Mifepristone followed by misoprostol for uterine evacuation in early pregnancy failure: a randomized, double blinded, placebo controlled pilot study.

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Abstract

Background: to analyze feasibility and optimize the final protocol testing the hypothesis that in early pregnancy failure (EPF) pre-treatment with mifepristone followed by misoprostol (M&M) is superior to placebo followed by misoprostol (P&M) in terms of complete evacuation.

Methods: two-centered, randomized, double-blinded, placebo-controlled trial at the Radboud University Medical Centre and Canisius-Wilhelmina Hospital, the Netherlands. Forty women with a diagnosis of EPF between 6-14 weeks of gestation were included after at least one week of expectant management. Women were randomized between pre-treatment (day one) with mifepristone 600mg or placebo, both followed by two doses of misoprostol 400µg on day three and on day four. Ultrasonography one week after treatment determined treatment effect. Three digital questionnaires about quality of life and patient satisfaction were sent.

Results: this pilot study confirmed feasibility of the study protocol. Complete evacuation was achieved in 68,4% in M&M versus 40% in P&M (p 0.057). The need for curettage in M&M was 10,5% compared to 50% in P&M (p 0.044). No serious adverse events were reported in either group. Quality of life was similar in both groups. The majority of women, 84,6%, in the M&M group versus 62,6% of women in the placebo group, would choose medical treatment again.

Conclusion: in case of early pregnancy failure, M&M appears more effective than treatment with misoprostol alone. This pilot study protocol reassured the methodology to confirm these findings by a large, prospective, randomized, and double-blinded trial, starting first half of 2018.

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Keywords: Early pregnancy failure, mifepristone, misoprostol, miscarriage, medical treatment.

Background

Approximately 15% of all pregnancies before 14 weeks end up in early pregnancy failure (EPF).[1] In the Netherlands, approximately 10,000 women per year undergo surgical or medical treatment after a minimum of one week expectant management (as prescribed in national guidelines) in order to give 50% spontaneous removal of products of conception from the uterus a chance.[2, 3] Surgical treatment is associated with risks of complications (0.01-1.2%; pelvic infection, cervical injury, uterine perforation, intra-uterine adhesions, excessive bleeding, anaesthesia, cervical insufficiency in following pregnancies) and costs.[4-6] Misoprostol, a synthetic prostaglandin E1 analogue, is widely used in the management of EPF.[7, 8] In the Netherlands, treatment is started after a minimum of one week of expectant management.[2, 3, 9] Therefore, because of selection, success rates of misoprostol treatment in the Netherlands are lower compared to the 84% reported by Zhang et al. treating women directly after diagnosis.[10] So, in the Netherlands, circa 50% of the women may still need a form of additional treatment due to retained products of conception.[9, 11] Intravaginal application of one or two doses of misoprostol 800 µg is most often prescribed. However, up to 23 different treatment regimens (dosages and routes of administration) are applied.[12]

A new medical treatment option combining mifepristone, an anti-progesterone and anti-glucocorticoid drug, followed by misoprostol (M&M treatment) seems more effective.[11, 13] Mifepristone increases the production of endogenous prostaglandin by the endometrium, as well as the sensitivity of the gravid uterus to exogenous prostaglandin, thus causing contractility of the myometrium, cervical softening and dilatation.[14, 15] Mifepristone is effective for medical termination of vital pregnancies and preparation for surgical abortion in first trimester, and labor induction in fetal death in utero in second and third trimester.[16] It appears reasonable to hypothesize that, also for EPF, the sequential combination of mifepristone and misoprostol may be superior to misoprostol alone.[11, 13, 14]

A randomized, double blinded, placebo-controlled trial with a sufficient number of patients is required to test the hypothesis that the sequential combination of mifepristone with misoprostol is superior to misoprostol alone in case of EPF.[11, 13] The aim of this pilot study is to test feasibility and recruitment in order to improve quality of the final protocol of a larger study.[17]

Methods

A two-centred, prospective, two-armed, randomized, double blinded and placebo-controlled pilot trial was performed, situated in an academic (Radboud University Medical Centre) and a teaching hospital (Canisius-Wilhelmina Hospital) in Nijmegen, the Netherlands, between October 2016 and May 2017. The aim of the pilot study was to test feasibility and logistics and to test recruitment pace for a larger study. We expect to achieve these results after inclusion of forty women. Participants were followed in an outpatient clinic; hospital admission followed only if medically necessary. Ethics approval was obtained; CMO Arnhem-Nijmegen, file number 2015-2264, NL 57892.091.16.

Patient selection and randomization

Woman with a diagnosis of EPF between 6 and 14 weeks of gestation were eligible, defined by transvaginal ultrasonography as an intra-uterine pregnancy and a crown-rump length ≥ 6 mm and no cardiac activity, or a gestational sac without embryonic pole confirmed by a second ultrasound at least one week later. Women could be included one week after diagnosis or immediately in case of a discrepancy of at least one week between crown-rump length and calendar gestational age because

of an expected spontaneous complete evacuation rate of around 50% during the first week after diagnosis.[3] Exclusion criteria were age < 18 years, hemodynamic instability, sign of infection, incomplete miscarriage, high risk of thrombosis, contra-indications for mifepristone or misoprostol, interaction between study-medication and other medication or the inability to give informed consent.

A computerized randomization list was prepared by an independent medical doctor not connected to the trial. Participants were randomized in a 1:1 ratio to mifepristone or placebo using computerized randomization tables. The randomization was conducted using block randomization (blocks of 4) and was stratified by hospital to prevent any imbalance between groups in aspects of maternal care that may differ between centres.

Medication

The study medication, mifepristone and placebo tablets, was supplied by Exelgyn (Groupe Nordic Pharma) as an unconditional grant. The university hospital pharmacy of the Radboud University Medical Centre (Nijmegen) was responsible for the shipment, receipt, labelling, disposition, return and destruction of the investigational medicinal products. The pharmacy was also responsible for delivery of the products to pharmacies of both participating hospitals. Misoprostol, part of the standard treatment was provided by local pharmacies.

Treatment protocols

After verbal and written informed consent and randomization, each patient received three blinded tablets containing 200 mg mifepristone each or placebo (day 1). The mifepristone tablets and placebo were identical in appearance so neither the patient nor the physician knew which product was taken. Both groups took the standard treatment with misoprostol at day three: two doses of misoprostol 400 µg orally (four hours apart). If no tissue was lost by day four, again two doses of misoprostol 400 µg orally (four hours apart) were taken. A transvaginal ultrasonography was performed six to nine days after treatment. Women were asked to document the amount of misoprostol tablets taken each day and possible side effects using a registration form (diary). Standard, validated questionnaires were sent by e-mail. The blinding of patients and physicians for treatment arm was maintained until the follow-up (questionnaire four weeks after treatment) of the last included patient was completed.

Outcome measures

Primary and secondary outcome measures were extracted from the patient medical record, diary, digital questionnaires and/or case report form. The primary outcome parameter, complete (success) or incomplete (failure) evacuation, was determined by transvaginal ultrasonography one week (six to nine days) after medical treatment. Expulsion of the gestational sac and an endometrial thickness < 15 mm (maximum anterior-posterior diameter) using only the allocated therapy by randomization was considered as complete evacuation.[7, 9, 18-20] D&C performed because of heavy vaginal bleeding during medical treatment was also considered as failure.

Secondary outcome parameters included complications, side effects and patient satisfaction. Each patient received a registration form (diary) to document the amount of misoprostol tablets taken and possible side effects. The treating gynaecologist documented complications and side effects using the case report form (CRF). Quality of life was measured at baseline, four days and four weeks after treatment started using standard, validated questionnaires: EuroQol-VAS and Short Form 36. Patient satisfaction with treatment was measured four weeks after treatment using the Client Satisfaction Questionnaire (CSQ-8).

Statistical analyses

Data were analysed according to intention to treat method. The main outcome variable was complete evacuation after medical treatment and was assessed by calculating success rates, relative risks and 95% confident intervals in both groups. To evaluate the potential of each of the strategies, we also performed a per protocol analysis, taking into account only those cases that were treated according to protocol.

SPSS version 24 was used for data analysis. Differences between groups were analysed using the Pearson's chi-square test or the Fisher's exact test for categorical variables. Mann-Whitney U test was used for non-normally distributed metric variables. Logistic regression analysis was performed to identify factors that were associated with treatment success. P-values smaller than 0.05, were considered significant.

Results

Forty women were included and randomized: twenty women were allocated to mifepristone and twenty to placebo (figure 1). Women were included in two hospitals within seven months, leading to an inclusion-rate of 0.9 women per week.

Since both arms were followed by misoprostol, treatment arms will further be called as "M&M" and "placebo" group. Baseline characteristics of the two groups were comparable (e.g. not significant, table 1). One woman in the M&M group was excluded post-randomization because she did not meet the inclusion criteria, which was only detected after randomization. She was included after only one day of expectant management instead of at least one week. So, 39 women were included in the intention to treat analysis.

Table 1: baseline characteristics.

Baseline characteristics	M&M N=19	Placebo N=20	P-value
Age (years) - Mean (SD) - Range - Unknown	 30,53 (5,274) 21 – 39 0	 32,00 (2,772) 28 –37 0	 0.288
Diagnosis - Embryo without cardiac activity - Anembryonic gestation	 13 6	 17 3	 0.219
Gestational age based on amenorrhea (days) - Mean (SD) - Range - Unknown	 73,76 (11,503) 56 – 96 2	 73,50 (10,541) 56 – 100 0	 0.760
Gestational age based on ultrasound (days) - Mean (SD) - Range - Unknown	 52,05 (10,799) 36 – 78 0	 49,00 (7,688) 38 – 64 1	 0.438
Duration expectant management (days) - Mean (SD) - Range - Exact period unknown	 20,94 (12,235) 7 – 53 2	 24,21 (9,953) 12 – 50 1	 0.302

Number of previous pregnancies - 0 - 1 - ≥2	 8 5 6	 10 4 6	0.857
Parity - 0 - 1 - 2	 12 6 1	 11 5 4	0.361
Prior miscarriage - Yes - No	 8 12	 6 14	0.507
Prior misoprostol treatment - Yes, successful - Yes, unsuccessful - No	 2 (N=8) 0 6 (N=8)	 1 (N=6) 0 5 (N=6)	1.000

Two women, one in each arm, who gave informed consent, experienced spontaneous miscarriage before medical treatment started. In the M&M group, one woman, who was included after informed consent, changed her mind afterwards and did not take the study medication. Another woman in the M&M group was not treated conform treatment protocol; she inserted misoprostol vaginally (two doses of 800 µg) 22 hours after taking the study medication instead of swallowing misoprostol orally (400 µg) 36-48 hours later. So, taken into account two spontaneous miscarriages and two protocol deviations, 35 women were treated conform study protocol and included in per protocol analysis.

One woman in the M&M group did not show up at the appointment six to nine days after treatment; she visited the hospital five weeks later and underwent transvaginal ultrasonography showing an endometrial thickness < 15mm without additional therapy. In the placebo group, one woman had an ultrasound at day 4 because she didn't want to wait any longer. A gestational sac was still intra-uterine; D&C was performed at day 11. The mean time between the start of medical treatment and performing ultrasonography to determine treatment success was 9.37 days (range 3 – 34 days).

In the M&M group, 13/19 (68,4%) had a complete evacuation one week after medical treatment. In the placebo group, 8/20 (40,0%) had a complete evacuation after one week (p 0.057, table 2). In addition to intention-to-treat analysis, per protocol analysis revealed success rates of 10/16 (62,5%) in the M&M group versus 7/19 (36,8%) in the placebo group (p 0.139). No differences in primary outcome were observed after adjusting for the difference between ultrasound gestational age, duration of expectant management, parity, prior miscarriages or prior successful misoprostol treatment.

Table 2: complete evacuation rates.

Complete evacuation rates	**M&M group, n/N (%)**	**Placebo group, n/N (%)**	**P value**
Complete evacuation rate, total	13/19 (68,4)	8/20 (40)	0.057
Anembryonic gestation	4/6 (66,7)	2/3 (66,7)	1.000
Embryo without cardiac activity	9/13 (66,7)	6/17 (35,3)	0.070

At the time of determining the main study outcome and the need for additional treatment in case of an incomplete evacuation (one week after treatment), physician and patient were both still blinded. In total, 18 women underwent additional treatment and reached complete evacuation afterwards

(table 3). In 1/19 (5,2%) of the M&M group versus 9/20 (45%) of the placebo group a gestational sac was still intrauterine, concluding that medical treatment has had no effect at all. Five women (5/18, 27,8%) reached complete evacuation after expectant management until approximately six weeks after treatment. Two women were treated with misoprostol treatment again and received two more doses of misoprostol (800 µg vaginally), of which one woman (placebo group) underwent emergency D&C because of heavy vaginal bleeding after the second misoprostol treatment. The need for D&C was significantly lower in the M&M group as compared to the placebo group: 2/19 (10,5%) versus 10/20 (50%) respectively (p 0.008, RR 1.789, 95% CI 1.124-2.848). D&C was mainly performed (8/12, 66,7%) because of a persistent intrauterine gestational sac, this was significantly different between both groups: only one woman in the M&M group versus seven women in the misoprostol group (p 0.044). Three women in the placebo group needed D&C because of heavy vaginal bleeding, of which one woman underwent D&C at day three because of heavy vaginal bleeding (750 cc) and sonographic retained products of conception. Another woman was scheduled for D&C a few days after determining the main study outcome, however, in the meantime she underwent emergency D&C because of heavy vaginal bleeding. Also, per protocol analysis revealed a significant difference between the need for D&C in the M&M and placebo group: 2/16 (12,5%) versus 10/19 (52,5%, p 0.013).

Table 3: additional treatment resulting in complete evacuation.

Additional treatment	**M&M group, n/N (%)**	**Placebo group, n/N (%)**	**P value**
Expectant management	4/19 (21,2)	1/20 (5)	0.134
- Residua	4/4 (100)	-	-
- Persistent gestational sac	-	1/1 (100)	-
Medical treatment	0/19 (0)	1/20 (5)	-
- Persistent gestational sac	-	1/1 (100)	-
D&C	2/19 (10,5)	10/20 (50)	0.008
- Residua	1/2 (50)	0/100 (0)	0.487
- Persistent gestational sac	1/2 (50)	7/10 (70)	0.044
- Haemorrhage	-	3/10 (30)	0.23

During treatment, women in the M&M group reported significantly more blood loss than women in the placebo group (p 0.007, figure 2). In the M&M group, 15/19 (78,9%) described their blood loss as “more than a menstruation” and 1/19 (5,3%) as “less than a menstruation”. In the placebo group, 8/20 (40%) classified their blood loss as “more than a menstruation” and 9/20 (45%) as “less than a menstruation”. However, one week later, during follow-up, this difference was no longer seen (p 0.081). The bleeding had stopped or was described as less than a menstruation in the M&M group in 16/18 (84,2%) and in the placebo group in 14/20 (70%). No blood transfusions during treatment and follow-up were needed.

Side effects in both groups were mainly experienced at day three and four during misoprostol treatment (figure 2). Nausea and gastrointestinal side effects were most reported in both groups. Concerning the reported side effects, only dizziness was significantly higher in the placebo group (p 0.047). The use of analgesics was not significant different between both groups.

Client satisfaction questionnaire

In total, 115 digital questionnaires were sent of which 75,4% in the M&M group, and 89,7% in the placebo group were completed. Women in both groups were equally satisfied with medical treatment (figure 3). In case of EPF, 11/13 (84,6%) women in the M&M group versus 10/16 (62,6%) women in

the placebo group would choose the same treatment again. In the M&M group 12/13 (92,3%) and in the placebo group 12/16 (75%) would recommend medical treatment to a friend in case of EPF.

Short Form-36 and EuroQol visual analogue scale

Health related quality of life, measured using short-form 36 (SF-36) and EuroQol-VAS as baseline, four days and four weeks after treatment started, was not significant different between the M&M and placebo group. In both groups, six dimensions of SF-36 were significantly different over time, and were most impaired four days after treatment (figure 4). Mental health, general health and general health change were not significant different over time. In the M&M group, no significant differences in health dimensions were seen between successful and unsuccessful treatment. Women in the placebo group with an unsuccessful treatment had significantly more pain, more impaired physical functioning and lower scores at the EuroQol-VAS compared to women with a successful treatment.

Discussion

Main findings

This randomized, double blinded, placebo controlled pilot study was designed to prepare for a sufficiently powered definitive trial. Accrual of study patients was as expected with completion of forty patients within seven months in one academic and one teaching hospital in the Netherlands. This pilot clinical trial showed an inclusion rate as expected, and almost no data loss: only one patient didn't show up at the follow-up appointment.

Complete evacuation measured one week after treatment was not significantly different: 68,4% (M&M) versus 40% (placebo). The need for D&C after medical treatment was significantly different: 10,5% versus 50%. A significant difference was reported between the incidence of persistent gestational sac: 1 woman in the M&M group versus 9 women in the placebo group. No serious adverse events were reported. More than 80% of the digital questionnaires were completed. Concerning patient preference, 84,6% (M&M) versus 62,6% (placebo) of the women would choose medical treatment again and 92,3% (M&M) versus 75% (placebo) would recommend medical treatment to a friend in case of EPF.

Strengths and Limitations

This pilot study was randomized, double blinded and placebo controlled. Baseline data showed no significant differences between both treatment groups. Primary and secondary outcome were objective and clearly defined. Of course, its small number of patients limits this *pilot* study aiming at a sufficiently powered RCT.

Interpretation

M&M has been studied before in retrospective and anecdotal trials.[1, 6, 21-27] In a systematic review published by our research group, data of sixteen studies were extracted.[13] Success rates varied between 52% and 95%. Unfortunately, large heterogeneity existed in treatment regimens between studies. Since our review, another four trials concerning M&M treatment in case of EPF were published.[28-31] A randomized double-blind placebo controlled trial concluded that M&M significantly increased the complete evacuation rate from 58% to 87%.[30] The need for surgical intervention was significantly reduced (from 42% to 13 %), and also side effects were significantly lower in women receiving mifepristone pre-treatment. However, treatment was started directly after diagnosis without one week of expectant management. A randomized trial by Schreiber reported a complete expulsion rate of 84 % with versus 67% without mifepristone pre-treatment. Unfortunately, inevitable and incomplete miscarriages were also included, and the trial was not placebo-controlled,

and a lower dose of mifepristone (200mg) was used.[31] In two retrospective studies, high efficacy rates of 82 and 92% were demonstrated.[28, 29] Unfortunately, the amount of patients enrolled in the first study was too low to draw firm conclusions. Both studies are limited by the lack of randomization.

Until now, mifepristone 200mg is advised by the World Health Organization (WHO) in case of termination of a vital pregnancy in the first trimester.[32] However, phase 2 trials have shown that 600 mg mifepristone was superior to the 200 mg dose in terms of complete abortion in case of medical abortion of a vital pregnancy (89% versus 63%).[33, 34] A Cochrane review included only one trial comparing low and high doses of mifepristone in case of medical abortion, reporting no significant difference in failure (91% vs 91%) and side effects.[35, 36] Studies directly comparing low and high doses of mifepristone in case of EPF do not exist up until now. Potentially, the reaction of the uterus after administration of mifepristone is different in non-vital pregnancies compared to vital pregnancies. A dose of mifepristone 600 mg was used before in several studies, concluding that it is a safe treatment option accompanied with low rates of complications and side effects. However, the authors highlighted the need for large randomized trials to further evaluate the success of the combination of mifepristone and misoprostol, as well as to define the optimal dosing and routes of administration.[13, 24, 28, 37] To achieve the most optimal effect, and because of a superior effect of 600 mg mifepristone in phase 2 trials with a comparable incidence of side effects, a dose of 600 mg mifepristone was used in our pilot trial. The effect of mifepristone develops over a time period of 24-48 hours; therefore prostaglandins were administered 36-48 hours later.[14, 35]

Misoprostol is part of the standard treatment; different treatment regimens (dose and route of administration) are described in literature. The International Federation of Obstetrics and Gynaecology (FIGO) advises misoprostol 800 µg per vaginam every 3 hours (maximum of 2 doses) or 600 µg sublingual every 3 hours (maximum of 2 doses).[32] However, recent reviews all conclude that further research is necessary to determine the most optimal treatment regimen.[38-40] Oral misoprostol leads to a more rapid absorption and higher peak levels compared to vaginal application, but plasma concentration may drops sooner.[41] Gastrointestinal side effects are dose and interval dependent.[41, 42] Although one would suspect that oral misoprostol leads to more side effects due to higher peak concentrations, a similar incidence of vomiting, nausea, diarrhoea and fever was found in a recent Cochrane review.[43] However, it should be mentioned that the quality of evidence is low. In contrast to this recent review regarding EPF, reviews including incomplete miscarriages or termination of vital pregnancies in the first trimester, report significantly more nausea and diarrhoea after oral misoprostol.[35, 44] Regarding effectiveness, a Cochrane review reported that misoprostol 800 µg orally is equally effective compared to misoprostol 800 µg vaginally.[1, 43] A split dosage of misoprostol (two or three doses of 400 µg) has been reported to be similar in success rates as a protocol using 800 µg at once.[35, 43] However, the mean time to expulsion was longer after oral intake of misoprostol compared to vaginal application.[45, 46] Clinical studies comparing oral and vaginal misoprostol have found increased patient satisfaction with the oral route because it is easy to use and more convenient to administer.[47, 48] Taken all this together, we have chosen oral administration of misoprostol because it appears equally effective compared to vaginal application, is easy to use, and may be preferred by patients. Since a split-dose regimen is equally effective, and may lead to a lower incidence of side effects, we have chosen a split dose of misoprostol 400 µg. Since misoprostol treatment was similar in both groups, this could not have influenced the difference in effectiveness between both groups.

With regards to the follow-up of women receiving medical treatment: there are no clear recommendations about the time period and optimal diagnostic tool to define success. Assessment

after one week was common practice in the Netherlands at the time of drafting the study protocol ~~(J. van den Berg, Dutch survey 2017, unpublished data)~~.[49] As reported in our results section, there was a significant difference in persistent intrauterine gestational sac one week after treatment between both groups. Therefore, performing ultrasonography shortly after medical treatment (one or two weeks) is important to determine treatment failure, and to offer further treatment to patients on short-term.

Recent studies do not provide any clear evidence which ultrasonographic criteria (endometrial thickness) correspond best to the presence of intrauterine pregnancy remnants.[50, 51] A study by Rulin et al. concludes that in case of a maximum anterior-posterior diameter of 15 mm or less, retained products are less likely to be confirmed histologically.[18] Also a recent study by Lavecchia et al demonstrated that in women with a cavity anterior-posterior distance of less than 15 mm, 87.1% did not need D&C afterwards.[19] In contrast, a study by Creinin et al. reported a wide range of endometrial thickness (1-31 mm) two weeks after expulsion of the gestational sac and a decreasing endometrial thickness over time, suggesting that clinical signs and symptoms should guide treatment decisions after medical treatment instead of anterior-posterior diameter.[52]

Evidence is growing that D&C may have major long-term consequences such as intra-uterine adhesions and increased spontaneous preterm birth rates in subsequent pregnancies.[9, 53, 54] The recent Dutch "MisoREST" study compared D&C and expectant management in case of an incomplete evacuation after misoprostol treatment defined as intra-uterine remnants at ultrasonography or an anterior-posterior diameter exceeding 10 mm.[50] These authors conclude that expectant management should be considered as first line treatment in women with incomplete evacuation after misoprostol treatment for EPF.[55] As a result of the aforementioned, we have made suitable adjustments in the definitive protocol concerning the primary endpoint.[17]

Practical and research recommendations

The following recommendations for improvement of the definitive study protocol for a multicenter, randomized, double-blinded and placebo controlled trial were made:[17]

- Two weeks after medical treatment: ultrasonography to evaluate the uterine cavity shortly after medical treatment.
    - No gestational sac and total endometrial thickness < 15mm: complete evacuation. No further evaluation necessary.
    - Suspected intra-uterine remnants > 15 mm without gestational sac: expectant management. Clinical signs and symptoms should guide treatment decisions during four weeks. In case of asymptomatic patients, no additional examination or treatment is necessary until six weeks after treatment. Additional treatment could be necessary in case of: no reaction after treatment (no bleeding or tissue loss), heavy or continuous bleeding, persistent abdominal pain, intra-uterine infection or on patient request.
- Six weeks after treatment: ultrasonography, counselling for surgical management (e.g. hysteroscopy) in case of intra-uterine remnants.

Conclusion

The sequential combination of mifepristone and misoprostol in case of early pregnancy failure appears more effective than treatment with misoprostol alone regarding complete evacuation after one week. This pilot study protocol reassured the methodology to confirm these findings by a large, prospective, randomized, and double-blinded trial, which started second half of 2018.

Abbreviations
EPF early pregnancy failure
D&C dilatation and curettage
M&M treatment mifepristone followed by misoprostol
CRF case report form
CSQ Client Satisfaction Questionnaire
WHO World Health Organization
FIGO Federation of Obstetrics and Gynaecology

Declarations

Ethics approval and consent to participate
Ethics approval was required for this study, and obtained by CMO Arnhem-Nijmegen (file number 2015-2264).

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
JB, MS, SC and FV conceived and developed the idea for the article. JB and MS were mainly responsible for the acquisition and analysis of the data. All authors took part in drafting the article or revising it for critically important intellectual content and all gave final approval of the version to be published.

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References

1. Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). Cochrane Database Syst Rev. 2009; 3:CD002253.
2. NHG-Standaard Miskraam (Derde herziening). [https://www.nhg.org/standaarden/volledig/nhg-standaard-miskraam]

3. Luise C, Jermy K, May C, Costello G, Collins WP, Bourne TH. Outcome of expectant management of spontaneous first trimester miscarriage: observational study. BMJ. 2002; 324(7342):873-875.
4. You JH, Chung TK. Expectant, medical or surgical treatment for spontaneous abortion in first trimester of pregnancy: a cost analysis. Hum Reprod. 2005; 20(10):2873-2878.
5. Soulat C, Gelly M. [Immediate complications of surgical abortion]. Journal de gynecologie, obstetrique et biologie de la reproduction. 2006; 35(2):157-162.
6. Niinimaki M, Jouppila P, Martikainen H, Talvensaari-Mattila A. A randomized study comparing efficacy and patient satisfaction in medical or surgical treatment of miscarriage. Fertility and sterility. 2006; 86(2):367-372.
7. . In: *Ectopic Pregnancy and Miscarriage: Diagnosis and Initial Management in Early Pregnancy of Ectopic Pregnancy and Miscarriage.* edn. London; 2012.
8. Committee on Practice B-G. The American College of Obstetricians and Gynecologists Practice Bulletin no. 150. Early pregnancy loss. Obstetrics and gynecology. 2015; 125(5):1258-1267.
9. Graziosi GC, Mol BW, Reuwer PJ, Drogtrop A, Bruinse HW. Misoprostol versus curettage in women with early pregnancy failure after initial expectant management: a randomized trial. Hum Reprod. 2004; 19(8):1894-1899.
10. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. The New England journal of medicine. 2005; 353(8):761-769.
11. van den Berg J, van den Bent JM, Snijders MP, de Heus R, Coppus SF, Vandenbussche FP. Sequential use of mifepristone and misoprostol in treatment of early pregnancy failure appears more effective than misoprostol alone: a retrospective study. European journal of obstetrics, gynecology, and reproductive biology. 2014; 183:16-19.
12. Verschoor MA, Lemmers M, Wekker MZ, Huirne JA, Goddijn M, Mol BW, Ankum WM. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. Obstet Gynecol Int. 2014; 2014:387860.
13. van den Berg J, Gordon BB, Snijders MP, Vandenbussche FP, Coppus SF. The added value of mifepristone to non-surgical treatment regimens for uterine evacuation in case of early pregnancy failure: a systematic review of the literature. European journal of obstetrics, gynecology, and reproductive biology. 2015; 195:18-26.
14. Mifegyne 200 mg tablets: Summary of Product Characeteristics (SmPC) [https://www.exelgyn.com]
15. Mifepriston - Mifegyne [http://www.farmacotherapeutischkompas.nl]
16. Pharma N. Mifegyne (Mifepristone) - Scientific information and guide to use; 2010.
17. Van den Berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP. Mifepristone and misoprostol versus misoprostol alone for uterine evacuation after early pregnancy failure: a randomized double blinded placebo-controlled comparison (Triple M Trial). Unpublished work. 2019.
18. Rulin MC, Bornstein SG, Campbell JD. The reliability of ultrasonography in the management of spontaneous abortion, clinically thought to be complete: a prospective study. American journal of obstetrics and gynecology. 1993; 168(1 Pt 1):12-15.
19. Lavecchia M, Klam S, Abenhaim HA. Effect of Uterine Cavity Sonographic Measurements on Medical Management Failure in Women With Early Pregnancy Loss. J Ultrasound Med. 2016; 35(8):1705-1710.
20. Jauniaux E, Johns J, Burton GJ. The role of ultrasound imaging in diagnosing and investigating early pregnancy failure. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2005; 25(6):613-624.

21. Wagaarachchi PT, Ashok PW, Narvekar N, Smith NC, Templeton A. Medical management of early fetal demise using a combination of mifepristone and misoprostol. Hum Reprod. 2001; 16(9):1849-1853.
22. Gronlund A, Gronlund L, Clevin L, Andersen B, Palmgren N, Lidegaard O. 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 obstetricia et gynecologica Scandinavica. 2002; 81(11):1060-1065.
23. Coughlin LB, Roberts D, Haddad NG, Long A. Medical management of first trimester miscarriage (blighted ovum and missed abortion): is it effective? Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology. 2004; 24(1):69-71.
24. Stockheim D, Machtinger R, Wiser A, Dulitzky M, Soriano D, Goldenberg M, Schiff E, Seidman DS. A randomized prospective study of misoprostol or mifepristone followed by misoprostol when needed for the treatment of women with early pregnancy failure. Fertility and sterility. 2006; 86(4):956-960.
25. Schreiber CA, Creinin MD, Reeves MF, Harwood BJ. Mifepristone and misoprostol for the treatment of early pregnancy failure: a pilot clinical trial. Contraception. 2006; 74(6):458-462.
26. Kollitz KM, Meyn LA, Lohr PA, Creinin MD. Mifepristone and misoprostol for early pregnancy failure: a cohort analysis. American journal of obstetrics and gynecology. 2011; 204(5):386 e381-386.
27. Torre A, Huchon C, Bussieres L, Machevin E, Camus E, Fauconnier A. Immediate versus delayed medical treatment for first-trimester miscarriage: a randomized trial. American journal of obstetrics and gynecology. 2012; 206(3):215 e211-216.
28. Bouschbacher L, Maatouk A, Collin P, Welter E, Morel O, de Malartic CM. [Association of mifepristone and misoprostol for the medical management of early pregnancy failure]. Gynecologie, obstetrique & fertilite. 2014; 42(12):832-837.
29. Colleselli V, Nell T, Bartosik T, Brunner C, Ciresa-Koenig A, Wildt L, Marth C, Seeber B. Marked improvement in the success rate of medical management of early pregnancy failure following the implementation of a novel institutional protocol and treatment guidelines: a follow-up study. Archives of gynecology and obstetrics. 2016; 294(6):1265-1272.
30. Sinha P, Suneja A, Guleria K, Aggarwal R, Vaid NB. Comparison of Mifepristone Followed by Misoprostol with Misoprostol Alone for Treatment of Early Pregnancy Failure: A Randomized Double-Blind Placebo-Controlled Trial. J Obstet Gynaecol India. 2018; 68(1):39-44.
31. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. The New England journal of medicine. 2018; 378(23):2161-2170.
32. Misoprostol Recommendations. International Federation of Gynecology and Obstetrics (FIGO). [http://www.figo.org/publications/miscellaneous_publications/Misoprostol_Recommendation_2012]
33. Maria B, Chaneac M, Stampf F, Ulmann A. [Early pregnancy interruption using an antiprogesterone steroid: Mifepristone (RU 486)]. Journal de gynecologie, obstetrique et biologie de la reproduction. 1988; 17(8):1089-1094.
34. Grimes DA, Mishell DR, Jr., Shoupe D, Lacarra M. Early abortion with a single dose of the antiprogestin RU-486. American journal of obstetrics and gynecology. 1988; 158(6 Pt 1):1307-1312.
35. Kulier R, Kapp N, Gulmezoglu AM, Hofmeyr GJ, Cheng L, Campana A. Medical methods for first trimester abortion. Cochrane Database Syst Rev. 2011(11):CD002855.

36. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. World Health Organisation Task Force on Post-ovulatory Methods of Fertility Regulation. BJOG : an international journal of obstetrics and gynaecology. 2000; 107(4):524-530.
37. Colleselli V, Schreiber CA, D'Costa E, Mangesius S, Wildt L, Seeber BE. Medical management of early pregnancy failure (EPF): a retrospective analysis of a combined protocol of mifepristone and misoprostol used in clinical practice. Archives of gynecology and obstetrics. 2013.
38. Wu HL, Marwah S, Wang P, Wang QM, Chen XW. Misoprostol for medical treatment of missed abortion: a systematic review and network meta-analysis. Sci Rep. 2017; 7(1):1664.
39. Chen BA, Creinin MD. Medical management of early pregnancy failure: efficacy. Seminars in reproductive medicine. 2008; 26(5):411-422.
40. Doggrell SA. Misoprostol for the treatment of early pregnancy failure. Curr Clin Pharmacol. 2007; 2(1):1-9.
41. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol. 2009; 2(3):159-168.
42. Misoprostol as a single agent for medical termination of pregnancy [https://www.uptodate.com]
43. Verschoor MAC. Management of first trimester miscarriage; new insight in old dilemmas; 2017.
44. Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. Cochrane Database Syst Rev. 2017; 1:CD007223.
45. Marwah S, Gupta S, Batra NP, Bhasin V, Sarna V, Kaur N. A Comparative Study to Evaluate the Efficacy of Vaginal vs Oral Prostaglandin E1 Analogue (Misoprostol) in Management of First Trimester Missed Abortion. J Clin Diagn Res. 2016; 10(5):QC14-18.
46. Ngoc NT, Blum J, Westheimer E, Quan TT, Winikoff B. Medical treatment of missed abortion using misoprostol. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2004; 87(2):138-142.
47. Alfirevic Z, Weeks A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev. 2006(2):CD001338.
48. Ho PC, Ngai SW, Liu KL, Wong GC, Lee SW. Vaginal misoprostol compared with oral misoprostol in termination of second-trimester pregnancy. Obstetrics and gynecology. 1997; 90(5):735-738.
49. van den berg J, Hamel CC, Snijders MP, Coppus SF, Vandenbussche FP: Current and future expectations of mifepristone treatment in early pregnancy failure: a survey among Dutch gynecologists. *Accepted*. In. Journal of Obstetrics and Gynaecology; 2019.
50. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, Huirne JA, Janssen CA, Radder C, Klinkert ER *et al*. MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial. Hum Reprod. 2016; 31(11):2421-2427.
51. Debby A, Golan A, Sadan O, Rotmensch S, Malinger G. Sonographic characteristics of the uterine cavity following first-trimester uterine evacuation. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2008; 31(5):555-559.
52. Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J, Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2004; 86(1):22-26.
53. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, Mol BW, Huirne JA. Systematic review and meta-analysis of intrauterine

adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. Human reproduction update. 2013.
54. McCarthy FP, Khashan AS, North RA, Rahma MB, Walker JJ, Baker PN, Dekker G, Poston L, McCowan LM, O'Donoghue K *et al*. Pregnancy loss managed by cervical dilatation and curettage increases the risk of spontaneous preterm birth. Hum Reprod. 2013; 28(12):3197-3206.
55. Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Bossuyt PM, Huirne JA, Janssen IA, Radder C, Klinkert ER, Langenveld J *et al*. MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study. European journal of obstetrics, gynecology, and reproductive biology. 2017; 211:83-89.

Figure titles

Figure 1.

CONSORT flow diagram.

Figure 2.

Side effects during medical treatment.

*Defined by patients as more than a menstruation.

Figure 3.

Satisfaction with treatment.

Figure 4.

Dimensions of Short Form 36.