CEOG Clinical and Experimental Obstetrics & Gynecology

Intra-cervical misoprostol for the treatment of second-trimester fetal demise

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Summary

Purpose: Misoprostol has gained wide use in the treatment of reproductive disease. Previous applications have been administered through oral or vaginal routes. The efficacy of intra-cervical administration is not well studied. The authors report the outcome of intra-cervical administration of misoprostol in three women treated for termination of second-trimester fetal demise. *Materials and Methods:* Three women with second-trimester fetal demise were treated using 50 μg of misoprostol administered in the cervical os. *Results:* Complete abortion was observed by 17 hours, ten hours and 15 minutes, and seven hours and 35 minutes, respectively. Two women received oral non-steroidal anti-inflammatory drugs for mild abdominal pain and one woman received intramuscular opiates for moderate to severe abdominal pain. There were no adverse side effects or complications of treatment. *Conclusions:* Intra-cervical misoprostol was useful in the termination of second-trimester fetal demise. The dose required was much less than that used for oral or vaginal administration. Further studies are needed to confirm the present findings.

Key words: Second-trimester; Abortion; Misoprostol.

Introduction

Misoprostol is a synthetic prostaglandin E_1 analogue that was originally approved for use in humans by the U.S. Food and Drug Administration (FDA) for the treatment of NSAID-induced gastric ulcers [1]. It is also included in the FDA-approved labelling of mifepristone for use in abortion [2]. Its greatest use, however, has been in obstetrics and gynecology for a variety of indications, including other regimens for abortion and early pregnancy loss, management of second-trimester fetal demise, labor induction, prevention and treatment of postpartum hemorrhage, and cervical priming before hysteroscopy [3]. Low cost, ease of administration, and efficacy have made misoprostol a drug of choice for termination in the setting of second-trimester fetal demise [4]. Most studies of misoprostol for terminating pregnancy in fetal demise investigated oral and vaginal administration routes [5], with a recent study comparing two doses of buccal misoprostol [6]. Across all studies, doses ranged from 25 to 600 μg given every three to 12 hours. There is very limited information on the intra-cervical administration of misoprostol. A small randomized trial compared an intra-cervical application of a misoprostol 200 μg tablet with extra-amniotic prostaglandin $F_{2\alpha}$ in 40 women with confirmed major fetal abnormalities or fetal demise, between 16 and 24 weeks' gestational age [7]. The intra-cervical administration of a misoprostol tablet was effective and well-tolerated with fewer side effects and no complications. A series of 20 women in the present hospital with early pregnancy failure were treated with one or two doses of intra-cervical 50 μg misoprostol in solution, with the second dose given 12 hours after the first dose if there was no vaginal bleeding or pain [8]. Complete abortion occurred within 24 hours in 14 (70%) women, after a mean of 10.6 hours. Treatment was well-tolerated, with pain managed with NSAIDS in 19 women and intramuscular opiates in one woman. These findings suggest that a lower dose of misoprostol could be effective in the termination of pregnancy. The objective of this pilot study is to evaluate the efficacy of low dose intra-cervical misoprostol in women with second trimester fetal demise.

Materials and Methods

This study was approved by the institutional review board (IRB) committee of King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The study was performed in accordance with relevant guidelines and regulations. Inclusion criteria were a diagnosis of second-trimester fetal demise requiring medical termination, patient age 20 to 45 years, hemoglobin greater than 10 g/dl, 13 to 28 weeks of gestation, as documented by menstrual dates with confirmatory ultrasonography or ultrasound dating if the menstrual dates were uncertain, no vaginal bleeding, no passage of tissues, and a closed cervix on physical examination. Exclusion criteria were hypersensitivity to misoprostol, chronic medical disease, previous uterine surgery, or the presence of congenital uterine anomalies. Eligible women received extensive counseling by the research team regarding the experimental nature of the study, expected side effects, and availability of other options. Written informed consent was obtained from each patient before treat-

Revised manuscript accepted for publication September 5, 2016

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLV, n. 3, 2018
doi: 10.12891/ceog3896.2018

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ment. A detailed history and physical examination were performed on patient admission to the hospital. Participants were treated using intra-cervical misoprostol. A single dose consisted of 50 μg dissolved in 5 ml normal saline. The dose was prepared by dissolving one 200 μg tablet in 20 ml of normal saline, producing a 10 μg/ml solution. The single dose of misoprostol was repeated after 12 hours if no vaginal bleeding or pain were observed. Speculum examination was performed to visualize the cervix prior to intra-cervical administration. Misoprostol was administered into the cervical os using an endometrial sampling cannula, as previously described [8]. Each patient was instructed to lay in bed for an hour after treatment in order to prevent back flow of medication into the vagina. The time to abortion was defined as the interval from medication administration to placental delivery.

Results

Three women were treated from August 23, 2015 to January 30, 2016 (Table 1). Patient age ranged from 23 to 28 years. Complete abortion was achieved in all women after one intra-cervical treatment. Abortion was complete by 7.6 to 17 hours in these women. Two women were administered NSAIDs for mild abdominal pain and one woman intramuscular pethidine for moderate to severe abdominal pain. There were no other side effects of treatment. No complications of treatment were observed.

Discussion

The use of misoprostol for the termination of pregnancy has undergone a rapid evolution. In cases of second-trimester fetal demise, misoprostol has enabled the evacuation of the uterus without the use of other methods that carry a high risk of morbidity and even mortality. Several interventional and observational studies have reported outcomes when misoprostol is used as a single agent to interrupt pregnancy in women with second-trimester fetal demise. In a systematic review reported in 2009, that included 14 qualifying randomized trials of misoprostol used for uterine evacuation in fetal demise during the second and third trimester, uterine evacuation was 100% successful at 48 hours [9]. In a recent review, a vaginal dose of 100 or 200 μg every four hours was associated with 24-hour expulsion rates of 84% to 100%, and higher doses (400 mg) did not provide improved outcomes. Mean and median expulsion times ranged from ten to 14 hours [5]. The International Federation of Gynecology and Obstetrics (FIGO) recommends 200 μg and 100 μg vaginally for intrauterine fetal demise at 13-17 weeks and 18-28 weeks, respectively [10]. The side effects of misoprostol, including nausea, vomiting, shivering, and hyperthermia depend on the dose and route of administration. While the efficacy of oral and vaginal administration of misoprostol for interrupting pregnancy in women with second-trimester fetal demise is well established, there is little data regarding the intra-cervical administration of misoprostol in this disease. However, there are very few reports on the efficacy of intra-cervical misoprostol for second-trimester fetal demise. In a randomized clinical trial, the intra-cervical administration of a misoprostol 200 μg tablet, every eight hours for a maximum of four doses, resulted in complete abortion in 17 (85%) women [7]. All women in the misoprostol group aborted within 20 hours, with 90% (18/20) of the women aborting within 13 hours. The intra-cervical approach offers the advantage of local administration, which may allow reducing the dose and frequency and minimizing side effects. The present authors evaluated the efficacy of low-dose intra-cervical misoprostol for pregnancy termination after second-trimester fetal demise in three women. Low dose intra-cervical misoprostol was found to be effective in inducing abortion an average of 10.6 hours after dosing. This study was a continuation of the authors' previous study of low-dose intra-cervical misoprostol where women received two doses 12 hours apart for the treatment of early pregnancy failure [8]. The results of this preliminary study are encouraging and a larger study is needed to confirm the present findings.

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Table 1. — *Efficacy of low dose of intra-cervical misoprostol for pregnancy termination in women with second trimester fetal demise.*

Case	Age (years)	Gravidity	Parity	BMI	Gestational age (weeks)	Outcome	Time to complete abortion	Complications
Case 1	23	4	3	17.8	21	Complete abortion after one dose	17 hours	None
Case 2	28	2	1	31.2	27	Complete abortion after one dose	10 hours and 15 minutes	None
Case 3	23	2	1	23.3	18	Complete abortion after one dose	7 hours and 35 minutes	None

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