Effect of Nonsteroidal Anti-Inflammatory Drugs on the Action of Misoprostol in Midtrimester Termination of Pregnancy

Thesis

Submitted for Partial Fulfillment of the Master Degree
in Obstetrics and Gynecology

By

Samar Mohammed Abdallah
M.B.B.Ch. Faculty of Medicine (2004)
Zagazig University – Resident in Bilbeis General Hospital

Under Supervision of

Prof. Dr. Waleed Hetlar Tantawy
Professor of Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Dr. Mohammed Salah El-Sokkary
Lecturer of Obstetrics & Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2011

تأثير مضادات الإلتهاب غير الإستيرويدية على عمل الميزوبروستول فى إنهاء الحمل فى الثلث الأوسط

رسالة

توطئة للحصول على درجة الماجستير
فى أمراض النساء والتوليد

مقدمة من

الطبيبة / سمر محمد عبد الله
بكالوريوس الطب والجراحة – جامعة الزقازيق (٢٠٠٤)
طبيب مقيم بمستشفى بلبيس العام

تحت إشراف

أ.د / وليد هتلر طنطاوى
أستاذ أمراض النساء والتوليد
كلية الطب – جامعة عين شمس

د / محمد صلاح السكرى
مدرس أمراض النساء والتوليد
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١١

Summary

In medical abortion using prostaglandins, analgesic treatment is important for the acceptability of the method. However, the best treatment schedule remains to be established. The pain is most pronounced following the administration of the prostaglandin (misoprostol or gemeprost). It has not yet been evaluated in a prospective study whether co-administration of a NSAID with misoprostol has an influence on the efficacy of the procedure.

Nonsteroidal anti-inflammatory drugs (NSAIDs) often were avoided in protocols studied for induction of abortion because of concern over their potential inhibition of prostaglandin-induced uterine contractions. However, a previous study had shown that the use of NSAIDs did not interfere with the action of misoprostol in inducing uterine contractions and pregnancy expulsion.

The aim of this study was to assess the effect of nonsteroidal anti-inflammatory drugs on misoprostol efficacy in induction of mid-trimesteric abortion.

Ninty healthy women seeking termination of second trimester pregnancy for medical indications were progressively enrolled in the study. All subjects gave informed consent to participation in the study.

بِسْمِ اللهِ الرَّحْمنِ الرَّحِيمِ

﴿وأنزل اللـه عليـك
الكتـــاب والحكمة وعَلَّمَكَ
مَا لَمْ تَكُن تَعْلَمُ وكَانَ فَضْلُ
اللَّهِ عَلَيْكَ عَظِيماً﴾

صدق الله العظيم

النساء .. آية رقم ١١٣

Acknowledgements

First of all, thanks to ALLAH, to whom I relate any success in achieving any work in my life.

Then I wish to express my sincere gratitude to **Prof. Waleed Hetlar Tantawy.** Professor of Obstetric and gynecology, Faculty of Medicine, Ain Shams University, who I had the privilege of doing this thesis under his supervision. My sincere thanks for dedicating so much of his precious time and efforts, and constant guidance to complete this work, words of thanks are so little for his great help in preparation and completing this work.

I would like to offer sincere thanks to **Dr. Mohamed Salah El Sokkary**. Lecturer of Obstetric and Gynecology, Faculty of Medicine, Ain Shams University, for his great help, continuous encouragement and support until the end of this thesis.

All thanks to my father, my mother and members of my family.

Samar Mohammed Abdallah

Contents

Page No.

List of Figures

Figure No.	Title	Page No.

List of Tables

List of Abbreviations

ACA	**:** Anticardiolipin antibodies
ADRs	**:** Adverse drug reactions
AEPs	**:** Abnormal early pregnancies
APS	**:** Antiphospholipid syndrome
CARS	**:** childhood autism rating scale
COX	**:** Cyclooxygenase
D & C	**:** Dilatation & curettage
DSM-IV	**:** Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ERPC	**:** Evacuation of retained products of conception
Hb	**:** Haemoglobin
IBD	**:** Inflammatory bowel disease
IUFD	**:** Intrauterine fetal death
LPD	**:** Luteal phase defect
µg	**:** Microgram
MVA	**:** Manual vacuum aspiration
NK	**:** Natural killer cells
NSAIDs	**:** Non steroidal anti inflammatory drugs
NSAIMs	**:** Non steroidal anti inflammatory medicines
OTC	**:** Over the counter
PGs	**:** Prostaglandins
RSA	**:** Recurrent spontaneous abortion
RU486	**:** Mifipristone
SD	**:** Standard Deviation
TPO	**:** Thyroid peroxidase

Introduction

Mid trimester abortion represents 10-15% of all induced abortions but is responsible for two-thirds of all major complications. Over the last 20 years there have been continuing efforts to improve abortion technology, in terms of efficacy, eases of performance, acceptability and reduction of side effects and complications ***(Lalitkumars et al., 2007).***

Abortion-related complications increase significantly as gestational age increases. Induction of abortion after 14 weeks of gestation is associated with a sharp rise in the rate of complications and in the consequent medical costs ***(Ngai et al., 2003).*** In addition, compared with women whose abortions were performed at or before 8 weeks of gestation, women whose abortions were performed in the second trimester were significantly more likely to die of abortion-related causes ***(Bartlett et al., 2004).***

Medical termination of pregnancy (medical induction of abortion) is the ending of pregnancy by a means other than surgery. Medical abortions are often performed using agents that induce abortion (Prostaglandins, RU486, Methotrexate) ***(CDC, 2004).***

Misoprostol is a prostaglandin E1 analogue originally intended for use to prevent NSAID-induced gastric ulcers. However, because of its cervical ripening and uterotonic

property, misoprostol has become one of the most useful drugs in obstetrics and gynecology. Misoprostol has proven to be a very convenient and flexible drug because of its formulation as a tablet that is stable and that can be administered orally, rectally, vaginally and by the sublingual route. Despite the large body of medical evidence about its efficacy and relative safety, serious complications and teratogenecity can occur with unsupervised use ***(Tang, et al., 2002).***

In medical abortion using prostaglandins, analgesic treatment is important for the acceptability of the method. However, the best treatment schedule remains to be established. The pain is most pronounced following the administration of the prostaglandin (misoprostol or gemeprost). It has not yet been evaluated in a prospective study whether co-administration of a NSAID with misoprostol has an influence on the efficacy of the procedure ***(Fiala and Gemzell-Danielesson, 2005).***

Nonsteroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects (reducing inflammation). The term "nonsteroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs are sometimes also referred to as nonsteroidal anti-

inflammatory agents/analgesics (NSAIAs) or nonsteroidal anti-inflammatory medicines (NSAIMs) ***(Stuart, 2010).***

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the biosynthesis of prostaglandins. It has been shown that treatment with NSAID significantly prolongs the induction-to-abortion interval in abortions not using exogenous prostaglandin such as intrauterine instillation of hypertonic saline or Rivanol®. An increase in endogenous prostaglandin production is essential for the effect on uterine contractility in this method and the induction-to-abortion time is significantly increased by NSAIDs ***(Ölund et al., 1979)***. Furthermore, dysmenorrhea is associated with an increased uterine contractility caused by an increased endogenous PGF2α production. In these women, NSAIDs are an effective treatment for pain and are believed to act via the reduction of endogenous prostaglandin. ***(Lundströmet al., 1976 and Smith, 1987)***.On the other hand, co-treatment with NSAIDs and exogenous prostaglandin does not seem to influence the effect of prostaglandin with regard to uterine contractility or cervical ripening ***(Norman et al., 1991 and Li et al., 2003).***

Nonsteroidal anti-inflammatory drugs (NSAIDs) often were avoided in protocols studied for induction of abortion because of concern over their potential inhibition of prostaglandin-induced uterine contractions. However, a previous study had shown that the use of NSAIDs did not interfere with the action of misoprostol in inducing uterine contractions and pregnancy expulsion ***(Creinin and Shulman, 1997).***

Aim of the work

The aim of this study is to assess the effect of nonsteroidal anti-inflammatory drugs on misoprostol efficacy in induction of mid-trimesteric abortion.

Abortion

Abortion is the termination of pregnancy, either spontaneously or intentionally, before the fetus develops sufficiently to survive. By convention, abortion is usually defined as pregnancy termination prior to 20 weeks gestation or less than 500g birthweight. Definitions vary, however, according to state laws for reporting abortions, fetal deaths and neonatal deaths ***(Cunningham et al., 2005).***

Current recommendation is that in early pregnancy loss the term abortion should be avoided and more sensitive terminology substituted. Spontaneous abortion should be replaced by miscarriage. Blighted ovum, missed abortion or anembryonic pregnancy should be replaced by incomplete miscarriage. Recurrent or habitual miscarriage should be replaced by recurrent miscarriage **(Slemons et al., 2004).**

Types of abortion:

A) Spontaneous abortion.

B) Induced abortion.

Spontaneous Abortion

Spontaneous abortion refers to pregnancy loss at less than 20 weeks' gestation in the absence of elective medical or surgical measures to terminate the pregnancy ***(Griebel et al., 2005).***

Etiology

A. Fetal factors:

Chromosomal abnormalities are a direct cause of spontaneous abortion. One meta-analysis found that a chromosomal abnormality occurs in 49 percent of spontaneous abortions. Autosomal trisomy was the most commonly identified anomaly (52 percent), followed by polyploidy (21 percent) and monosomy X (13 percent). Most chromosomal abnormalities that result in spontaneous abortion are random events, such as maternal and paternal gametogenesis errors, dispermy, and nondisjunction. Structural abnormalities of individual chromosomes (e.g., translocations, inversions) were reported in 6 percent of women who had spontaneous abortions, and approximately one half of these abnormalities were inherited. Chromosomal abnormalities are more likely to be associated with recurrent spontaneous abortion, but are uncommon even in that instance (4 to 6 percent) ***(Griebel et al., 2005).***

B. Maternal factors:

1. Infections:

Various infections are uncommon causes of abortion in humans ***(American Colleage of Obstetricians and Gynecologists, 2001a).***

Bacterial vaginosis**,** a polymicrobial anaerobic infection, has been implicated in the etiology of preterm labor and late miscarriage ***(Lhahicamp et al., 1996).*** However antibiotic treatment for bacterial vaginosis carriers during pregnancy only