Efficacy of intravaginal administration of isosorbide mononitrate together with misoprostol versus misoprostol alone in induction of labor in postdate women

A Thesis

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By

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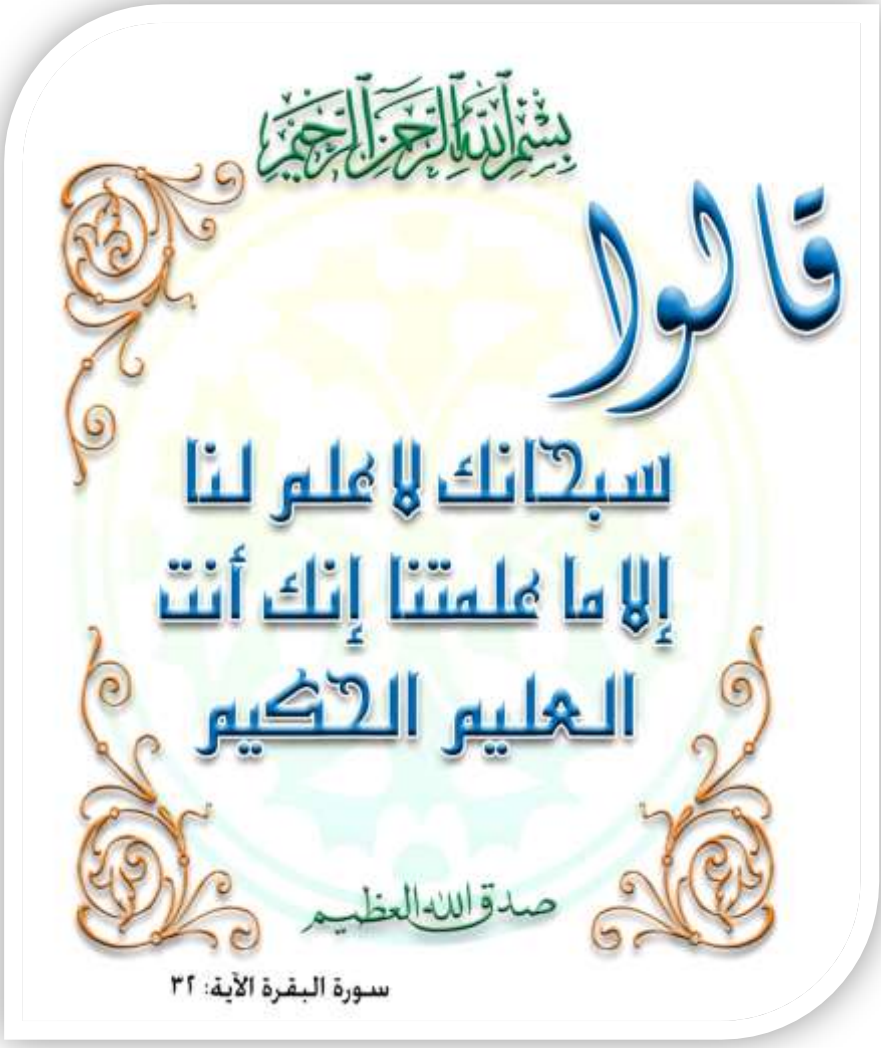
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✍ *Abdelrahman Ali Fadel Youssef Mohamed*

List of Contents

List of Abbreviations

Abbrev.	Full-term
BMI	**:** Body mass index
COX-2	**:** Cyclooxygenase 2
CTG	**:** Cardiotocography
FHR	**:** Fetal heart rate
GTN	**:** Glyceryl trinitrate
IMN	**:** Isosorbide mononitrate
NO	**:** Nitric oxide
NOD	**:** Nitric Oxide donor
NOS	**:** Nitric Oxide Synthases
PG	**:** Prostaglandins
PGE2	**:** Prostaglandin E2
PGF2-α	**:** Prostaglandin F2-α
PGI2	**:** Prostaglandin I2
PLA2	**:** Phospholipase A 2
PPROM	**:** Premature preterm rupture of membrane
SD	**:** standard deviation
SNP	**:** Sodium nitroprusside
SPSS	**:** Statistical package for social science

List of Tables

List of Figures

Abstract

Objective: to assess the efficacy of intravaginal administration of isosorbide mononitrate (IMN) together with misoprostol in reducing the duration of induction of labor in post-date women.

Setting: Ain Shams University Maternity hospital, labor ward.

Methods: one hundred women with postdate pregnancies and unfavorable cervices scheduled for labor induction were recruited and assigned randomly to IMN 40mg with misoprostol 25 µg or misoprostol 25 µg alone administrated vaginally. The main outcome is the duration of induction to the active phase duration.

Results: The two groups were matched according to the maternal age, parity, gestational age and Bishop's score. Women receiving IMN plus misoprostol showed significant reduction of the induction to active phase duration compared to misoprostol alone (10.6 ± 1.5 versus 8.8 ± 1.3 $p<0.001$) and from the beginning of induction to the time of delivery (17.2 ± 2.3 versus 12.2 ± 2.7 $p<0.001$) there was no significant difference between both groups according to the uterine contractile abnormalities in the form of tachysystol, hypertonus, and hyperstimulation. there was no significant difference between the two groups according to the maternal side effects in the form of flushing, hypotension, tachycardia, diarrhea and postpartum hemorrhage but there was a significant difference in the rate of headache. In group B (IMN and misoprostol) 15(30%) versus group A (misoprostol alone) 2(4%).

Conclusion: The use of IMN in combination with misoprostol in the induction of labor is effective in the reduction of the duration of induction and safe on the mother and fetus.

Keywords Misoprostol, induction, isosorbide mononitrate

Introduction

Induction implies stimulation of contractions before the spontaneous onset of labor, with or without ruptured membranes. When the cervix is closed and uneffaced, labor induction will often commence with cervical ripening, a process that generally employs prostaglandins to soften and open the cervix ***(ACOG, 2009).***

Induction is indicated when the benefits to either mother or fetus outweigh those of pregnancy continuation. The more common indications include membrane rupture without labor, gestational hypertension, oligohydramnios, nonreassuring fetal status, postterm pregnancy, and various maternal medical conditions such as chronic hypertension and diabetes Several factors affect the ability of labor induction to achieve vaginal delivery ***(ACOG, 2009).***

Favorable factors include younger age, multiparity, body mass index (BMI) <30, favorable cervix, and birth weight <3500 ***(Gibson and Water, 2015).***

In many cases, the uterus is simply poorly prepared for labor. One example is an "unripe cervix." Indeed, investigators reported that elective induction resulted in vaginal delivery in 97 percent of multiparas and 76 percent of nulliparous, but that induction was more often successful with a ripe cervix ***(Laughon et al., 2012).***

Cervical ripening agents are routinely used in women with an unfavorable cervix which is often defined as Bishops score of ≤6. Ripening of the cervix may be achieved by both pharmacological and non-pharmacological (mechanical) methods ***(Soliman, 2013).***

Since the late 1960s prostaglandins (PG) have been used for the induction of labor at term, and PG and their analogs have been administered by various routes to induce labor with mostly comparable results ***(Kelly et al., 2003).***

Several findings have prompted a search for clinical agents that stimulate nitric oxide (NO) production locally ***(Chanrachakul et al., 2000).***

First, NO is likely a mediator of cervical ripening. Also, cervical NO metabolite concentrations are increased at the beginning of uterine contractions. And, cervical NO production is very low in postterm pregnancy ***(Väisänen-Tommiska et al., 2004).***

Bullarbo and colleagues reviewed rationale and use of two NO donors isosorbide mononitrate and glyceryl trinitrate. Isosorbide mononitrate induces cervical cyclooxygenase 2 (COX-2), and it also initiates cervical ultrastructure rearrangement similar to that seen with spontaneous cervical ripening ***(Bullarbo et al., 2007).***

But the results of a published trial suggest that Nitric Oxide donor (NOD) are safe, but less effective for labor induction than dinoprostone ***(Nicoll et al., 2001).***

In clinical observations, several NOD such as isosorbide mononitrate (IMN), glyceryl trinitrate, and sodium nitroprusside were reported to reduce the cervical resistance ***(Carlan et al., 2002).***

Aim of the Work

To assess the Role of intravaginal administration of isosorbide mononitrate together with misoprostol in reducing the time of induction of labor in postdate women.

Induction of labor

Introduction:

Induction of labor is an obstetric procedure to artificially stimulate uterine contraction and labor. It usually consists of two steps: ripening of the cervix and stimulation of uterine contractions. Ripening of cervix usually by misoprostol or mechanical ways and uterine contractions stimulated by Oxytocin ***(SOGC, 2011).***

A ripe cervix is a very important factor for the successful induction of labor. Therefore, the cervix must be assessed by Bishop's score before the beginning of induction. If the Bishop's score is less than 6. The induction must be preceded by the ripening of the cervix **(Pevzner et al., 2009)**

Prevalence:

Between 1990 and 2012, the overall frequency of labor induction more than doubled in the United States, rising from 9.5 in 1990 to a high of 23.8 percent in 2010, before declining to 23.3 percent in 2012 **(Osterman and Martin, 2014)**.

Indications:

Induction of labor is indicated when the maternal/ fetal risks associated with continuing the pregnancy are more than the maternal/fetal risks associated with delivery **(ACOG, 2009).**

One of the most common indications of induction of labor is post-date pregnancy, especially after 41 gestational age. Induction for this indication leads to the reduction of the intrauterine fetal death rate **(Crowley, 1997)**.

Common indications for induction of labor include:

1. Postdate pregnancy (more than 41 weeks).
2. Pre-labor spontaneous rupture of membranes.
3. Maternal diseases:
    - Diabetes mellitus.
    - Hypertensive / renal diseases.
    - Autoimmune diseases (e.g. SLE).
    - Significant pulmonary disease.
4. Pregnancy related disorders:
    - Pre-eclampsia.
    - Intrahepatic cholestasis related to pregnancy.
    - Antepartum hemorrhage.
    - Abruption placenta.
    - Antiphospholipid syndrome.
5. Fetal:
    - Intrauterine growth restriction.
    - Oligohydramnios.
    - Isoimmunization.
    - Non-reassuring fetal surveillance.
    - Intrauterine fetal demise.

This list is not meant to be all-inclusive **(Kehila et al., 2016)**.