Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Pretreatment with Misoprostol Reduces Intrauterine Adhesions After Surgical Termination of Missed Abortion

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OBJECTIVE: The present study aims to utilize hysteroscopy in order to determine whether pretreatment with misoprostol reduces intrauterine adhesions after a missed abortion is terminated surgically.

STUDY DESIGN: This study reviews 100 women who were diagnosed with missed abortion between 6 and 10 weeks of gestation and who were to be treated with curettage.

RESULTS: The visual analogue scale score was significantly lower and the convenience of curettage was significantly better for women who were treated with misoprostol before curettage (respectively, p=0.035 and p=0.001). Acquired intrauterine adhesions were significantly less and the convenience of hysteroscopy was significantly better for women who received pretreatment with misoprostol (respectively, p=0.046 and p=0.001).

CONCLUSION: Misoprostol reduces intrauterine adhesions after surgical termination of missed abortion, possibly by improving the convenience of curettage. Pretreatment with misoprostol can be justified for women who have history of infertility or recurrent pregnancy loss and who are to undergo curettage.

Key Words: Curettage, Hysteroscopy, Misoprostol, Missed abortion

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Introduction

An abortion can be defined as the natural end of a pregnancy at a stage where the embryo or fetus is incapable of surviving independently, generally defined in humans at prior to 20 weeks of gestation. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred. It is also referred to as delayed or missed miscarriage.[1]

Traditionally, the standard management of early pregnancy failure has been dilatation and curettage. Curettage bears a small risk of pelvic infection, cervical injury, uterine perforation, incomplete evacuation, excessive bleeding and the risk associated with anesthesia. Another risk is intrauterine adhesions, or Asherman's syndrome. Approximately 14-16% of women who had one or two sharp curettage procedures for miscarriage develop some adhesions while women who underwent three sharp curettage procedures for miscarriage have a 32% risk of developing adhesions. The risk of Asherman's syndrome was found to be 30.9% in women who had curettage following a missed abortion, and 25% in those who had curettage 1-4 weeks postpartum. According to recent case reports, use of vacuum aspiration can also lead to intrauterine adhesions.[2,3]

Hysteroscopy is the inspection of the uterine cavity by endoscopy with access through the cervix. It allows for the diagnosis of intrauterine pathology and serves as a method for surgical intervention, thus, being named as operative hysteroscopy.[4,5]

Treatment with misoprostol, as an alternative to curettage, causes expulsion in 50-99% of women with early pregnancy failure up to the 14th week of gestation. However, most data on the effectiveness and safety of misoprostol are based on the absence of incomplete evacuation, cervical injury, excessive bleeding, uterine perforation, pelvic infection and adverse effects related with prostaglandins.[6] The present study aims to utilize hysteroscopy in order to determine whether pretreatment with misoprostol reduces intrauterine adhesions after a missed abortion is terminated surgically.

Material and Method

The present study was approved by the Institutional Review Board and Ethical Committee of Dr. Sadi Konuk

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Research and Education Hospital where the study was conducted between March 2008 and December 2009. All women were asked to participate in the study by their treating gynecologist at the time missed abortion was diagnosed, and written informed consent was obtained before study entry.

A total of 100 women aged 19-40 years with a diagnosis of missed abortion between 6 and 10 weeks of gestation who were to be treated with curettage were eligible for the trial. A diagnosis of missed abortion was made by transvaginal ultrasonography, and defined as an intrauterine gestational sac (sac diameter >15 mm or <15 mm not showing any growth after a 7 day interval) with or without an embryonic pole and absence of cardiac activity. Women with incomplete abortion were not eligible for the study. Exclusion criteria were hemodynamic instability, a history of cesarean section, known uterine anomalies, multiple pregnancies, infection, suspicion of extra-uterine pregnancy, coagulopathies, allergy to misoprostol, severe pulmonary disease, congenital or acquired heart disease, liver diseases, glaucoma, sickle cell disease, prolonged use of corticosteroids or adrenal gland insufficiency.

At the time women requested intervention, randomization was performed by their treating gynecologist using a computer program with a block randomization sequence, thus guaranteeing the concealment of allocation. Randomization was stratified for previous vaginal birth and duration of amenorrhea. Therefore, the recruited women were randomized into two groups. Group 1 consisted of 50 women who received misoprostol before undergoing curettage while group 2 included 50 women who were directly managed with curettage.

Pretreatment with misoprostol was performed in an in-patient setting, and consisted of 400 mg doses of misoprostol (two ts each time) placed in the posterior fornix four hours apart. The participants were allowed to use non-steroid anti-inflammatory drugs (NSAIDs). Curettage consisted of evacuation of the uterus by suction curettage under general anesthesia in a day care setting. The patients in group 1 underwent curettage two hours after the second dose of 400 mg of misoprostol was admisnistered. All of the tissues obtained by curettage were examined histopathologically. The convenience of curettages was defined as “very easy”, “easy”, “difficult” and “very difficult” by the same gynecologist who performed them.

Women were asked to complete a questionnaire one week after the intervention, including duration and intensity of bleeding, intensity of pain, need for analgesics and side effects of treatment. Intensity of pain and severity of bleeding were measured using a visual analogue scale (VAS); the VAS score zero indicates no pain or no bleeding and 10 indicates severe pain or severe bleeding. Complications were defined as infection, need for transfusion and surgery-related complications such as perforation and cervical tear. Misoprostol related adverse effects were identified for each woman who treated with this prostaglandin analogue.

All of participants were evaluated by hysteroscopy within five days after the first menstrual bleeding ceased following the surgical termination of missed abortion. The facility of hysteroscopic evaluations was labeled as “very easy”, “easy”, “difficult” and “very difficult” by the same gynecologist who performed them.

Statistical Analysis

Collected data were analyzed by Number Cruncher Statistical System 2007 & Power Analysis and Sample Size 2008 Statistical Software (Utah, USA). Continuous variables were expressed as mean±standard deviation (range: minimum-maximum). Continuous variables of two groups were compared by student t test if they had normal distribution whereas continuous variables of two groups were compared by Mann Whitney U test if they had abnormal distribution. Continuous variables of the same group changing within a period of time were compared by paired samples t test. Chi-square test and Fisher’s exact test were utilized to compare the categorical variables. $P<0.05$ was accepted to be statistically significant.

Results

A total of 100 women aged 19–40 years with a diagnosis of missed abortion between 6 and 10 weeks of gestation who were to be treated with curettage were eligible. The recruited women were randomized into two groups. Group 1 consisted of 50 women who received misoprostol before undergoing curettage while group 2 included 50 women who were directly managed with curettage. The average dose of misoprostol administered was 1.2±1.3 (range: 0-4) while the average duration of misoprostol pretreatment was 4.2±4.5 hours (range: 1-14).

Group 1 and group 2 are statistically similar in aspect of age, gravidity, parity, previous miscarriages, previous curettages and duration of amenorrhea (Table 1).

Table 2 compares the clinical features of both group 1 and group 2. Accordingly, VAS score was significantly lower and the convenience of curettage was significantly better for women who received misoprostol before curettage (respectively, $p=0.035$ and $p=0.001$). However, pretreatment and postreatment hemoglobin concentrations as well as adverse effects were statistically similar in both groups. No adverse effects such as diarrhea, fever or sepsis were observed in any of the participants.

Table 3 demonstrates the findings related with hysteroscopic evaluation of both study groups. Acquired intrauterine adhesions were significantly less and the convenience of hys-

teroscopy was significantly better for women who were treated with misoprostol before curettage was done for missed abortion (respectively, p=0.046 and p=0.001). Both study groups were statistically similar in aspect of congenital anomalies and other acquired pathologies including polyps, myomas and placental retention.

Women with hysteroscopic findings were significantly older when compared with women who had normal hysteroscopic evaluation (p=0.028). Moreover, these women had significantly higher gravidity, higher number of previous miscarriages and longer duration of amenorrhea (respectively, p=0.001, p=0.001 and p=0.001) (Table 4).

Table 1: Demographic Characteristics of the Participants

	Group 1 n=50	**Group 2 n=50**	**p**
Age (years)	28.1 ± 4.7	28.1 ± 4.8	0.983
Gravidity	2.1 ± 1.2	2.3 ± 1.1	0.551
Parity	0.6 ± 0.8	0.7 ± 0.9	0.728
Previous miscarriages	1.5 ± 0.7	1.5 ± 0.7	0.728
Previous curettages	1.5 ± 0.7	1.5 ± 0.7	0.862
Duration of amenorrhea (weeks)	7.9 ± 1.2	7.9 ± 1.1	0.795

Table 2: Clinical Features of the Participants

	Group 1 n=50	**Group 2 n=50**	**p**
Pretreatment hemoglobin (g/dl)	12.2 ± 1.3	12.5 ± 1.1	0.223
Posttreatment hemoglobin (g/dl)	11.9 ± 1.3	12.3 ± 1.1	0.083
Visual analogue scale	4.8 ± 0.9	5.2 ± 0.9	0.035*
Adverse effects			
Nausea	14 (28.0%)	8 (16.0%)	0.148
Vomiting	5 (10.0%)	2 (4.0%)	0.436
Convenience of curettage			
Very easy	37 (74.0%)	8 (16.0%)	0.001*
Easy	9 (18.0%)	26 (52.0%)	
Difficult	3 (6.0%)	11 (22.0%)	
Very difficult	1 (2.0%)	5 (10.0%)	

**p<0.05 was accepted to be statistically significant.*

Table 3: Hysteroscopic Evaluation of the Participants

	Group 1 n=50	**Group 2 n=50**	**p**
Congenital Anomalies			
Uterine subseptum	4 (8.0%)	4 (8.0%)	1.000
Uterine septum	5 (10.0%)	6 (12.0%)	0.749
Arcuate uterus	3 (6.0%)	1 (2.0%)	0.617
Vaginal septum	1 (2.0%)	0 (0.0%)	1.000
Acquired Pathologies			
Acquired adhesions	2 (4.0%)	8 (16.0%)	0.046*
Endometrial polyps	5 (10.0%)	6 (12.0%)	0.749
Submucous myomas	2 (4.0%)	1 (2.0%)	1.000
Placental retention	1 (2.0%)	4 (8.0%)	0.362
Convenience of curettage			
Very easy	24 (54.5%)	21 (37.5%)	0.001*
Easy	15 (34.1%)	20 (35.7%)	
Difficult	5 (11.4%)	9 (16.15)	
Very difficult	0 (0.0%)	6 (10.7%)	

**p<0.05 was accepted to be statistically significant.*

Table 4: Demographic and Clinical Characteristics according to Hysteroscopic Findings

	Hysteroscopic finding (+) n= 53	Hysteroscopic finding (-) n= 47	p
Age (years)	29.3±3.6	27.2±5.3	0.028*
Gravidity	2.6±0.9	1.9±1.2	0.001**
Parity	0.7±0.7	0.6±0.8	0.193
Previous miscarriages	1.9±0.8	1.2±0.5	0.001**
Duration of amenorrhea (weeks)	8.4±1.0	7.5±1.1	0.001**
Nausea	6 (%13,6)	16 (%28,6)	0,074
Vomiting	1 (%2,3)	6 (%10,7)	0,131

**p<0.05 was accepted to be statistically significant.*

Discussion

Vacuum aspiration is commonly adopted for the surgical termination of missed abortions. However, various complications may occur in case cervical dilatation is limited. These complications account for cervical and uterine rupture (0-4%), cervical laceration (0-3%) and cervical insufficiency within a longer period of time. Therefore, a certain amount of cervical dilatation should be provided before vacuum aspiration is performed.[7]

Misoprostol is an analogue of prostaglandin E1 which is frequently utilized for cervical priming. Misoprostol is a relatively cheaper agent and requires no cold chain. Also it may be administered via oral, buccal, sublingual, vaginal and anal routes.[6,8] In 1997, Royal College of Obstetricians and Gynecologists has recommended the vaginal administration of 800 mcg misoprostol three to four hours before surgical termination of missed abortion in order to achieve cervical priming.[9,10]

The present study has been designed as a randomized controlled study which aims to utilize hysteroscopy in order to determine whether pretreatment with misoprostol reduces intrauterine adhesions after a missed abortion is terminated surgically. This study reviews 100 women aged 19-40 years with a diagnosis of missed abortion between 6 and 10 weeks of gestation who were to be treated with curettage. Thus, one limitation of the present study is the relatively smaller study cohort. Yet, all of the curettages were performed by the same gynecologist who also assessed their convenience. Similarly, all of the hysteroscopies were done by the same gynecologist who also assessed their convenience. Therefore, it can be expected that bias related with these assessments is minimized.

Previously published studies have demonstrated that pretreatment with misoprostol provides cervical dilatation and, thus, reduces the related blood loss and increases the convenience of surgical termination for early pregnancy failure.[9-13] Although the present study indicates significantly better convenience of curettage for women who were treated with misoprostol, no statistically significant alteration was noted in serum hemoglobin concentrations of these women. This discrepancy may be caused by the relatively smaller study cohort.

It has been reported that pain related with misoprostol pretreatment increased as higher doses of misoprostol were administered. Another confounding factor was gestational age. That is, the pain caused by misoprostol pretreatment or curettage became more severe as duration of amenorrhea increased.[7,14] As for the present study, the women who received pretreatment with misoprostol had significantly lower VAS scores. This finding may be attributed to the significantly better convenience of curettage because pain related with curettage is caused by the stimulation of sympathetic nerves. Since pretreatment with misoprostol allows wider cervical dilatation within a longer period of time, the associated pain may be less severe and more tolerable. The pain related with misoprostol administration can be managed with NSAIDs or narcotic analgesics. Although NSAIDs reduce the synthesis of prostaglandins through the inhibition of cyclooxygenase pathway, the utilization of these drugs does not affect the success of pretreatment with misoprostol.[9-14] The participants of the present study were allowed to use NSAIDs and there was no failure in any of the curettages.

Administration of misoprostol may cause side effects such as nausea, vomiting, diarrhea, fever, tremor and sepsis.[6,15] Previously conducted studies have reported that vaginal route is associated with fewer and less serious side effects than oral or sublingual route for misoprostol treatment.[8] As for the present study, the frequencies of nausea and vomiting were statistically similar in both misoprostol and curettage groups (respectively, 28.0% vs 16.0%, p=0.148 for nausea and 10.0% vs 4.0%, p=0.436 for vomiting). No adverse effects such as diarrhea, fever or sepsis were observed in any of the participants.

The true incidence of congenital uterine anomalies is unknown. A number of values differing between 2% and 27%% have been reported for various populations.[16] The present study

yields an incidence of 25% for congenital uterine malformations. This relatively higher number may be attributed to the adoption of "gold standard" hysteroscopy as the diagnostic tool. According to the literature, uterine septum accounts for more than 80% of the congenital uterine anomalies and, thus, is the most frequent congenital malformation of the uterus.[17] In accordance, uterine septum has been found in 79% of the women with congenital uterine anomalies in the present study.

The incidence of complications related with curettage has been computed to be 9/1000. Placental retention and intrauterine adhesions are the most important of complications related with curettage. It has been documented that placental retention occurs in 0.1-4.7% of all curettages. On the other hand, placental retention has been diagnosed in 2.0% of the misoprostol group and 8% of the curettage group for the present study. The reason for these relatively higher numbers may be the utilization of "gold standard" hysteroscopy for the detection of congenital and acquired intrauterine pathologies .[18,19] Post-abortal and postpartum curettage has been found to be responsible for the majority of Asherman's syndrome cases. Despite the fact that pregnancy is the most frequent reason for curettage, intrauterine adhesions related with curettage may result in infertility or pregnancy loss. That is, nearly half of the women with intrauterine adhesions are unable to conceive while the other half of the women with intrauterine adhesions are able to conceive and have a relatively higher risk of spontaneous abortion (20%-40%) and preterm labor (20-40%)[20,21]

The present study concludes that misoprostol reduces intrauterine adhesions after surgical termination of missed abortion, possibly by improving the convenience of curettage. However, pretreatment with misoprostol lengthens the time interval required for the termination of missed abortions and, thus, impairs cost effectivity. Therefore, pretreatment with misoprostol can be justified for women who have a history of infertility or recurrent pregnancy loss and who are to undergo curettage. More research is required to clarify the efficiency and safety of misoprostol in termination of first trimester pregnancies.

In conclusion, delay in subculture and harvest time does not predict chromosomal aberrations.

Küretaj Öncesi Misoprostol Uygulaması Missed Abort Sonrası İntrauterin Adezyonları Azaltıyor

AMAÇ: Sunulan çalışma, missed abort için uygulanması planlanan küretaj öncesi gerçekleştirilen misoprostol uygulamasının müdahale sonrası intrauterin adezyonları azaltıp azaltmadığını anlamak amacıyla histeroskopinin kullanılmasını amaçlamaktadır.

GEREÇ VE YÖNTEM: Bu çalışmada, gestasyonel yaşı 6 ila 10 hafta arasında değişen ve missed abort nedeniyle küretaj uygulanması planlanan 100 kadın değerlendirilmiştir.

BULGULAR: Küretaj öncesi misoprostol tedavisi uygulanan kadınlarda görsel analog ölçek skoru anlamlı olarak daha düşüktü ve küretajın uygulanabilirliği anlamlı olarak daha fazlaydı (sırasıyla, p=0.035 ve p=0.001). Küretaj öncesi misoprostol tedavisi uygulanan kadınlarda, müdahale sonrası intrauterin adezyonlar anlamlı olarak daha azdı ve histeroskopinin uygulanabilirliği anlamlı olarak daha fazlaydı (sırasıyla, p=0.046 ve p=0.001).

SONUÇ: Küretaj öncesi misoprostol uygulaması, müdahalenin gerçekleştirilmesini kolaylaştırarak intrauterin adezyon oluşumunu azaltmaktadır. İnfertilite veya tekrarlayan gebelik kaybı öyküsü olan kadınlarda küretaj öncesi misoprostol tedavisi uygun olabilir.

Anahtar Kelimeler: Histeroskopi, Küretaj, Misoprostol, Missed abort

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