Evaluation of low-dose vaginal misoprostol in pregnancy terminations below 34 weeks of gestation: Time to change the dose?

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Abstract

Objective: To evaluate of the effectiveness of low-dose (LD) vaginal misoprostol administration, where dose adjustment was made by taking into account the gestational week and cesarean section (C/S) history in termination of pregnacy (ToP). Design: Retrospective observational cohort study. Setting: A single tertiary center Population: 563 patients who opted ToP under 34 weeks of gestation. Methods: Outcomes were ascertained by health record review and compared between subgroups according to gestational weeks and previous C/S history. Main Outcome Measures: Total misoprostol administration time, total labor time, total misoprostol dose, >1 ToP method, uterin rupture, uterine atony Results: 63% (357) of 563 cases with pregnancy termination were below the 24th gestational week (Gx). The remaining 206 cases (Gy) (37%) were between 24 and 34 weeks of gestation. The rate of C/S history was statistically significantly higher in Gx (p=0.030). While a single termination method below 24 weeks was sufficient in 94% of cases, this rate remained at 86% in Gy (p=0.002). There was no difference in the complication rate between the groups according to the gestational week or the presence of a prior C/S (p>0.05). Concusions: The present regimen is an effective method with low maternal morbidity and high success without increasing the total treatment time. Especially in patients with a history of C/S where the 'experience of ToP with misoprostol' have relatively high risk , and in all ToPs below 34 weeks, achieving a high birth rate without increasing the uterine rupture rate suggests that it is a safe approach.

INTRODUCTION

Prenatal sonography makes it possible to diagnose structural anomalies, aneuploidies or genetic syndromes incompatible with life starting from early weeks of gestation.[1] The termination of pregnancy (ToP) option has been offered to the families according to these findings and this limit of gestational week varies from country to country. Among the few methods recommended for ToP so far, misoprostol is still the cheapest, most effective pharmaceutical with a known side-effect profile.[2-4] Misoprostol stands out because mifepristone is not available in some countries and oxytocin is not a good option for inappropriate cervix.[2]

A guideline was published by the International Federation of Gynecology and Obstetrics (FIGO) in 2017 for use in pregnancy terminations.[5] In this guideline, it is recommended to use misoprostol doses at <13, 13-26, >26 weeks of gestation at varying doses and intervals. However, the recommended vaginal doses of misoprostol in this guideline are relatively high, and countries are recommended to use their own local protocols in the presence in patients with a history of cesarean section. The most important reason for this is the increased risk of uterine rupture, placental retention and postpartum bleeding associated with them in the presence of a history of cesarean section.[3, 6-10]Therefore, with increasing cesarean rates, the management of pregnancy terminations is becoming an important problem.[2, 11]From past to present, many studies using misoprostol for pregnancy termination in patients with previous cesarean section (C/S) have

been presented.[3, 6-12] The misoprostol dose, route, dose ranges and gestational week limits used in these studies vary. This situation prevents reaching a certain standardization in management in patients planned for ToP, whether or not they have a history of C/S. Moreover, not only the history of C/S, but also the number of prior C/S is an important factor that can affect these results.[10-12] Therefore, there is a need for standardized protocols that can be used safely at all gestational weeks regardless of cesarean section history, and that are effective and have a low side-effect profile.

In this study, the efficacy of low-dose vaginal misoprostol administration in which dose adjustment was made according to the gestational week and previous cesarean section history in pregnancy terminations below 34 weeks of gestation was investigated.

METHODS

Study design and patient selection

The current study was designed retrospectively between January 1, 2019 and December 31, 2021 in a single tertiary center. A five-hundred-sixty-three pregnant women who decided to terminate pregnancy were included in the study. This study was undertaken with the Institutional Review Board's approval (Approval number: 1105085). All of the patients included in the study were below the 34th gestational week and were evaluated by dividing them into four groups. Group 1 (G1) consists of patients below 23 6/7 weeks of gestation without a prior cesarean section (C/S), and group 2 (G2) consists of patients below 23 6/7 weeks of gestation with at least one prior C/S. Group 3 (G3) consists of patients between 24-34 weeks of gestation without a prior C/S, and group 4 (G4) consists of patients between 24-34 weeks of gestation with at least one prior C/S. Gx and Gy refer to G1-2 and G3-4, respectively (Table 2 and 3).

Among the dates specified in the study, cases with a fetal anomaly incompatible with life (prenatally diagnosed with aneuploidy, microdeletion/duplication syndromes, severe or lethal fetal structural anomalies diagnosed with ultrasound were included), cases who were below 34 weeks of gestation and whose pregnancy was terminated due to intrauterine demise (IUD), missed abortion or other reasons (preterm premature rupture of membranes below 22 weeks of gestation) were included. The cases at 34 weeks of gestation and above, the cases with a history of non-C/S uterine surgery, pregnancies terminated by methods other than vaginal misoprostol as a first-line treatment, the cases with contraindication for misoprostol use and the cases who underwent elective hysterotomy as a first-line treatment due to prior C/S history were excluded from the study. In all cases above 22 0/7 weeks of gestation, feticide with fetal intracardiac KCl injection was administered before termination of pregnancy (ToP). All of the patients was followed up to the hospital as inpatient and discharged after 24 hours if vaginal delivery had been occured and 48 hours if elective hysterotomy had done. Before start of treatment, treatment-related informed consent was obtained from all patients.

The treatment protocol was defined as follows in cases which ToP is planned: In patients without a history of prior (C/S) below 23 6/7 weeks of gestation, 400 mcg misoprostol vaginally was given as a loading dose, the subsequent doses were given 200 mcg vaginally in every 4 hours, a maximum dose is 1400 mcg (G1). Above 24 0/7 weeks of gestation, 200 mcg misoprostol vaginally was administered as a loading dose, the subsequent vaginal doses are administered as 100 mcg in every 4 hours, a maximum dose is 700 mcg (G3). If the patient has at least one or more prior C/S history, the doses which are previously described were halved below (G2) and above the 24th gestational week (G4) (a maximum dose is 700 mcg and 350 mcg, respectively). When the abortion or delivery did not occur after first regimen, patients were rested for 12 hours and the same regimen was repeated once more. When a method used after the second failured (vaginal misoprostol regimen, this was named as more than one (>1) ToP procedure. Sublingual misoprostol administration, cervical ripening balloon or oxytocin induction were chosen based on cervical assesment in cases where vaginal delivery/abortion did not occur following the second failured vaginal misoprostol regimen. If there was a prior C/S history, hysterotomy was discussed with the patient after two failured vaginal misoprostol regimens. The primary outcome was the success rate of ToP by vaginal delivery after two LD vaginal misoprostol regimen (single method). None of the patients in the current study had a contraindication for

prostaglandin use.

Outcome measures

Uterine rupture and uterine atony at or after vaginal misoprostol administration were defined as major complications in all groups. Total misoprostol administration time was calculated as the time from the first dose of misoprostol to the administration of the last dose. Total labor time refers to the time from the first dose of misoprostol to delivery. If a method other than vaginal misoprostol was used during the period until delivery, it was included in the 'total labor time' period. Time intervals were defined as hours.

Statistical analysis

SPSS Statistics for Windows, Version 20.0 (IBM, NY, USA) was used for the statistical analysis. The Kolmogorov–Smirnov test evaluated the normality of the distribution. All continuous variables were presented as mean and standard deviation values, while categorical variables were defined as a percentage of the total group. A p-value of <0.05 was considered statistically significant, and all statistical tests were planned by comparing the two groups. Chi-squared and Fisher's exact tests compared the categorical variables. Independent samples t-test was used to compare categorical variables in two groups.

RESULTS

Table 1 shows the characteristics of included cases in the study according to the medical history and cause of ToP. The number of cases included in the study between the specified years was 563. ToP was performed in 357 (63%) of these cases below 24th ([?]23 6/7) gestational week. The termination week of the remaining 206 (37%) cases was between 24th and 34th gestational weeks. In the comparative analysis of the demographic data of the two groups, there was no statistical difference in the numbers of gravida, parity and abortion ($p>0.05$) (Table 1). The rate of prior cesarean section in cases below the 24th gestational week was significantly higher than the cases between 24-34 weeks of gestation ($p=0.030$) (Table 1). As described in the material method section, feticide procedure was performed in all cases (except 19 cases with in utero demise) above the 22th gestational week. A single ToP method was sufficient in 94% of all cases terminated before 24 weeks of gestation (termination with misoprostol), but this rate remained at 86% in cases between 24 and 34 weeks of gestation, and a statistically significant difference was found ($p=0.002$) (Table 1).

Comparison between all groups according to total misoprostol dose, administration and labor time are shown in the Table 2. In accordance with the protocol described in the material method section, the total misoprostol administration time was statistically significantly higher due to the decrease in misoprostol doses administered between 24 and 34 weeks of gestation ($p=0.000$) (Table 2). Below the 24th gestational week, both the delivery process and the lenght of hospital stay were found to be shorter in pregnancy terminations ($p=0.000$) (Table 2). There was no statistical difference between the two groups in terms of need for transfusion and admission to maternal intensive care unit (MICU) ($p=0.149$, $p=0.535$, respectively) (Table 2).

Comparative results of all groups according to the number of ToP procedure and complications are given in the Table 3. When we divide both groups (G1-G4) into two groups in terms of the presence of cesarean section within themselves; The rate of needing more than one ToP method was found to be statistically significantly higher in the cesarean section group with terminations below the 24th gestational week (0.007). However, in ToPs between 24-34 weeks of gestation, whether there was a prior cesarean section or not did not change the number of ToP methods needed. (Table 3). There was no difference in the complication rate between the groups according to the gestational week or the presence of a prior cesarean section ($p>0.05$) (Table 3).

Uterine rupture occurred in a total of 3 cases. The most important common feature of these cases was that all of them were below the 24th gestational week. Two cases had a history of previous C/S (one C/S history in one case and two C/S history in the other case). There was a previous cerclage operation history in one case in G1. One of the three cases had to be performed hysterectomy. Two cases required blood transfusion (Table 4).

DISCUSSION

Main Findings

Based on our study results, when low dose (LD) vaginal misoprostol (as a single method) is used in pregnancy terminations under 34 weeks of gestation, the rate of vaginal delivery without the need for additional termination method is found 91%. This rate is similar to the results obtained in other studies using high-dose vaginal misoprostol or multiple methods (mifepristone, cervical balloon catheter, oxytocin).[8, 10-13] In the current study, a very low-dose misoprostol regimen had given according to both the recommendations in the FIGO guideline and the studies published in the literature.[5, 8, 10-12] In a previous study presented by Torriente et al., a comparison was made between patients with and without prior C/S history in the second trimester, and the success rate was found to be 88-93%.[10] However, in that study, the distribution of gestational weeks (13-20 weeks) was quite different from our study, and high-dose misoprostol (1200-1400 μg) was preferred in both groups.[3] In the present study, the rate of delivery below 24 weeks of gestation with the LD vaginal misoprostol regimen (single method) was 94%; it was found 86% above 24 weeks of gestation. Although prior C/S (31.1% vs 22.3%) rate was higher in the group under <24 gestational weeks, the difference was found significantly higher. Cetin et al reported in their study compared the regimen by FIGO with a different LD regimen of misoprostol.[11] However, in this study, the gestational week was limited to 12-24, and the effect of pregnancies with and without a history of cesarean section was not compared. In many studies in which the efficacy of misoprostol was discussed, it was stated that this positive effect may be mostly related to dose and dose range.[9, 14] Despite the higher a prior history of C/S rate in Gx group, the higher birth rate with the single method may be associated with the use of misoprostol at a higher dose below the 24th gestational week (Gx) than in the other group (Gy).

In the present study, when the group below 24 weeks of gestation (Gx) was compared with 24-34 weeks of gestation (Gy), there was an inverse correlation between total misoprostol dose and total treatment time, time until delivery and hospital stay, and the result was statistically significant. Since higher doses of misoprostol were used in patients without a history of cesarean delivery (G1-G3), both under 24 weeks of gestation and between 24-34 weeks of gestation compared to patients with a history of cesarean section (G2-G4), delivery took place in a shorter time, therefore the hospital stay has also been shortened. Since the most important difference between the regimens administered in our study was the misoprostol dose used, it is inevitable to obtain this result between the groups. However, no significant difference was found in the rates of transfusion need (0.8-2.5%) and admission to MICU (0.4-0.9%) in the groups using higher doses. Upon this result, it shows that it is possible to reach effective treatment with lower doses at all gestational weeks without increasing maternal comorbidity compared to other studies in the literature using higher doses in ToP.[2, 9, 14]

Strengths and Limitations

In the present study, in which data from an experienced tertiary center is presented, is valuable because the results of a particular clinical protocol are evaluated. However, the most important limitations of our study are its retrospective design and relatively low number of the patients among the group 2 and 4. Since the most common cause of pregnancy termination (75%) in the study was fetal structural anomalies, 63% of the patients were below the 24th gestational week. In addition, after second failured treatment, delivery with a another method other than LD vaginal misoprostol according to previous cesarean section history or cervical assessment may have affected the total length of hospital stay and time to delivery in all patient groups. However, considering that the high success rate with a single method is like 91% in our study, we believe that this is not an important variable.

Interpretation

So far, in many studies, while discussing the effect of vaginal misoprostol use on ToP in patients with a history of C/S, the second trimester was mostly considered as reference and different gestational weeks were taken as the limit.[3, 6, 7, 10, 12] Since the association of increased doses of misoprostol with increased risk of complications in termination of pregnancy is known, so our study offers the opportunity to compare the

efficacy of misoprostol at low doses in all patients below 34 weeks of gestation and its relation with history of C/S. Accordingly, when patients with a history of C/S below 24 weeks of gestation (G2) and above (G4) were compared among themselves, as the total misoprostol dose (673,8 ± 457,3 µg vs 443,5 ±212,8 µg) descreased, the duration of treatment (19,4 ±15,9 hours vs 25,3 ±12,6 hours) and induction to labor interval (23,5 ±14,2 hours vs 31,5 ±19,9 hours) increased and the difference between them was found significant. It has been reported in many studies that the induction-labor time shortens as the vaginal misoprostol dose is increased, but it is noteworthy that the misprostol dose used in these studies is higher than the regimens in the current study.[8, 10]

In the present study, although the need for transfusion (0,9% vs 2,2%) increased as the gestational week progressed among patients with prior C/S history below and above 24 weeks of gestation, the difference was found not significant. In addition, admission to MICU (0,9% vs 0%) rates were very low and similar between the two groups. In other words, a decrease in the dose of misoprostol used does not cause a significant change in comorbidities, although it prolongs the induction-labor time. In a systematic review by Berghella et al discussed that the results of patients with a prior history of C/S between 16 and 28 weeks of gestation who underwent pregnancy termination with misoprostol.[3] In this review, the need for transfusion was found 0,2%, but the weeks of gestation, administration route and dose of misoprostol of the patients included in the review were highly variable.

One of the major disadvantages of LD vaginal misoprostol therapy in ToP cases is the need for an auxillary treatment if the current protocol fails. The need for an auxillary treatment increases the risk of treatment non-compliance by prolonging the period until delivery and causing some psychological side effects for the patient.[2, 11] In the present study, >1 ToP procedure was required in 14% of patients between 24-34 weeks of gestation and 5,8% of patients under <24 weeks of gestation. In other words, when the entire patient group was considered, regardless of the history of cesarean section, the highest success with the single ToP method was found in the Gx (G1-2) group, which results were similar to previous studies.[3, 8, 13] The group in which more than one ToP procedure is needed the least (3,7%) is the patients (G1) without a history of cesarean section at <24 weeks of gestation. Accordingly, in the presence of a progress with gestational week or a history of cesarean delivery, LD vaginal misoprostol administration may result in unsuccessful results, increasing the need for an auxillary treatment. However, there was no evidence of increased complications (uterine rupture or atony) when all groups were compared among themselves. To date, the highest uterine rupture rate reported in the literature is 11,5%, and in this study, unlikely a minimum of 1200 µg misoprostol was administered in patients with a history of two or more C/S (14-26 weeks).[12] In the systematic review presented by Berghella et al, uterine rupture rate was reported 0,43% in one prior history of C/S, but the doses used were highly variable.[3] In the current study, uterine rupture was observed only in 3 cases (0,8%) below 24 weeks of gestation, and uterine atony was observed in 2 cases (0,9%) above 24 weeks of gestation. We think that the low complication rate in our study is related to the misoprostol dose and dose range administered.

Conclusion

Misoprostol is an inexpensive and effective method of termination of pregnancy and is a good alternative in countries where mifepristone is not available.[2] Considering all the data in the literature to date, achieving effective results with the LD misoprostol regimen compared to previously reported doses in pregnancies with or without a history of cesarean section below 34 weeks of gestation may lead to a review of algorithms even presented by FIGO.[3, 5] The 'low-dose vaginal misoprostol' regimen is an effective method with low maternal morbidity and high success without increasing the total treatment time. Especially in patients with a history of cesarean section where the 'experience of ToP with misoprostol' have relatively high risk , and in all ToP's below 34 weeks, achieving a high birth rate without increasing the uterine rupture rate suggests that it is a safe approach.

Disclosure of interests: The authors report no conflict of interest.

Contribution to authorship: All authors conceptualised and designed the study. TSS designed the study,

wrote the first draft of the paper, interpreted the data. OD analysed and interpreted the data, and wrote the article. SBT, OT, HC, SBI and EY were involved in the sample collection. IHK and RH revised and contributed to the intellectual content of the manuscript. All the authors approved the final article.

Details of ethics approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the local Institutional Review Board (IRB) (approval number: 1105085).

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