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Efficacy of intra-cervical misoprostol in the management of early pregnancy failure

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The aim of this prospective study was to assess the efficacy of intra-cervical misoprostol in the management of early pregnancy failure. Twenty women with early pregnancy failure received intra-cervical misoprostol via an endometrial sampling cannula. The first dose was 50 μg of misoprostol dissolved in 5 ml of normal saline. The administration was repeated after 12 h if there was no vaginal bleeding or pain. Nine (45%) women received 1 dose and 11 (55%) women received 2 doses of intra-cervical misoprostol. Abortion within 24 h occurred in 16 (80%) women, and complete abortion was achieved in 14 (70%) cases. Two women with incomplete abortion were managed with 600 μg of misoprostol orally (1 case) and surgical intervention (1 case). The mean time interval between the first dose and the abortion was 10.6 ± 6.3 h. Two women did not respond within 24 h of treatment initiation, 1 woman withdrew consent after the first treatment, and 1 woman developed heavy vaginal bleeding after the first dose and underwent surgical management. Intra-cervical misoprostol is a promising method of medical treatment of early pregnancy failure. Further randomized clinical trials are needed to validate its safety and efficacy.

Early pregnancy failure is one of the most common complications of pregnancy. It occurs in up to 50% of conceptions, 15% of clinically recognized pregnancies, 2–6% of pregnancies where fetal heart is detected, and it will affect 1 in 4 women during their lifetime[1,2]. Historically, dilatation and curettage was the commonly accepted treatment option for abortion. Medical abortion with mifepristone, also known as RU-486, followed by misoprostol has become increasingly available, and it is currently the standard method[3]. When mifepristone is not available, misoprostol-only is the preferred choice for medical abortion[4]. However, for early pregnancy failure, pretreatment with mifepristone adds no advantages when compared to misoprostol only-regimen[2,5]. This may be due to a difference in response of nonviable and viable pregnancies to antiprogesterone[6]. Misoprostol is a stable, synthetic analog of prostaglandin El[7] which was first introduced to prevent gastric ulcer in patients treated with non-steroidal anti-inflammatory drugs[8]. The effects of misoprostol on cervical ripening have been extensively studied[9]. Pharmacokinetic studies have shown that misoprostol is readily absorbed after sub-lingual, buccal, vaginal or rectal administration. Data are lacking on the pharmacokinetics of intra-cervical misoprostol. It has been reported that misoprostol is more effective and has fewer side effects if it is used vaginally rather than orally[10]. There is a growing body of evidence supporting the use of oral misoprostol in solution for labor induction[11]. However, there is very limited information on intra-cervical administration of misoprostol. This study was designed to determine the efficacy of intra-cervical administration of misoprostol in the management of early pregnancy failure.

Results

A total of 20 women with early pregnancy failure were included in the study. They were 34.6 ± 7.3 (mean ± SD) years old and para 2.9 ± 2.6. The body mass index (BMI) was 28.3 ± 6.1. The gestational age was 7.8 ± 1.3 weeks as determined by ultrasonography. Nine (45%) women received one dose and 11 (55%) women received 2 doses of intracervical misoprostol. Abortion within 24 h of treatment initiation occurred in 16 (80%) women. Complete abortion within 24 h occurred in 14 (70%) women. Two women with incomplete abortion were managed with 600 μg of misoprostol orally (1 woman) and surgical intervention (1 woman). The mean time interval between the first dose and the abortion was 10.6 ± 6.3 h. Two women did not respond within 24 hours of treatment initiation, 1 withdrew consent after the first treatment, and 1 developed heavy vaginal bleeding 3 hours after the

first dose and underwent surgical management. Adverse events included 1 case of shivering, which resolved spontaneously, and 1 case of mild pyrexia. Pain was managed in 19 women by oral non-steroidal anti-inflammatory drugs, and one received intramuscular opiates.

Discussion

Misoprostol is readily available, stable at room temperature, inexpensive, and has an acceptable safety profile. It has been administered orally, sublingually, buccally, vaginally, or rectally in several treatment regimens for medical abortion with varying degree of success. The main disadvantage of the oral, buccal, and sublingual routes is frequent gastrointestinal side effects including nausea, vomiting, shivering and hyperthermia[12]. Mifepristone and misoprostol is the most commonly used medical abortion regimen in the first trimester of pregnancy in the United States and Western Europe. Since pretreatment with mifepristone does not increase the success rate of early pregnancy failure[2,5], current clinical guidelines recommend the use of misoprostol only[9,13]. However, there are inconsistencies in the recommended regimens. The International Federation of Gynecology and Obstetrics (FIGO) recommends vaginal administration of 800 μg of misoprostol every 3 h for a maximum of 2 doses or sublingual administration of 600 μg every 3 h for a maximum of 2 doses[9]. In contrast, the National Institute for Health and Care Excellence (NICE) recommends a single 800 μg dose given vaginally but allows, oral administration based on the woman's preference[13]. Finally, the World Health Organization recommends vaginal or sublingual administration of 800 μg every 3 h for a maximum of 3 doses[4]. Several regimen modifications have been proposed over the past 2 decades, including reducing the dose, exploring different administration routes, and home use of misoprostol.

Induction of labor at term has been successfully achieved by placing one-fourth of a misoprostol tablet in the cervix under speculum vaginal examination[14–16]. However, there is a paucity of data on efficacy of intracervical misoprostol for medical management of incomplete pregnancy loss or early pregnancy termination. A randomized-controlled trial (RCT) compared the efficacy of intracervical misoprostol with extra-amniotic PG-F2α for terminating second-trimester pregnancies with congenital anomalies or intrauterine fetal death[17]. All women in the misoprostol group aborted within 20 h. The ability of intra-cervical misoprostol to induce cervical ripening prior to surgical evacuation was investigated in a RCT of intra-cervical treatment with 400 μg of misoprostol in a gel formulation given every 3 h up to a maximum of 4 doses[18]. Although 40% of the 30 subjects received the maximum dose, the primary endpoint of cervical ripening $>$8 mm 12 h after the treatment was achieved in only 70% of cases. In contrast, the corresponding value reached 97% in women who were treated intra-cervically with isosorbide dinitrate. The results of our small study demonstrate the efficacy of the intracervical administration of misoprostol with the 24-h abortion rate of 80% and with the mean time from the first dose to abortion of 10.6 $\pm$ 6.3 h. This is in contrast with the 50–93% success rates of different regimens 1 to 10 days after the administration[19]. Furthermore, the intra-cervical approach offers the advantage of local administration, which may allow reducing the dose and frequency and minimizing side effects. On the basis of these results, we are conducting a randomized clinical trial to assess the efficacy and safety of this regimen compared with those of the conventional vaginal route.

Methods

This prospective study was conducted at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia after obtaining approval from the institutional review board (IRB). The study was performed in accordance with relevant guidelines and regulations. Upon admission to the hospital, a detailed history was obtained, general and gynecological examinations were performed, and pelvic ultrasonography was done to confirm the diagnosis and estimate the gestational age. The inclusion criteria were: early pregnancy failure (anembryonic gestation, and embryonic or fetal demise) of a singleton intrauterine pregnancy of $\leq$12 weeks as documented by ultrasound with no vaginal bleeding, passage of tissues, or cervical dilation. Patients with chronic medical diseases, previous uterine surgery, allergy to misoprostol, or uterine anomalies were excluded. Eligible women received extensive counseling by the research team regarding the experimental nature of the study, expected side effects, availability of other options, and need for a surgical procedure if the intracervical misoprostol in solution regimen failed. Written informed consent was obtained. The first dose was 50 μg (one-fourth of a 200 μg tablet) of misoprostol (Cytotec; Searle Pharmaceuticals, Leicester, UK) dissolved in 5 ml of normal saline. This was repeated after 12 h if there was no vaginal bleeding or pain. Speculum examination was performed to visualize the cervix. Administration was performed with an endometrial sampling cannula (MedGyn Endosampler TM, UK) introduced under direct vision into the cervical canal until resistance was encountered, at which time the misoprostol solution was injected. After the injection of the dissolved misoprostol into the cervix, the woman was instructed to lie on bed for almost an hour to prevent the flow back via the vaginal canal. No leakage of the fluid occurred. The primary outcome was abortion within 24 h after treatment initiation. Secondary outcomes included proportion of complete abortions comprising complete uterine evacuation without surgical intervention, time interval between first treatment and abortion, and frequency of side effects.

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Author contributions

A.R. Design of the study, clinical selection, analysis of the data, and writing of the manuscript. N.A. Clinical selection, diagnosis of patients, and performance of the study. N.S. Clinical selection, diagnosis of patients, performance of the study, and analysis of the data. N.A. Clinical selection, diagnosis of patients, and performance of the study. H.A. Clinical selection, diagnosis of patients, and performance of the study. K.D: Clinical selection, diagnosis of patients, and performance of the study. N.B. Diagnosis of patients, and reading of the manuscript. All authors reviewed the manuscript.

Additional information

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