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GENERAL GYNECOLOGY

The role of repeat misoprostol dose in the management of early pregnancy failure

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Abstract

Purpose We aimed to assess the role of repeat misoprostol administration in those with thickened endometrium in the management of early pregnancy failure (EPF).

Methods A retrospective cohort study in two university hospitals among women receiving misoprostol treatment for EPF. Those with thickened endometrium at the first follow-up visit, who received a repeat 800 µg dose of vaginal misoprostol in institution B and no treatment in institution A, constituted the study group. The primary outcome was treatment success, defined as complete uterine evacuation without the need for any operative intervention

Results Overall, 608 women with thickened endometrium as assessed by transvaginal ultrasonography 2 days following initial misoprostol administration for EPF were included. Of them, 427 did not receive repeat misoprostol dose, and 181 received repeat misoprostol dose. The rate of surgical intervention did not differ between those who received a repeat misoprostol dose (6.1%) and those who did not (4.3%) ($P=0.32$). The median endometrial thickness was similar in those that did and did not require subsequent surgical intervention ($P=0.65$), and was a poor predictor of treatment outcome.

Conclusions Repeat misoprostol administration among women with thickened endometrium following initial misoprostol administration for EPF was not associated with improved treatment success rates.

Keywords Misoprostol · Early pregnancy failure · Medical management · Repeat dose · Retained products of conception · Thickened endometrium

Abbreviations

ART	Assisted reproductive technologies
D&C	Dilatation and curettage
EPF	Early pregnancy
GA	Gestational age
MVA	Manual vacuum aspiration

Introduction

Early pregnancy failure (EPF) is a common condition, affecting 15% of all clinically recognized pregnancies [1–4]. Management approaches include expectant management, medical treatment, and surgical intervention. In recent decades, misoprostol, a prostaglandin E1 analogue, has become the most commonly used medical agent in the setting of EPF, due to its favorable safety and efficacy profiles, allowing for planned, expedited expulsion of the nonviable pregnancy tissue, while avoiding surgical intervention and its attendant risks [5–8].

The recommended initial dose of misoprostol by the American College of Obstetricians and Gynecologists (ACOG) in the treatment of EPF is 800 µg administered vaginally [5]. The ACOG allows for one repeat dose of misoprostol in case of incomplete uterine evacuation after the first dose [5]. Nevertheless, there is no consensus in the literature regarding the adequate criteria to define complete expulsion of pregnancy tissue in the absence of a gestational sac, with a variety of endometrial thickness values

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used across different studies [5]. Moreover, the role of repeat misoprostol administration among those with a thickened endometrial stripe is not well established, with conflicting results reported [9, 10].

Given the paucity of publications on this topic, we aimed to evaluate the role of repeat misoprostol administration among women with a thickened endometrium after initial medical treatment for EPF.

Materials and methods

Patients

This is a retrospective cohort study. The study group comprised all women with EPF ≤ 12 weeks' gestation (fetal demise or anembryonic gestation with closed cervix and minimal vaginal bleeding) referred to two university hospitals at a tertiary-care medical center for medical treatment with vaginal misoprostol during 2010–2017. The hospitals serve greater Jerusalem and comprise a heterogeneous, multicultural and multinational population from a heavily populated urban center and from rural, scarcely populated areas. We excluded women who had a gestational sac or endometrial thickness ≥ 20 mm identified on the first follow-up visit, those who underwent dilatation and curettage (D&C) prior to the first follow-up visit, multifetal gestation, and the diagnoses of inevitable, incomplete and complete miscarriages. Thus, those who did not meet the exclusion criteria and had endometrial thickness of 15–19 mm at the first follow-up visit were included. The diagnosis of EPF was made according to the recommendations published by the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy [11].

Study protocol

At admission, the patients' medical history, hemoglobin level, and Rh-antigen status were assessed and a physical exanimation was performed. All women diagnosed with EPF were presented three options upon diagnosis: (1) expectant management, (2) medical treatment with misoprostol, and (3) surgical intervention (D&C). Those with hemodynamic instability, hemoglobin level < 9.5 g/dL, history of inflammatory bowel diseases, cerebrovascular disease and ischemic heart disease, known bleeding disorder, current anticoagulation therapy, misoprostol allergy and a nonviable embryo that measured greater than a 12-week size, were ineligible for medical treatment with misoprostol. All subjects primarily opting for medical management provided written informed consent prior to treatment with misoprostol. These women had four 200 µg tablets (800 µg) of misoprostol (Cytotec, Piramal Healthcare Ltd, UK) inserted into the posterior fornix of the vagina by the treating physician (day 1). If vaginal bleeding was within normal limits after 4 h of surveillance on the gynecology ward, the patient was discharged home. All patients returned 2 days (day 3) after misoprostol treatment for a follow-up evaluation including transvaginal ultrasonography. If the gestational sac was still present at the first follow-up visit, a second 800 µg dose of vaginal misoprostol was administered in both institutions. If the gestational sac was expelled, the maximal anteroposterior diameter of the endometrial cavity was measured on midsagittal plane by transvaginal ultrasonography. In institution A, when endometrial thickness was measured ≥ 20 mm, a second 800 µg dose of misoprostol was administered. In institution B, when endometrial thickness was measured ≥ 15 mm, a second 800 µg dose of misoprostol was administered. Therefore, those with endometrial thickness measured between 15 and 19 mm, received a repeat dose in institution B and no treatment in institution A. None of the patients received misoprostol via other modes of administration (e.g., sublingual, oral) during the study period. All women with Rh-negative blood type were given 300 µg of anti-D intramuscularly within 72 h after admission. All women were instructed to return for a follow-up visit on day 15. Manual vacuum aspiration (MVA), operative hysteroscopy, or D&C were offered only when clinically indicated including persistent bleeding or suspected retained products of conception (RPOC) (i.e., these interventions were not performed solely because of thickened endometrium or patient's request). The treatment algorithm in both institutions is shown in Fig. 1.

Data collection

We abstracted emergency room encounters, hospital admissions and outpatient clinic follow-up visits from the electronic medical record database of the gynecology departments of the two hospitals. Records were reviewed by a single reviewer (AR). The following data were extracted: patient characteristics (demographics, gravidity, parity), gestational age, prior cesarean deliveries, use of assisted reproductive technologies (ART), gestational age (GA), type of EPF (fetal demise or anembryonic gestation), endometrial thickness at the first follow-up visit and treatment outcome. The primary outcome was treatment success, defined as complete uterine evacuation without the need for any operative intervention (MVA, operative hysteroscopy, or D&C). Endometrial thickness did not serve to define treatment success, as operative intervention was not performed solely due to thickened endometrium, as aforementioned. The secondary outcomes were rates of emergency D&C, fever, and pelvic infection. Fever was defined as two measured oral temperatures of 38 °C at least 4 h apart, not attributed

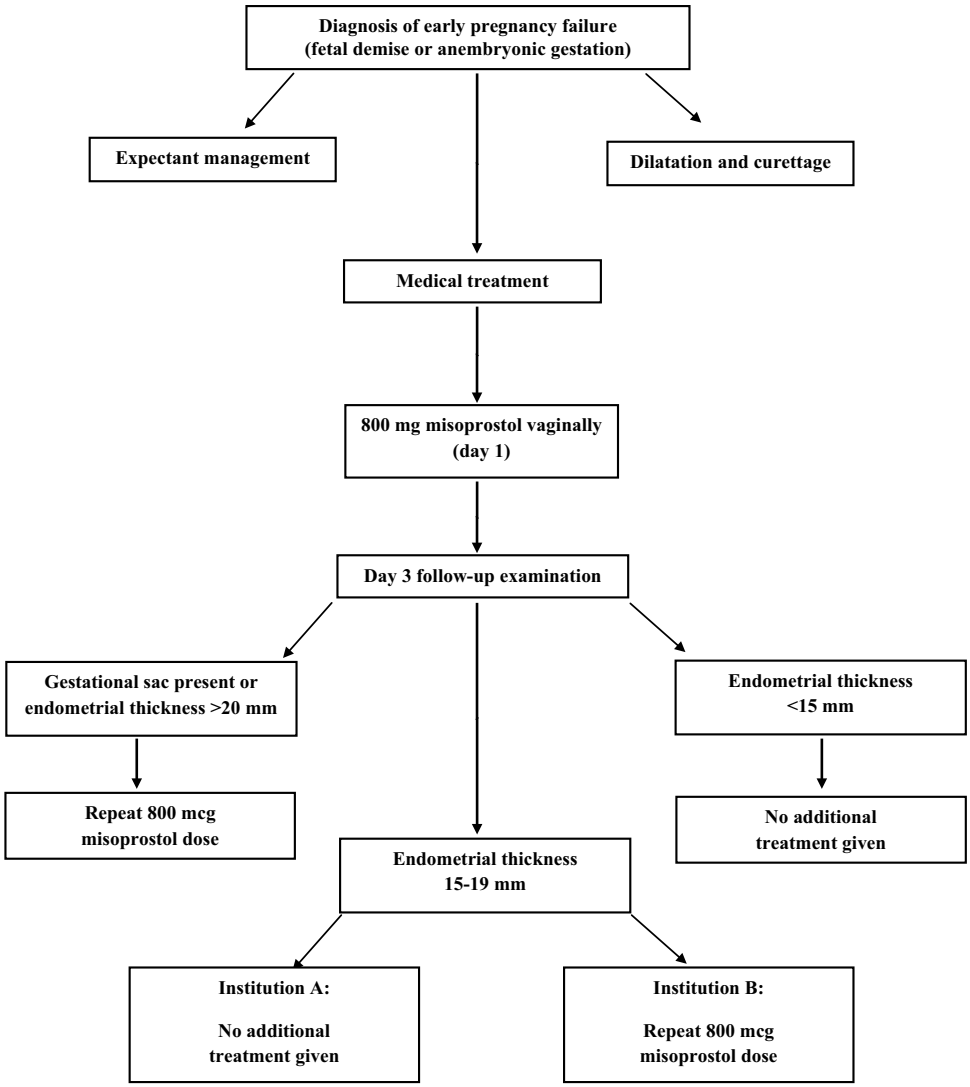

Fig. 1 Flow diagram illustrating the medical management protocol for early pregnancy failure in both institutions

to misoprostol administration. Pelvic infection was defined according to the CDC diagnostic criteria [12].

Statistical analysis

Patient characteristics are described as proportions for categorical variables and as medians and interquartile ranges for continuous variables without a normal distribution. Significance between groups was assessed by the Chi square test and Fisher's exact test for categorical variables and the Mann–Whitney *U* test, for continuous variables without a normal distribution. A univariate logistic regression model was applied to all clinical and laboratory parameters. A 2-sided P value < 0.05 indicated statistical significance. The data were analyzed using Software Package for Statistics and Simulation (IBM SPSS version 22, IBM Corp, Armonk, NY, USA). Sample size calculation: $\alpha = 0.05$ and 80% power, required 280 patients in the whole cohort to detect a significant difference of 10% in the rate of successful treatment outcome.

Ethical issues

The study was approved in January 2018 by the Human Investigation Review Board of Hadassah Hebrew University Medical center (IRB Approval No. HMO-0157-18).

Results

A total of 4060 women received misoprostol due to EPF in both institutions during study period. Of them, 608/4060 (15.0%) met the inclusion criteria at the first follow-up visit (2 days after initial treatment). The median gestational age was 6.6 weeks in both institutions ($P = 0.70$). The distribution of fetal death and anembryonic gestation was similar in both institutions ($P = 0.66$). Baseline characteristics of the

women were similar between the groups, except for higher median age in institution A as compared to institution B (32 vs. 30 years, $P=0.002$) (Table 1).

Among the 608 women with endometrial thickness 15–19 mm at the first follow-up visit, 29/608 women (4.8%) subsequently required surgical intervention (Table 2). The rate of surgical intervention did not differ between those who received a repeat misoprostol dose (11/181, 6.1%, institution B) and those who did not (18/427, 4.3%, institution A) ($P=0.32$). The indications for intervention were persistent bleeding in 21/29 (72.4%) cases and suspected RPOC (i.e., in follow-up sonographic examinations or diagnostic hysteroscopy) in 8/29 (27.6%). Of those who underwent surgical intervention, 15/29 (51.7%) underwent D&C, 13/29 (44.8%) operative hysteroscopy and 1/29 (3.4%) MVA. Emergency D&C due to excessive bleeding was performed in 7 cases, 4 in institution A and 3 in institution B ($P=0.44$). Rates of fever ($P=0.51$) and pelvic infection ($P=1.0$) were comparable in both hospitals (Table 2).

The endometrial thickness was similar in those who did and did not require subsequent surgical intervention (median 17 mm in both groups, $P=0.65$).

Evaluating the factors associated with successful treatment outcome, no association was found with any of the baseline and clinical parameters, including parity ($P=0.11$) and endometrial thickness ($P=0.65$) (Table 3).

Table 2 Outcomes of women with early pregnancy failure (EPF) at the two treating centers

Outcomes	Institution A[a] $n=427$	Institution B[a] $n=181$	*P* value
Need for surgical intervention	18 (4.3%)	11 (6.1%)	0.32
D&C[b]	8 (44.44%)	7 (63.6%)	
Operative hysteroscopy[b]	9 (50.0%)	4 (36.4%)	
MVA[b]	1 (5.6%)	0	
Emergency D&C	4 (0.9%)	3 (1.6%)	0.44
Fever	1 (0.2%)	1 (0.5%)	0.51
Pelvic infection	3 (0.7%)	1 (0.5%)	1.0

All continuous variables are expressed as medians [interquartile range] (mean). The Mann–Whitney *U* test was used for continuous variables without a normal distribution

D&C dilatation and curettage, *MVA* manual vacuum aspiration

[a]In institution A, those with thickened endometrium measuring 15–19 mm at day 3 following initial misoprostol administration, did not receive a repeat dose, whereas in institution B, a repeat dose was administered in this subset of patients

[b]The denominator is the total number of women who underwent surgical intervention in each institution

Table 1 Characteristics of women with early pregnancy failure (EPF) at the two treating centers

Characteristics	Institution A[a] $n=427$	Institution B[a] $n=181$	*P* value
Age, years	32 [27–37] (32)	30 [24–35] (30)	0.002
Estimated gestational age, days	46 [42–55] (49)	46 [42–56] (49)	0.70
Gravidity	2 [2–4] (3)	2 [1–4] (3)	0.55
Parity	1 [0–2] (2)	1 [0–2] (2)	0.47
Nulliparous (%)	139 (32.6%)	67 (37.0%)	0.30
Previous cesarean delivery (%)	153 (35.8%)	66 (36.4%)	0.93
ART conceived pregnancy (%)	51 (11.9%)	23 (12.7%)	0.79
Type of EPF (%)			0.66
Fetal demise	353 (82.6%)	147 (81.2%)	
Anembryonic gestation	74 (17.4%)	34 (18.8%)	
Endometrial thickness (mm)	17 [16–18] (17)	17 [16–18] (17)	0.14
15 mm	105 (24.6%)	39 (21.5%)	
16 mm	93 (21.8%)	34 (18.8%)	
17 mm	76 (17.8%)	34 (18.8%)	
18 mm	90 (21.1%)	40 (22.1%)	
19 mm	63 (14.8%)	34 (18.8%)	

All continuous variables are expressed as medians [interquartile range] (mean). The Mann–Whitney *U* test was used for continuous variables without a normal distribution

ART assisted reproductive technologies

[a]In institution A, those with thickened endometrium measuring 15–19 mm at day 3 following initial misoprostol administration, did not receive a repeat dose, whereas in institution B a repeat dose was administered in this subset of patients

Table 3 Factors related to misoprostol treatment outcome for early pregnancy failure (EPF)

Characteristics	Success $n=579$	Failure $n=29$	P value
Age, years	31 [26–37] (31)	34 [27–38] (33)	0.25
Estimated gestational age, days	46 [42–55] (49)	45 [42–53] (48)	0.43
Gravidity	2 [2–4] (3)	2 [2–4] (3)	0.93
Parity	1 [0–2] (2)	1 [0–2] (1)	0.81
Nulliparous (%)	192 (33.2%)	14 (48.3%)	0.11
Previous cesarean delivery (%)	105 (18.1%)	2 (6.8%)	0.14
ART conceived pregnancy (%)	72 (12.4%)	2 (6.8%)	0.37
Type of EPF (%)			0.94
Fetal demise	476 (82.2%)	24 (82.7%)	
Anembryonic gestation	103 (17.8%)	5 (17.3%)	
Endometrial thickness (mm)	17 [16–18] (17)	17 [16–18] (17)	0.65
15 mm	140 (24.2%)	4 (13.8%)	
16 mm	119 (20.6%)	8 (27.6%)	
17 mm	103 (17.8%)	7 (24.1%)	
18 mm	125 (21.6%)	5 (17.2%)	
19 mm	92 (15.9%)	5 (17.2%)	

All continuous variables are expressed as medians [interquartile range] (mean). The Mann–Whitney U test was used for continuous variables without a normal distribution

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Discussion

In this retrospective cohort study, a repeat misoprostol dose administered to those with residual endometrial thickness following initial medical treatment of EPF was found not to be associated with lower rates of subsequent surgical intervention. In addition, no association was found between increased endometrial thickness and treatment outcome.

The role of a second dose of misoprostol in asymptomatic women with thickened endometrium following initial misoprostol treatment in the medical management of EPF is understudied. In the large randomized trial by Zhang et al. assessing the role of vaginal misoprostol in the treatment of EPF, a repeat 800 μg dose of misoprostol administered vaginally was given to patients in whom gestational sac or endometrial lining > 30 mm were visualized on day 3 following the initial treatment [9]. Following this approach, treatment success rate was increased from 71% on day 3 to 84% after a second dose was administered if needed [9]. In contrast, in a recent randomized trial, administration of a repeat dose of misoprostol among those with residual gestational sac or endometrial thickness > 15 mm at the first follow-up visit, did not improve success rates [10]. In both of these randomized trials, due to practical reasons, randomization occurred at study enrollment (day 1) and not at the first follow-up visit in which the decision regarding the administration of a repeat misoprostol dose was made. Moreover, as in these studies a second misoprostol dose was given to all patients with residual gestational sac, its effect in those with thickened endometrium alone could not be directly assessed. In the current retrospective study, the different protocols of care in the two institutions of our center, allowed us to evaluate the role of misoprostol specifically in those with residual endometrial thickness with no gestational sac present. The results of the aforementioned randomized studies coupled with the current study findings, which show no added benefit for repeat misoprostol administration in those with residual endometrial thickness, suggest that a second dose of misoprostol is beneficial only in those with a residual gestational sac. With this regard, in the recent PreFaiR study, which assessed the role of mifepristone pretreatment prior to misoprostol in the management of EPF, a second dose of misoprostol was offered only to those women with gestational sac present following the initial dose [13]. In addition, repeat misoprostol administration is not without risks and was previously shown to be associated with higher degree of pain [10, 14], which further supports avoiding its use in a setting where its utilization does not confer any benefit. Obviously, a repeat dose protocol also involves higher costs for medications, medical staff and facilities and potentially increased rate of related adverse events.

Understanding the relationship between endometrial thickness and treatment outcome in the setting of EPF is of paramount importance. Previous studies have demonstrated a wide variation in endometrial thickness after expulsion of the gestational sac [15]. Moreover, in the current literature, there is considerable inconsistency regarding the definition of incomplete expulsion of pregnancy tissue in the absence

of gestational sac following initial medical treatment of EPF [9, 10, 14, 16–21]. Nevertheless, in all these studies, no correlation was found between the need for subsequent surgical intervention and increased endometrial thickness [15, 19], which generally decreased spontaneously and uneventfully with time [9, 15, 22]. It is worth noting, that even endometrial thickness above 30 mm was not a reliable predictor of D&C in a previous report [19]. The lack of association of endometrial thickness with management outcome demonstrated in these studies, even when higher cutoff values (> 20 mm) were used, along with the current study results, call into question the use of any cutoff values for universally defining incomplete abortion, and precludes the need of an additional treatment in those with thickened endometrium to improve patient outcomes. Thus, for women choosing medical management of EPF, the use of ultrasonography for any diagnostic purpose other than confirming expulsion of the gestational sac is not recommended, and once expulsion of the gestational sac has been confirmed, endometrial thickness should not be used to guide decision making [5, 18].

The retrospective design subjects this study to biases inherent to such data collection including the lack of randomization and involvement of different operators. In addition, the current investigation might lack statistical power to demonstrate clinically relevant differences in infrequent outcomes. Moreover, baseline characteristics were similar between the groups in both institutions; nevertheless, we could not exclude the possibility that other additional parameters (e.g., endometrial vascularity) could account for the current study findings. Finally, as the study was conducted in a single medical center, it may limit the generalizability of the current study findings. On the other hand, the relatively large sample size and the standardized treatment protocol represent the main strengths of our study. Moreover, as the decision regarding repeat misoprostol administration strictly followed the local protocol in each institution, the potential for selection bias is minimal. Future prospective studies are warranted to confirm our findings, identify those who are most likely to benefit from a repeat misoprostol dose, and better delineate and tailor the optimal management approach for those with thickened endometrium. Given that the condition studied is not uncommon, performing such a study would be feasible.

In conclusion, this study shows that repeat misoprostol dose among women with thickened endometrium 2 days following initial misoprostol administration for EPF, is not associated with improved treatment success rates. The findings of the current study, together with those of previous studies showing that endometrial thickness is not a useful clinical predictor of subsequent surgical intervention, provide further support against the administration of a repeat misoprostol dose in those with thickened endometrial lining at the first follow-up visit following the initial treatment. Furthermore, follow-up ultrasound examination for women choosing medical management of EPF should not be used for purposes other than documenting the absence of a gestational sac.

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Author contributions AR: project development, data collection, data analysis, manuscript writing. GL and SY: manuscript writing/editing. SP: data collection and management, manuscript writing/editing. AB: project development and manuscript writing. All the authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have nothing to disclose and that they have no financial or non-financial conflict of interest.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local institutional review board of Hadassah Medical Center Helsinki Committee (IRB Approval No. HMO 0157-18).

References

1. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE et al (1988) Incidence of early loss of pregnancy. N Engl J Med 319:189–194
2. Wang X, Chen C, Wang L, Chen D, Guang W, French J (2003) Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril 79:577–584
3. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG (1996) Estimates of human fertility and pregnancy loss. Fertil Steril 65:503–509
4. Alberman E (1992) Spontaneous abortions: epidemiology. In: Stabile I, Grudzinskas G, Chard T (eds) Spontaneous abortion: diagnosis and treatment. Springer- Verlag, London, pp 19–20
5. ACOG practice bulletin No. 200: Early Pregnancy Loss. Obstet Gynecol. 2018;
6. Neilson JP, Hickey M, Vazquez JC (2006) Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD002253.pub3
7. Graziosi GC, Bruinse HW, Reuwer PJ, van Kessel PH, Westerweel PE, Mol BW (2005) Misoprostol versus curettage in women with early pregnancy failure: impact on women's health-related quality of life: a randomized controlled trial. Hum Reprod 20(8):2340–2347
8. Graziosi GC, Bruinse HW, Reuwer PJ, Mol BW (2006) Women's preferences for misoprostol in case of early pregnancy failure. Eur J Obstet Gynecol Reprod Biol 124(2):184–186
9. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM (2005) A comparison of medical management with misoprostol and surgical management for early pregnancy failure: National Institute of Child Health Human Development (NICHD) Management of Early Pregnancy Failure Trial. N Engl J Med 353:761–769

10. Mizrachi Y, Dekalo A, Gluck O, Miremberg H, Dafna L, Feldstein O, Weiner E, Bar J, Sagiv R (2017) Single versus repeat doses of misoprostol for treatment of early pregnancy loss—a randomized clinical trial. Hum Reprod 32:1202–1207
11. Doubilet PM, Benson CB, Bourne T et al (2013) Diagnostic criteria for nonviable pregnancy early in the first trimester. N Engl J Med 369:1443–1451
12. CDC/NHSN surveillance definitions for specific types of infections. Available at: https://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf. Accessed 22 Dec 2018
13. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT (2018) Mifepristone pretreatment for the medical management of early pregnancy loss. N Engl J Med 378(23):2161–2170
14. Fernlund A, Jokubkiene L, Sladkevicius P, Valentin L (2018) Misoprostol treatment vs expectant management in women with early non-viable pregnancy and vaginal bleeding: a pragmatic randomized controlled trial. Ultrasound Obstet Gynecol 51(1):24–32
15. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J (2004) Endometrial thickness after misoprostol use for early pregnancy failure. Int J Gynaecol Obstet 86(1):22–26
16. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, Schiff E, Seidman DS (2006) A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertil Steril 86(4):956–960
17. Bagratee JS, Khullar V, Regan L, Moodley J, Kagoro H (2004) A randomized controlled trial comparing medical and expectant management of first trimester miscarriage. Hum Reprod 19:266–271
18. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne T (2002) Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ 324:873–875
19. Reeves MF, Lohr PA, Harwood BJ, Creinin MD (2008) Ultrasonographic endometrial thickness after medical and surgical management of early pregnancy failure. Obstet Gynecol 111:106–112
20. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O (2002) Management of missed abortion: comparison of medical treatment with either mifepristone + misoprostol or misoprostol alone with surgical evacuation: A multi-center trial in Copenhagen County. Denmark. Acta Obstet Gynecol Scand. 81:1060–1065
21. Ravn P, Rasmussen A, Knudsen UB, Kristiansen FV (2005) An outpatient regimen of combined oral mifepristone 400 mg and misoprostol 400 microg for first-trimester legal medical abortion. Acta Obstet Gynecol Scand 84(11):1098–1102
22. Creinin MD, Huang X, Westhoff C, Barnhart K, Gilles JM, Zhang J (2006) Factors related to successful misoprostol treatment for early pregnancy failure. Obstet Gynecol 107(4):901–907