Safety and Efficacy of Vaginal Misoprostol In Second Trimester Pregnancy Termination In women With Previous Cesarean Section

Thesis

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فى أمراض النساء و التوليد

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INTRODUCTION

The progressive increase in the incidence of cesarean birth has been a notable feature of contemporary obstetric practice and cesarean delivery is now the most frequent major surgical procedure performed in obstetrics and gynecology ***(Martin et al., 2002).***

With the expanding subpopulation of women with prior cesarean births, second trimester pregnancy termination in the scenario of a prior cesarean delivery has become an increasingly common circumstance facing obstetricians ***(Martin et al., 2002).***

There is limited information on the safety profile of any termination technique in the setting of a prior uterine surgery, and no method is risk free. The technique used for second trimester termination is probably influenced more by physician's opinion and expertise than objective outcome data (***Dickinson, 2005).***

Prenatal diagnosis is an accepted component of contemporary obstetric practice and has permitted the detection of many fetal abnormalities before birth, in this situation, medical termination of pregnancy is often performed. The usual agents employed to induce a medical termination of pregnancy in the second trimester are prostaglandin preparations. The synthetic prostaglandin misoprostol is

commonly used as an abortifacient ***(Tang et al., 2002 and Elsheikh et al., 2001).***

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).***

Misoprostol has been widely studied in different dosages and routes for the second-trimester TOP. Various studies have used doses ranging from 200 to 800 ug at intervals ranging from 3 to 12 h. Doses of 600 and 800 ug have shown comparable successful abortion rates but are associated with high rates of fever, diarrhea, nausea and vomiting. It has been seen that 3-h interval is more effective than 6-h interval ***(Lalitkumar et al., 2007).***

In the Obstetrics and Gynecology department of Baskent University Hospital 57 pregnant women consecutively underwent second trimester pregnancy termination with oral misoprostol. The regimen used in all women was 200 ug of misoprostol orally every hour for a maximum of 6 tablets (1200

ug) per day. There were no significant differences regarding total amount of misoprostol used for induction, induction-to-delivery interval, duration of hospital stay, and hemoglobin levels before induction and after delivery. There were no differences in the incidence of nausea or fever and none of the women experienced diarrhea. All reported some degree of abdominal pain. There was no adverse outcome such as uterine rupture ***(Chong et al., 2002).***

In the department of Obstetrics and Gynecology of King Abdulaziz University Hospital, 59 consecutive pregnant women underwent second-trimester pregnancy termination with vaginal misoprostol. Six women had had one low transverse cesarean section and five women had had two cesarean sections. The regimen used was 200 ug of misoprostol (Cytotec; Searle Pharmaceuticals, United Kingdom) vaginally every 6 h for a maximum of 3 doses. The mean gestational age was 19.8 weeks. All women aborted or were delivered within 24 h after insertion of the first tablet of misoprostol. The average duration between the start of therapy and fetal expulsion was 13.1 h. One woman needed removal of placental tissues in the operating room. The mean estimated blood loss was 300 ml. No uterine rupture or other complications occurred and the women were discharged in good general condition 2-3 days after admission to the hospital ***(Rouzi et al., 2003).***

A study was conducted at the department of Obstetrics and Gynecology, Chiang Mai University consisted 247 pregnancies including 53 cases of fetal death and 194 of live fetuses, were

indicated for second trimester termination using misoprostol and 21 singleton pregnancies had a history of previous low transverse cesarean section. All of five cases with dead fetus in utero were successfully terminated with the regimen of 400 ug orally every 4 h. However, the dosage for live fetuses was varied from case to case but mostly 400 ug was given transvaginally every 3-12 h. The time interval from misoprostol use to fetal delivery was 16.66 h., uterine rupture was not found at all. Failure of termination was considered if labor had not established within 48 h of administration ***(Pongsatha et al., 2003).***

Ongoing data collection and audits from institutions using misoprostol as a primary abortifecient in second-trimester pregnancy termination are still required to accumulate sufficient patient numbers to accurately ascertain the drug's safety profile in women with prior uterine surgery ***(Dickinson, 2005).***

AIM OF THE WORK

To determine the safety and efficacy of vaginal misoprostol in termination of second trimester pregnancy in women with previous single lower segment cesarean section.

MISOPROSTOL

Prostaglandins

Introduction:

Prostaglandins are hormone-like chemicals occurring naturally in all mammals. They are fatty-acid derivatives found in almost all tissues in the human body. More than a dozen biologically important forms of prostaglandins occur, affecting many essential physiological functions. Although they were first identified in 1935 by the Swedish physiologist Ulf von Euler, research into their actual composition, structure, functions, and medical uses began in the late 1960s. The first uses of prostaglandins were in obstetrics. By constricting blood vessels in the uterus, some prostaglandins stimulate contractions, making them useful in delivery or therapeutic abortion ***(Prostaglandins,"Microsoft® Encarta® Online Encyclopedia 2008 http://encarta.msn.com).***

Mechanism of action of prostaglandins:

Many of the actions of Prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G proteins, which subsequently activate or inhibit adenylcyclase or stimulate phospholipase C3. This causes an enhanced formation of diacylglycerol and inositol 1, 2, 5- triphosphate (IP3). Prostaglandin F2α, the leukotrienes, and thromboxane A2 mediate certain actions by

activating phosphatidtylinositol metabolism and causing an increase of intracellular Ca ***(Howland et al., 2006).***

Metabolism:

The metabolism of prostaglandins occurs primarily in the lungs, kidneys and liver. The lungs are important in the metabolism of E and F prostaglandins. Any active prostaglandins in the circulation are metabolized during passage through the lungs. Therefore members of prostaglandin family have short half-life and is most of instances, exert autocrine/paracrine actions at the site of their synthesis ***(Smith, 1992).***

Prostaglandin E1 Analogue "Misoprostol"

Development:

Misoprostol is a synthetic potent orally active analogue of prostaglandin E1 that has a strong inhibitory effect on gastric acid secretion; it was developed by Searle pharmaceuticals for that purpose in early seventies. It was released into international markets in 1986 and now sold in 60 countries in the world. It is safe and well tolerated anti-ulcer agent within the recommended dose of 800 microgram/day. In the more than 7000 patients worldwide who have received it, no clinically significant adverse hematological, endocrinal, biochemical immunological or respiratory outcomes have been reported. Pre-clinical toxicological studies also indicate the

safety margin of misoprostol to be at least 500-1000 folds to lethal doses in animals and therapeutic doses in humans ***(Toppozada et al., 1997 and Collins et al., 1985).***

The combination of misoprostol with mifeprestone has high success rates for termination of second trimester pregnancies. However, because of ethical difficulties of marketing, mifeprestone is not available in most countries. For this reason, misoprostol alone remains one of the common methods for pregnancy termination ***(El-Refeay et al., 1995).***

Misoprostol, as a single agent, has reliable success rates in second trimester pregnancy termination. However, it has been reported that the use of misoprostol for second trimester termination of pregnancy is associated with uterine rupture, especially when combined with oxytocin infusion ***(Jain et al., 1999 and Costa et al., 1993).***

Pharmacology:

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a synthetic prostaglandin E1 analogue. It was developed for the prevention and treatment of peptic ulcer because of its gastric acid anti-secretory properties and its various mucosal protective properties. It has become an important drug in obstetric and gynecological practice because of its uterotonic and cervical priming action. In comparison to other prostaglandin analogues, misoprostol has the advantages of being cheap, widely available, stable at room temperature and

having few side effects. Its clinical applications include medical abortion, medical evacuation for miscarriage, cervical priming before surgical procedure, induction of labor and management of postpartum hemorrhage ***(Watkinson et al., 1988).***

Structure and chemistry:

The naturally occurring prostaglandin E series was discovered to inhibit gastric acid secretion in 1967 by Robert et al. However, naturally occurring prostaglandins have three drawbacks that hindered their clinical application. These problems were: (1) rapid metabolism resulting in a lack of oral activity and a short duration of action when given parenterally, (2) numerous side effects, and (3) chemical instability leading to a short half life. Misoprostol differs structurally from prostaglandin E by the presence of a methyl ester at C-1, a methyl group at C-16 and a hydroxyl group at C-16 rather than at C-15. The methyl ester at C-1 increases the anti-secretory potency and duration of action of misoprostol, whilst the movement of the hydroxyl group from C-15 to C-16 and the addition of a methyl group at C-16 improves oral activity, increases the duration of action, and improves the safety profile of the drug ***(Robert et al., 1967).***

Misoprostol contains approximately equal amounts of the two diastereomers presented below with their enantiomers indicated by (±):