug, can reverse the inhibitory effect of Beta-agonist

isoproterenol on human uterine motility ***(Sanchez-Ramos et al., 1996)***.

In a study, its intravenous use once or twice in a 20 mg dose was found to shorten the duration of labor induction, without any adverse effects on neonates ***(Palomaki et al., 2006).*** In another study, intravenous propranolol was found to increase uterine activity in pregnant and in the non-pregnant participants ***(Direkvand-Moghadam and Rezaeian, 2012).***

The first uncontrolled study on the use of propranolol in dysfunctional labor was conducted about four decades ago. The results showed that administration of intravenous propranolol causes normal uterine activity and delivery without any significant maternal or fetal complications ***(Mitrani et al., 1957).***

AIM OF THE WORK

This study aims to review the efficacy of propranolol in association with misoprostol as a substitute to misoprostol use only in induction of abortion during the second trimester of pregnancy.

Research Question

Does the use of propranolol in association with misoprostol versus misoprostol use only, decrease the induction-expulsion time during the second trimester of pregnancy?

Research hypothesis

In Women undergoing induction of abortion during the second trimester of pregnancy, the use of propranolol with misoprostol versus misoprostol use only, decreases the induction-expulsion time.

Chapter 1
MYOMETRIAL CONTRACTILITY

The growth and activity of the uterus are mainly under the control of hormones. In wide terms, the myometrial activity is stimulated by estrogen, action potentials in muscles become more frequent and thus the activity and the excitability of the muscle is more prominent. An 'estrogen primed' uterus is also more sensitive to oxytocin. On the other hand, progesterone action on uterus depresses the excitability of the musculature by decreasing spontaneous electrical activity and sensitivity to oxytocin ***(Abbas and Monaghan, 2014)***.

In pregnancy, the size of the uterus increases from 30 - 60 g to 750 -1000g under the control of estrogen that acts on the myometrium resulting in its hyperplasia and hypertrophy. Muscle cell size increases from 50 to 500 mm, glycogen is laid down and there is an increase in adenosine triphosphate (ATP). Muscle contraction is induced by intracellular liberation of calcium from intracellular stores and from extracellular fluid. Spontaneous depolarizing pacemakers occur and if these exceed a critical threshold a sharp increase in intracellular calcium is seen and a contraction follows. Contractility can therefore be modulated by changing pacemaker potentials and the threshold for contraction. Prostaglandins enhance the liberation of intracellular calcium and oxytocin lowers the excitation threshold for contraction ***(Abbas and Monaghan, 2014).***

Myometrial activity phases:

The regulation of myometrial activity during pregnancy can be divided into four different phases ***(Challis and Gibb, 1996)***:

Phase 0: (inhibitors active)

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

- Progesterone
- Relaxin
- Prostacyclin (prostaglandin I2)
- Nitric oxide
- Parathyroid hormone-related peptide
- Vasoactive intestinal peptide
- Calcitonin gene-related peptide

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 contracts under the effect of uterotonic agonists, such as the stimulatory prostaglandins F2 alpha, estradiol (E2) and oxytocin.

Phase 3: (involution)

Finally, the uterus undergoes a process of involution that occurs after delivery and is mediated mainly by oxytocin.

Hormones

A parturition cascade involves the following hormones:

1. Prostaglandins:

Prostaglandins are genrally classified as 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, 1979).***

It is likely that hormonal factors influencing the final pathway of labor initiation in women, both at term and near term, is a result of increased biosynthesis of prostaglandins of

the E and F cascades within the uterine compartment, primairly 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 and MacDonald, 1988)***.
- Moreover, prostaglandin levels appear to increase before the onset of myometrial contractions 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 and MacDonald, 1988)***.
- Prostaglandins have been implicated in the three events most importantly 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., 1982)***.

- 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 and MacDonald, 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, 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, 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 and Mesiano, 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, 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