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An analysis of misoprostol effectiveness in second trimester pregnancy terminations

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Ethics Committee Approval
The study was approved by Erciyes University Clinical Research Ethics Committee (2016/18). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Misoprostol is frequently used as a single agent in pregnancy terminations. However, it increases the risk of uterine rupture in patients who have had previous uterine surgery and terminations due to stillbirths. Therefore, it is used with concern by clinicians. The aim of this study was to evaluate the clinical features of the groups that responded and did not respond to termination treatment with misoprostol in a tertiary center and to investigate its efficacy and safety.
Methods: The study design was comprised of a retrospective cohort study. A total of 114 second trimester pregnancies (between 13-24 weeks gestational age) were included in the study. These pregnancies were indicated for termination based on the prenatal diagnosis unit for fetal or maternal causes. According to the International Federation of Gynecology and Obstetrics (FIGO) directions, misoprostol was applied in the following dosages: for 13-17 weeks gestational ages, one tablet per 6 hours; for 18-26 gestational ages, ½ tablet per 6 hours; and for other indications 2 tablets per 3 hours were administered. If the patient had had a previous cesarean operation, all doses were halved. After the first 24 hours, the percentage and demographics results, such as age, body mass index (BMI), gravida, number of cesareans, number of curettages, cervical lengths, BISHOP scores, gestational age, amniotic fluid index, and fetal cardiac beat of the patients with miscarriage, were recorded.
Results: The number of cases resulting in miscarriage within 24 hours were 84 (73.7%) and within 48 hours were 14 (12.2%). The total of misoprostol doses used were 8 tablets of 200 mg, mean time until the complete abortion was 17 hours. Sixteen patients required additional treatment, of whom four required Foley catheterization, five required D&E, seven required resting, and no one required a hysterectomy. Uterine rupture occurred in two patients who needed laparotomic surgery. The maternal age (P=0.340), BMI (P=0.790), gravida (P=0.270), previous cesarean history (P=0.390), previous curettage number (P=0.520), cervical length (P=0.380), Bishop score (P=0.190), gestational age (P=0.072), amniotic fluid index (P=0.470) and presence of fetal cardiac beat (P=0.350) were similar between groups
Conclusion: Our results indicated that misoprostol is a safe, useful, and effective treatment option for second trimester medical terminations. Caution should be exercised in its use in patients with a history of uterine surgery.

Keywords: misoprostol, medical abortion, second trimester, pregnancy termination

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Introduction

One of the most important aims of obstetrics is to minimize the trauma experienced by the mother during childbirth and conclude the pregnancy with the birth of a healthy baby. However, it may be necessary to terminate at any time during pregnancy due to maternal or fetal reasons. There is no consensus yet on the most optimal method for termination of pregnancy in case of fetal anomaly or fetal death in second trimester pregnancies [1].

It was estimated that 42 million abortions were induced in 2003 worldwide. The induced abortion rate In 2003, the induced abortion rate was 29 per 1000 women aged 15–44 years. Second trimester abortions accounted for 10–15% of all induced abortions [1].

Nowadays prostaglandin-derived drugs (misoprostol) are frequently used to provide cervical maturity and induction of labor [2]. The main problem in the use of misoprostol is at which week of gestation, at which indication, and at which dose it should be administered, especially in patients having had previous uterine surgery. It is, therefore, important that procedures for the induction of second trimester abortion minimize long- and short-term morbidity.

The aim of this study to evaluate misoprostol according to the International Federation of Gynecology and Obstetrics's (FIGO) dose directions [3] in terms of efficacy, safety, and complications and to investigate clinical and demographic features between responders and nonresponders to misoprostol in the first 24 hours.

Materials and methods

The present study employs a prospective, non-randomized method conducted at the Department of Gynecology and Obstetrics at the Erciyes University Faculty of Medicine Hospital from December 2015 to May 2016. Informed consent was obtained from all patients participating in the study. The study was approved by the Erciyes University Clinical Research Ethics Committee (2016/18).

Patient selection

A total of 114 second trimester (between 13-24 weeks gestational age) pregnancies were included in the study indicated for pregnancy termination by prenatal diagnosis unit with fetal or maternal causes. Inclusion criteria consisted of the following: 13-24 weeks gestational age, singleton pregnancy, no regular uterine contractions, and no preterm premature rupture of membranes (PPROM).

Misoprostol application

The misoprostol to be used for the termination was applied vaginally at the appropriate dosage and time intervals according to the conditions specified in the FIGO dose directives. Accordingly, misoprostol was administered for intrauterine ex fetus between 13-17 weeks gestational at one tablet every 6 hours; for fetuses between 18-26 gestational ages; ½ tablet per 6 hours; and for other indications, 2 tablets per 3 hours. If the patient had had a previous cesarean operation, all doses were halved. FIGO recommended dosages are shown in Figure 1. Application of misoprostol was continued for 48 hours. If the abortion did not occur after 48 hours, other methods were administered, such as dilatation and evacuation (D&E), Foley catheterization, resting, or hysterectomy.

Figure 1: FIGO recommended dosages

<table>
<tr><th></th><th>1st Trimester</th><th>2nd Trimester</th><th>3rd Trimester</th><th>Postpartum</th></tr>
<tr><td rowspan="2">25 µg</td><td></td><td></td><td>Induction of labour 25µg pv 6 hourly or 25µg po 2 hourly</td><td></td></tr>
<tr><td></td><td></td><td>Intrauterin foetal death 25µg pv 6 hourly or 25µg po 2 hourly</td><td></td></tr>
<tr><td>100 µg</td><td></td><td>Intrauterin foetal death 13-17 weeks 100µg pv 6 hourly (max4)</td><td></td><td></td></tr>
<tr><td>200 µg</td><td></td><td>Intrauterin foetal death 13-17 weeks 100µg pv 6 hourly (max4)</td><td></td><td></td></tr>
<tr><td rowspan="2">400 µg</td><td>Cervical ripening pre-instrumentation 400µg pv 3 hours or sl 2-3 hrs before procedure</td><td>Induced abortion/Interruption of pregnancy 400µg pv or sl 3 hourly(max5)</td><td></td><td></td></tr>
<tr><td rowspan="3">Incomplete abortion 600µg po or 400µg sl single dose</td><td></td><td></td><td></td></tr>
<tr><td>600 µg</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">800 µg</td><td rowspan="2">Missed abortion 800µg pv 3 hourly (max2) or 600µg sl hrly(max2)</td><td></td><td></td><td>Postpartum hemorrhage prophylaxis 600µg po single dose</td></tr>
<tr><td></td><td></td><td>Postpartum hemorrhage treatment 800µg sl single dose</td></tr>
<tr><td></td><td>Induced abortion 800µg pv or sl 3 hourly(max3)</td><td></td><td></td><td></td></tr>
</table>

pv-vaginal,sl-under the longue,po-oral,µg-microgramme

References-FIGO misoprostol recommended Dosages 2012

After the first 24 hours, the percentage and demographic results, such as age, BMI, gravida, number of cesareans, number of curettages, cervical lengths, Bishop scores, gestational age, amniotic fluid index, and fetal cardiac beat of the patients with miscarriage were recorded.

Statistical analysis

Descriptive data of the study group were given as mean, median, standard deviation, quartile, minimum, and maximum values. The distributions of the variables were evaluated by the Kolmogorov-Smirnov test and histogram, mean and standard deviation for normal distributed variables, and median, quartile, and minimum-maximum values for variables not showing normal distribution. In the comparisons between the groups, the independent-sample t-test was used for the variables that showed normal distribution, and the Mann-Whitney U test was used for the variables that did not distribute normally. Categorical variables and percentages were evaluated using the chi-square test. Binary logistic regression analysis was used to determine the independent factors that affect the logistic termination within 24 hours. Statistical significance was determined as $P<0.05$ for all analyses. The R package program was used for statistical analysis.

Results

Of 114 patients, 45 were terminated due to in utero-fetal death, 11 were open NTD, 7 were cystic hygroma, 7 were with multiple anomalies, and 7 were anencephaly. The other termination indications were Down syndrome, HELLP syndrome, intrauterine growth restriction (IUGR), severe preeclampsia, encefalocel, hydrops fetalis, fetal bladder agenesis, partial mole pregnancy, acrania, omphalocel, cardiac and skeletal anomalies,

chisencephaly, inencephaly, holoprecencephaly, and pregnancy with abuse.

Demographics and clinical values of the patients are shown in Table 1. The mean maternal age was 28.5 (5.4), mean BMI was 27.1 (5.2), mean gravida was 3 (1-9), mean cervical length was 35.8 (8.8), mean Bishop score was 2 (0-5), mean gestational age was 124.2 (22.3), and mean amniotic fluid index was 9.1 (4.1).

Table 1: Demographics and clinical values of the patients

Variable	Mean (standard deviation) median (range)
Age (years)	28.5 (5.4)
BMI (kg/m2)	27.1 (5.2)
Gravida	3 (1-9)
Previous cesarean history	0 (0- 4)
Previous curettage number	0 (0-5)
Cervical length (cm)	35.8 (8.8)
BISHOP score	2 (0-5)
Gestational age (days)	124.2 (22.3)
Amniotic fluid index (cm)	9.1 (4.1)

Comparative data of cases with and without response to misoprostol within 24 hours are shown in Table 2. Maternal age (*P*=0.340), BMI (*P*=0.790), gravida (*P*=0.270), previous cesarean history (*P*=0.390), previous curettage number (*P*=0.520), cervical length (*P*=0.380), Bishop score (*P*=0.190), gestational age (*P*=0.072), amniotic fluid index (*P*=0.470), and presence of fetal cardiac beat (*P*=0.350) were similar between groups.

Table 2: Comparative data of cases with and without response to misoprostol within 24 hours

Variable	Responsive (n=84)	Unresponsive (n=30)	*P*-value
Maternal age (years)	28.5 (6.9)	29.9 (6.8)	0.340
BMI (kg/m^2)	27.2 (4.7)	26.88 (6.5)	0.790
Gravida	3 (1-9)	3 (1-7)	0.270
Previous cesarean history	0 (0-3)	0 (0-4)	0.390
Previous curettage number	0 (0-5)	0 (0-1)	0.520
Cervical Length (cm)	36.2 (9.4)	34.5 (7)	0.380
BISHOP score	2 (0-5)	2 (0-5)	0.190
Gestational age (days)	122 (22.8)	135 (25.8)	0.072
Amniotic fluid index(cm)	8.9-(3.8)	9.5 (4.9)	0.470
Presence of fetal cardiac beat	53 (63%)	16 (53%)	0.350

Binary logistic regression analysis to determine the independent factors affecting the termination variable within 24 hours are shown in Table 3. The maternal age OR was 0.97 (0.89-1.05); gestational age OR was 0.98 (0.96-1.0), when the number of gravida 1-4 OR was 0.95 (0.11-8.3), when the number of gravida >4 OR was 0.3 (0.7-1.5), when the previous curettage number was 1, OR was 0.001 (0.001-5.2) , when the previous curettage number >1 OR was 0.001 (0.001-4.3), BMI OR was 1.02 (0.93-1.1), presence of fetal cardiac beat OR was 0.55 (0.19-1.6), cervical length OR was 1.0 (0.96-1.07). The Bishop score OR was 0.88 (0.64-1.2), amniotic fluid index OR was 0.96 (0.85-1.0) and previous cesarean history >1 OR was 2.0 (0.4-9.8).

Table 3: Binary logistic regression analysis to determine the independent factors affecting the termination variable within 24 hours

	OR (95% CI)
Maternal age (years)	0.97 (0.89-1.05)
Gestational age (days)	0.98 (0.96-1.0)
Gravida	
1-4	0.95 (0.11-8.3)
>4	0.3 (0.7-1.5)
Previous curettage number	
1	0.001 (0.001-5.2)
>1	0.001 (0.001-4.3)
BMI (kg/m^2)	1.02 (0.93-1.1)
Presence of fetal cardiac beat	0.55 (0.19-1.6)
Cervical length (cm)	1.0 (0.96-1.07)
Bishop score	0.88 (0.64-1.2)
Amniotic fluid index (cm)	0.96 (0.85-1.0)
Previous cesarean history	
1	1.3 (0.3-5.7)
>1	2.0 (0.4-9.8)

Data's related to misoprostol application

The number of cases resulting in miscarriage within 24 hours were 84 (73.7%); the number within 48 hours were 14 (12.2%). Total misoprostol doses used were 8 tablets of 200 mg (5-10 tablets), and the mean time until complete abortion was 17 hours (12-26 hours). The number of patients requiring additional treatment were 16 (14%). Of those, four required Foley catheterization (3.5%), five required D&E (4.3%), seven required resting (6.1%), and no one required a hysterectomy. Uterine rupture occurred in two patients (1.7%) and needed a laparotomic operation. The first one was 16 weeks pregnant and terminated for anencephaly. The other case was with 20 weeks pregnant and terminated for intrauterine death fetus. Both had previously had two cesarean sections. The ruptures were at the previous incision shape. Seven patients needed curettage to remove the rest placenta (6.4%). During the first 24 hours, the response rate was 73.7%, and in 48 hours, it was 85.9%

Discussion

In the present study, we evaluated the effect of misoprostol application on termination of pregnancy during the second trimester. In order to maintain the current location of the regular obstetrics practice, and because obstetricians are often undecided on the dosages of misoprostol, application times, and individualization of patients according to these parameters, we decided to publish our experience with the application of misoprostol.

When it is decided to terminate the pregnancy, the cervix must be mature and given appropriate time to delivery [4]. It has been determined in the termination of first and second trimester pregnancies that the use of misoprostol is non-invasive, easy to apply, cost-effective, quick, and reliable [5]. The current literature indicates that prostaglandin E1- misoprostol may be used for delivery induction in the presence of an inappropriate cervix [6]. However, there is no consensus on the effective and safe administration and dosage of misoprostol [7]. Carbonella et al. [8], reported 85% complete abortion rates at 9-12 weeks of gestation and 80% complete abortion rates at 12-15 weeks gestation with misoprostol. In another study, given two vaginal misoprostol every three hours and applied a total of five times achieved 80% abortion rate in the first 24 hours and 95% abortion rate in the first 48 hours [9]. In our study, 84 (73.3%) patients had complete abortions in the first 24 hours, and 98 pregnancies terminations were provided (85.9%) in 48 hours.

There are many factors that affect abortion rate within the first 24 hours with misoprostol. In some studies, the Bishop score was found to be more significant than the cervix size [10], whereas in others, abortus time was correlated with cervical length [11]. While it was determined that the abortion time decreased as correlated with gestational age [12,13] and inversely correlated with parity [13], BMI was not found to be related to abortion time [14]. While it was suggested that previous surgery had no effect on abortion duration [15,16], in some studies, it was determined that the rate of bleeding and incomplete abortion increased [16]. In our study, no statistically significant results were obtained regarding the factors mentioned above.

At times, additional methods are needed to shorten the duration of abortion. Although Foley catheterization was one of

these methods, contradictory results were obtained in the studies. While in one study it was observed that Foley catheterization and misoprostol use decreased the term of termination compared to misoprostol alone [17], another study determined that the use of Foley catheterization with misoprostol did not make a significant difference in termination time [18]. In our study, use of the Foley catheter resulted in abortion in patients who failed with misoprostol.

Another important variable affecting abortion duration is fetal cardiac activity. In a study including 89 cases, at the 12th, 24th and 48th hours, while the rate of abortion success of patients with alive fetuses were 15%, 54% and 92%, respectively, of the patients with intrauterine death fetuses were 50%, 83% and 92%, respectively [19]. Dilbaz et al. [20], found that if the fetus was alive and gestational age >16 weeks, the abortion duration was prolonged. In another study, it was detected that misoprostol dose and termination intervals were shorter in pregnancy terminations by reason of intrauterine ex fetuses [21,22]. In our study, 84 of 114 cases responded to treatment in the first 24 hours. In 53 of the patients who received response to treatment, and in 16 of the 30 unresponsive patients, fetal cardiac activity was available. Although the ratio was higher in responding patients, it was not statistically significant. In a study by Vitner et al. [13], nulliparity, young mothers' ages, and advanced gestational age were associated with abortion duration. This was not the case in our study; however it was the result in another Turkish study [23]. This may be associated with the demographic characteristics of Turkey.

After the second trimester medical abortions, incomplete abortion or remaining placenta is an important problem and requires surgical intervention. In the first studies on this subject, more than 80% of patients after misoprostol required curettage [9,24]. It was observed that this rate decreased below 5% in later studies [5]. In our study, curettage was performed for misoprostol failure in five patients and in seven patients because of remaining placenta. Our curettage rate was 6.4%, and this rate was similar to other studies.

In this study, we investigated effect and complicates of misoprostol alone. In a study achieved by misoprostol alone, 54 of 55 pregnancies terminated. Mean abortion duration was 12.7 hours and only one patient needed curettage for rest placenta [26].

Both the mother and the obstetrician are concerned during the termination of pregnancy. It has been shown that the use of misoprostol in these weeks is safe. This situation before the treatment and the guarantee thereafter will guide the reduction of the slowdown with the family.

Limitations

One limitations of this study is that the surgeons who performed previous operations on pregnant women with previous cesarean section births was different, and they may have used different techniques. In our study, the rate of abortion in the first 24 hours was 73.7% and in 48 hours was 85%. The reason for the low success in our study compared to other studies, may be caused by the usage of low doses of misoprostol on patients who had experienced intrauterine fetal death and previous surgery history. The guidelines followed were in accordance with FIGO directions.

Conclusion

Our results indicated that misoprostol is a safe, useful, and effective treatment option for second trimester medical terminations. Caution should be exercised in its use in patients with a history of uterine surgery.

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