Elective Induction of Labour in Normal Pregnant Nulliparous Women at 39 Weeks versus Expectant Management:

Randomized Controlled Trial

Thesis

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Mohamed Dosoky Mohamed

List of Contents

List of Tables

Table No.	Title	Page No.

List of Figures

List of Abbreviations

Abb.	Full term
µg	*Microgram*
ACOG	*American college of Obstetricians and Gynecologists*
AROM	*Artificial Rupture Of Membranes*
BMICI	*Body Mass IndexConfidence Interval*
Cm	*Centimeter*
COX-2C.N.S	*Cycloxygenase-2Central Nervous System*
CS	*Cesarean section*
CTGFHR	*Cardio TocographyFetal Heart Rate*
GTN	*Glyceryl Trinitrate*
HBsAg	*hepatitis B surface antigen*
hPGDS	*Hematopoietic prostaglandin D synthases*
Hrs	*Hours*
IUGR	*Intra Uterine Growth Restriction*
lPGDS	*Lipocalin prostaglandin D synthases*
Mg	*Milligram*
Min	*Minutes*
Ml	*Milliliter*
mU	*Milliunit*
NADPH	*Nicotinamide Adenine Dinucleotide Phosphate-Oxidase*
NICU	*Neonatal intensive care unit*
NO	*Nitric Oxide*
NSAIDs	*Non-steroidal anti-inflammatory drugs*
NST	*Non Stress Test*
PROM	*Pre-Labor Rupture Of Membranes*
RCT	*Randomized controlled trial*
ROM	*Rupture Of Membranes*

List of Abbreviations cont...

Abb.	Full term

SD.....*Standard Deviation*
T.....*Student t-test*
TENS.....*Transcutaneous nerve stimulation*
TNF .....*Tumor Necrosis Factor*
TXA.....*Thromboxane*
TxAS.....*Thromboxane A synthase*
U□S.....*Ultrasonography*
Wks .....*Weeks*
Yrs.....*Years*

INTRODUCTION

Parturition is the culmination of a period of pregnancy with the expulsion of one or more newborn infants from a woman's uterus. The process of normal childbirth is categorized in three stages of labor: the shortening and dilation of the cervix, descent and birth of the infant, and birth of the placenta ***(Wiberg-Itzel et al., 2016).***

Induction of labor is defined as the process of artificially initiating uterine contractions, prior to their spontaneous onset, with progressive effacement and dilatation of the cervix and ultimately, the delivery of the baby ***(Martin et al., 2005)***.

Induction of labor is indicated when it is thought that delivering the baby will be safer for the baby and/or the mother, than for the baby to remain *in utero*. There are many indications for induction of labor in the obstetric practice, of which prolonged gestational age stands as the most common indication, maternal health problems include hypertension, pre-eclampsia, diabetes and obstetric cholestasis, Fetal growth restriction premature rupture of membranes (>37 weeks' gestation), intrauterine fetal death. Induction of labor should be offered if mother is physically well with intact membranes ***(Josie, 2003)***.

Absolute Contraindications for induction of labor are cephalopelvic disproportion, placenta praevia, vasa praevia, cord prolapse, transverse lie, active primary genital herpes, previous

classical Caesarean section, breech presentation, triplet or higher order pregnancy, previous low transverse caesarean sections.

Unsuccessful labor induction is most likely when the cervix is unfavorable, and in this circumstance prostaglandin preparations have proved to be beneficial. Those prostaglandins, which have been registered for cervical ripening and labor induction, are expensive and unstable and require refrigerated storage ***(Weeks et al., 2006).***

Timing of delivery is a vital component of a healthy pregnancy. An increase in morbidity and mortality exists on both ends of the gestational age at delivery spectrum. On one hand, preterm birth is the leading cause of neonatal morbidity and mortality in the United States and is associated with substantial societal and healthcare costs. On the other, late-term and post-term pregnancies are also associated with increased maternal, fetal and neonatal risks. Because of these risks, the American College of Obstetricians and Gynecologists (ACOG) states that a provider may consider induction of labor between 41 0/7 and 41 6/7 weeks gestational age and recommends induction of labor after 42 0/7 weeks gestational age ***(Rachel et al., 2018).***

While obstetricians generally agree on the management of late- and post-term pregnancies, uncertainty exists over the optimal timing of delivery among pregnancies between 39 and 41 weeks gestation. On one hand, elective induction of labor at 39 weeks gestational age avoids potential risks of ongoing

pregnancies including preeclampsia and stillbirth. One European analysis quantified the total pregnancy loss rate at 39, 40 and 41 weeks as 1.4%, 2.4% and 2.8%, respectively. Additionally, elective induction decreases the risk of macrosomia with its attendant risk of shoulder dystocia with or without permanent brachial plexus injury. Both preeclampsia and fetal macrosomia increase the risk of cesarean delivery. However, induction of labor also carries risk. Women who undergo induction of labor have higher rates uterine hyperstimulation and Category II and III fetal heart rate tracings. Additionally, nulliparous patients with an unfavorable cervix undergoing induction of labor may carry a higher rate of cesarean delivery ***(Vahratian et al., 2005).***

Available literature to guide clinicians is biased by retrospective data and prospective studies that are underpowered to detect differences in several clinically important outcomes. When empirical studies do not exist or are difficult to conduct, mathematical modeling may be the best option available to derive rational policy. Therefore, in light of this clinical equipoise, our objective was to perform a comparative effectiveness analysis of elective induction of labor at 39 weeks gestational age among nulliparous women with uncomplicated pregnancies as compared to expectant management with induction of labor for standard medical or obstetrical indications or at 41 weeks gestation in undelivered mothers ***(Stock et al., 2015).***

AIM OF THE WORK

The aim of this study is to compare between elective induction of labour at 39 weeks gestation in nulliparous women versus expectant management as regard rate of ceasrean section.

Research Question:

In normal pregnant nulliparous women at 39 weeks gestation, does elective induction of labour have similar rate of cesarean section (CS) to expectant management at term?

Research Hypothesis:

Elective induction of labour in normal pregnant nulliparous women at 39 weeks gestation have the same rate of cesarean section as expectant management.

Chapter 1

PHYSIOLOGY OF LABOR

Labor is a physiologic process during which the products of conception (i.e., the fetus, membranes, umbilical cord, and placenta) are expelled outside the uterus after the age of fetal viability. Labor is achieved with biochemical changes in the 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 ***(ACOG, 2013).***

Labor is a clinical diagnosis. The onset of labor is defined as regular, painful uterine contractions resulting in progressive cervical effacement and dilatation ***(Chong et al., 2004).***

Although the precise mechanisms that underlie the initiation of parturition in humans remain to be elucidated, a series of natural experiments and clinical observations provide valuable insights. Conditions that disrupt the fetal hypothalamic-pituitary adrenal (HPA) axis (e.g., anencephaly in the absence of polyhydramnios) or the synthesis of estrogen by the placenta (e.g., placental sulfatase deficiency) lead to prolonged gestation. That prostaglandins play a crucial role is suggested by the finding that prostaglandin synthetase inhibitors delay parturition, whereas administration of prostaglandins initiates parturition. Thus, theories of the initiation of parturition in humans must reconcile the need for

an intact fetal HPA axis, increasing placental estrogen synthesis, and enhanced reproductive tract prostaglandin activity ***(Lockwood, 2004).***

In most mammalian species, including humans, estrogen levels increase in the amniotic fluid and plasma before the onset of term parturition ***(Challis et al., 2000).***

In most mammals, maturation of the fetal HPA axis and development of the transient "fetal inner zone" of the fetal adrenal gland cause an abrupt increase in circulating cortisol levels that activate the placental 17 α-hydroxylase and 17,20-lyase enzyme to shunt steroid precursors away from the progesterone to the estradiol synthetic pathway ***(Lockwood, 2004).***

Fetal control of human parturition:

The role of the fetal hypothalamic-pituitary-adrenal axis:

Many lines of evidence suggest that development and maturation of the fetal HPA axis are the primary regulators of the onset of parturition ***(Lockwood, 2004).***

Plasma Corticotropin Releasing Hormone levels increase dramatically during the second half of pregnancy, peak during labor, and rapidly decline in the postpartum period, whereas levels of its inactivating binding protein decrease in the third trimester ***(Mastorakos et al., 2003).***

Although CRH levels increase sharply at term, labor also is associated with increased expression of the CRH receptor-2 in the chorion and myometrium and of the type-1 receptor in the amnion, chorion, and myometrium ***(Jirecek, 2002).***

Using data that were obtained from cordocentesis, they showed that fetal CRH and cortisol also increase during the second half of gestation and that fetal cortisol levels correlate most strongly with placental CRH secretion. This suggests that placental CRH expression drives fetal HPA activation. One explanation for this paradoxic cortisol stimulation of placental CRH expression may rest with the decreased levels of prostaglandins receptor expression in trophoblasts and progesterones weak antagonist effects on the Glucocorticoid Receptor (GR) ***(Lockwood et al., 1996).***

Increasing maternal and fetal cortisol levels at term progressively overcome progesterones tonic inhibition of cortisol/GR-mediated CRH expression, however. The resulting increase in placental-derived CRH "inappropriately" stimulates maternal and fetal pituitary corticotropin production, which normally would be suppressed significantly by the increasing cortisol levels. This feed-forward loop is more pronounced in the fetus than in the mother, that maternal corticotropin concentrations decrease modestly, whereas fetal corticotropin levels increase with increasing gestational age, despite increasing cortisol levels in both compartments ***(Lockwood et al., 1996).***