Prostaglandin E1 before Elective Caesarean Section to reduce Transient Tachypnea of the Newborn (TTN)

A Randomized Control Trial

Thesis

Submitted for Partial Fulfillment of Master Degree in Obstetrics and Gynaecology

By

Hossam Hassan Ahmed Mohamed

Resident in Obstetrics and Gynecology
MB.B.Ch 2012,
Police Hospital -Nasr City,
Faculty of Medicine, Cairo University

Supervised By

Prof. Dr. Noha Hamed Rabei

Professor of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Dr. Noha Abd El Sattar Sakna

Lecturer of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Dr. Marwa Saber Sayed

Lecturer of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2017

Acknowledgement

First and foremost, I feel always indebted to **ALLAH** *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Noha Hamed Rabei,** *Professor of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University for her keen guidance and kind supervision.*

I am also delighted to express my deepest gratitude and thanks to **Dr. Noha Abd El Sattar Sakna,** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine – Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Dr. Marwa Saber Sayed,** *Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University, valuable advices and continuous encouragement, which made the completion of this work possible.*

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.

Hossam Hassan

Contents

List of Abbreviations

Abb.	Full term
ACOG	American college of obstetricians and gynecologist
CDMR	Cesarean delivery at maternal request
CI	Confidence interval
CRF1	Case record form 1
CRF2	Case record form 2
CS	Cesarean section
ECS	Elective cesarean section
ERCS	Elective repeat cesarean section
N-CPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
NIH	National institutes of health
PBF	Pulmonary blood flow
PG E1	Prostaglandins E1
PPHN	Persistent pulmonary hypertension of the newborn
PVR	Pulmonary vascular reabsorption
RD	Respiratory distress
RDS	Respiratory distress syndrome
RR	Risk ratio
SMFM	Society of maternal fetal medicine
TTN	Transient tachypnea of new porn
VBAC	Vaginal birth after previous cesarean delivery

List of Tables

List of Figures

Prostaglandin E_1 before Elective Caesarean Section to reduce Transient Tachypnea of the Newborn (TTN)

A Randomized Control Trial

Submitted for partial fulfillment of Master Degree
In *Obstetrics and Gynaecology*

By

Hossam Hassan Ahmed Mohamed

Resident in Obstetrics and Gynecology
MB.B.Ch 2012,
Police Hospital -Nasr City,
Faculty of Medicine, Cairo University

Under Supervision Of

Dr. Noha Hamed Rabei

Professor of Obstetrics and Gynecology,
Faculty of Medicine- Ain Shams University

Dr. Noha Abd El Sattar Sakna

Lecturer in Obstetrics and Gynecology,
Faculty of Medicine, Ain Shams University

Dr. Marwa Saber Sayed

Lecturer in Obstetrics and Gynecology,
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2016

Introduction

Cesarean delivery is the most common major surgical procedure performed on women worldwide and its rates continue to rise steadily in both developed and developing countries **(Gibbons et al., 2012).** In 2007, the global cesarean delivery rate was estimated to be 15% **(Betran et al., 2007).**

Neonatal respiratory distress occur more in preterm newborn than term newborn, and whether born vaginally or through caesarean section, but in a higher percentage after elective caesarean than after normal vaginal delivery **(Zanardo et al., 2004)** or emergency caesarean section **(Hansen et al., 2007)**.

It is responsible for 30% of neonatal deaths **(Harrison, 2008)**. It has several subdivisions:

One is the respiratory distress syndrome (RDS) which is called hyaline membrane disease, it can occur in about 1% of pregnancies as a result of a pathology in lung surfactant either qualitative or quantitative **(Whitsett et al., 2005)**, and usually in preterm neonates **(Bland et al., 2008)**.

Another is transient tachypnea of the newborn (TTN) in which there is respiratory distress and increased respiratory rate due to delayed resorption of pulmonary fluid, as a result of defective catecholamine surge **(Faxelius et al., 1983)** occurs in about 11% of live births **(Whitsett et al., 2005)**.

And also includes persistent pulmonary hypertension in which the foetal pulmonary vascular resistance remains high and the pulmonary blood flow still low after delivery **(Whitsett et al., 2005)**.

In infants suffering from respiratory distress syndrome, adrenaline (epinephrine) and noradrenaline (norepinephrine) concentrations have been found to correlate with measures of illness severity. Extreme baseline catecholamine concentrations and a reduced noradrenaline response to opiate sedation are associated with subsequent mortality **(Barker and Rutter, 1996).**

Catecholamines can stimulate pulmonary fluid reabsorption through acting upon beta-adrenergic receptors in foetal lung which present more late in gestation, and thus enable the secretion of surfactant **(Whitsett et al., 2005)**.

This surge of catecholamines can be provoked through prostaglandins given before caesarean section to pregnant females **(Singh et al., 2004)** as those who are born vaginally are found to be adapted metabolically through a higher catecholamine level at birth **(Hagnevik et al., 1984)**.

So, prostaglandins may be given about one hour before an elective caesarean section after excluding the presence of contraindication to their use to decrease the neonatal respiratory diseases and thus, the number of children who suffered from bronchopulmonary dysplasia that occurs frequently in children who had previously TTN will diminish **(Whitsett et al., 2005)**.

The prostaglandins in common use are misoprostol (prostaglandin E_1) and dinoprostone (prostaglandin E_2).

Misoprostol can be effectively administered vaginally, rectally, bucally, orally and sublingually. Pharmacokinetic studies have demonstrated the properties of misoprostol after various routes of administration. The rate of absorption varies considerably between routes, and care must be taken to use the correct dose and frequency for the specified route. The dosage range is also widely variable for different obstetric indications, working as a

confounder relating to safe dosages for reproductive health indications. If unsafe dosage is used, side effects are more prone to occur because they seem to be dose-related **(Tang et al., 2007).**

In a previous similar prospective study of 36 women scheduled for an elective caesarean section beyond 38weeks **(Motaze et al., 2013),** 18 women received intravaginal prostaglanadin E_2 gel and 18 received placebo, there was one neonatal respiratory distress case in the control group which was reported as transient tachypnea of the newborn (risk ratio (RR) 0.33, 95% confidence interval (CI) 0.01 to 7.68) with similar Apgar score at one and five minutes and no need to mechanical ventilation nor side effects related to treatment in either group, so no difference in respiratory outcome reported although there was a significantly higher catecholamine level in the intervention group.

The aim in our work is to evaluate the effect of Misoprostol (Prostaglandin E_1) when given to women undergoing caesarean section on decreasing the incidence of the neonatal respiratory distress.

Aim of the work

The aim of this study is to determine the role of Prostaglandin E1 on the reduction of the neonatal respiratory morbidity specially (TTN).

Research Question

In pregnant women planned for elective caesarean section, does Misoprostol (prostaglandin E_1) can reduce the neonatal respiratory morbidity specially (TTN).

Research Hypothesis

In pregnant women planned for elective caesarean section, Misoprostol (prostaglandin E_1) may reduce the neonatal respiratory morbidity specially (TTN).

Methods, Participants, Intervention, and Outcomes

-Study Setting:

This study will be conducted in Ain Shams University Maternity Hospital (ASUMH), and Police Hospital- Nasr City starting from November 2016.

-Trial Design:

Parallel, randomized placebo controlled trial, comparing the use of Misoprostol (Prostaglandin E_1) use in the form of Misoprostol E_1 vaginal tablets with non medicated similar vaginal tablet (placebo) to decrease the neonatal respiratory distress specially (TTN) .

-Eligibility Criteria:

- **Inclusion criteria**

1) Age: 18 years or more.
2) Term pregnancy (38 - < 39 weeks).
3) Pregnant women planned for elective transverse lower segment caesarean section with an indication.
4) Written informed consent signed by the participating women.

- **Exclusion criteria**

1) Women with history of significant cardiac disease, D.M, eclampsia, pre eclampsia, epilepsy, severe asthma, severe allergic condition, vascular disease, renal or hepatic disease.
2) Women with contraindication to prostaglandins as Glucoma or known hypersensitivity to prostaglandins or specifically for Misoprostol.
3) Psychological problem or mental disease that renders the patient not able to understand the nature, scope, and sequences of the study.
4) Pregnancies with known foetal malformation/s or chromosomal aberration.

-Intervention:

i. Subjects:

The population in this study consists of a sample of pregnant women between (38 - < 39) weeks gestation scheduled for elective caesarean section, selected according to inclusion and exclusion criteria, sample size would determined according to the power of the test during sampling then reevaluated every 50 cases to be randomely distributed into two groups:

A. The first group (group E) will include 25 women, will be given Misoprostol (prostaglandin E_1).
B. The second one (group P) will consist of 25 women, will be given placebo.

Misoprostol (Prostaglandin E1) containing vaginal tablet will be in the form of Cytotec ® 200 microgram Misoprostol (manufactured by: Pfizer) administered about 60 minutes before scheduled caesarean section.

Placebo will be given in the form of non Prostaglandin E_1medicated vaginl tab. containing only the inactive ingredients (Hydrogenated castor oil, Microcrystalline cellulose, Crospovidone) which will be synthetised with the help of Laboratories of Ain Shams Faculty of Pharmacy to be administered vaginally for the purpose of research.

The participants will be approached around the 36^{th} week of gestation, to be given a handout explanation of the study details (information sheet) from the trained participating personnel and then written informed consents signed if agreed upon to be documented **(Appendix 1)**.

The treatment will be brought and stored in independent premises in a refrigerator at a temperature of 2-8 degree centigrade on Celsius scale away from the usual