human reproduction

ORIGINAL ARTICLE *Early Pregnancy*

MisoREST: surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: a randomized controlled trial

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STUDY QUESTION: Is curettage more effective than expectant management in case of an incomplete evacuation after misoprostol treatment for first trimester miscarriage?

SUMMARY ANSWER: Curettage leads to a higher chance of complete evacuation but expectant management is successful in at least 76% of women with an incomplete evacuation of the uterus after misoprostol treatment for first trimester miscarriage.

WHAT IS KNOWN ALREADY: In 5–50% of the women treated with misoprostol, there is a suspicion of incomplete evacuation of the uterus on sonography. Although these women generally have minor symptoms, such a finding often leads to additional curettage.

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STUDY DESIGN, SIZE, DURATION: From June 2012 until July 2014, we conducted a nationwide multicenter randomized controlled trial (RCT). Women who had had primary misoprostol treatment for miscarriage with sonographic evidence of incomplete evacuation of the uterus were randomly allocated to either curettage or expectant management (1:1), using a web-based application.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We included 59 women in 27 hospitals; 30 were allocated to curettage and 29 were allocated to expectant management. A successful outcome was defined as sonographic finding of an empty uterus 6 weeks after randomization.

MAIN RESULTS AND THE ROLE OF CHANCE: Baseline characteristics of both groups were comparable. Empty uterus on sonography or uneventful clinical follow-up was seen in 29/30 women (97%) allocated to curettage compared with 22/29 women (76%) allocated to expectant management (RR 1.3, 95% CI 1.03–1.6) with complication rates of 10% versus 10%, respectively (RR 0.97, 95% CI 0.21–4.4). In the group allocated to curettage, no woman required re-curettage, while two women (6.7%) underwent hysteroscopy (for other or unknown reasons). In the women allocated to expectant management, curettage was performed in four women (13.8%) and three women (10.3%) underwent hysteroscopy.

LIMITATIONS, REASONS FOR CAUTION: Due to a strong patient preference, mainly for expectant management, the targeted sample size could not be included and the trial was stopped prematurely.

WIDER IMPLICATIONS OF THE FINDINGS: In women suspected of incomplete evacuation of the uterus after misoprostol, curettage is more effective than expectant management. However, expectant management is equally safe and prevents curettage for most of the women. This finding could further restrain the use of curettage in the treatment of first trimester miscarriage.

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Key words: abortion / miscarriage / uterus / surgery / expectant management

Introduction

Miscarriage, defined as the spontaneous loss of pregnancy before the foetus reaches viability, occurs in 10–15% of pregnant women (Regan, *et al.*, 1989). In the past, women diagnosed with a miscarriage in the first trimester of pregnancy were either managed expectantly, where complete expulsion of the products of conception is known to occur within 2 weeks in 50% of cases, or were offered curettage (Wieringa-de Waard, *et al.*, 2002, Graziosi, *et al.*, 2004, Ankum, 2008).

More recently medical treatment with misoprostol has been introduced as a third treatment option. It is non-invasive, inexpensive, available on demand, and easy to administer. Misoprostol has been shown to be effective in 50–95% of women with miscarriage (Bagratee, *et al.*, 2004, Graziosi, *et al.*, 2005, Zhang, *et al.*, 2005, Neilson, *et al.*, 2006, Trinder, *et al.*, 2006, Shankar, *et al.*, 2007, Ankum, 2008, Prasad, *et al.*, 2009). It is associated with high patient satisfaction rates and is cost-effective over immediate curettage (Graziosi, *et al.*, 2005, You and Chung, 2005, Petrou, *et al.*, 2006, Rausch, *et al.*, 2012).

A problem in the treatment with misoprostol is that 5–50% of the women show signs of an incomplete expulsion on sonographic follow-up (Creinin, *et al.*, 2004, Davis, *et al.*, 2007). Although these women generally have minor symptoms, this finding often leads to an additional curettage. Curettage could be unnecessary in these situations, as sonographic findings are given a higher priority than clinical symptoms, while expectant management might be uneventful in a majority of cases (Debby, *et al.*, 2008). This is of a concern, since curettage increases costs and bears the risk of both short- and long-term complications, including cervical tears, uterine perforation, infection, adhesions and an increased risk of subsequent preterm birth (Hooker, *et al.*, 2014, Lemmers, *et al.*, 2015).

We compared the effectiveness and safety of curettage versus expectant management in a randomized trial in women with an incomplete evacuation of the uterus after misoprostol therapy. Women who did not want to be randomized were treated according to their own preference and were asked for consent to take part in the observational study, which followed the same protocol. Here, we report on the results of the randomized women only.

Materials and Methods

Study design

We conducted a multicenter open label randomized controlled trial (RCT) in 27 hospitals within the Dutch consortium for research on women's health. The trial was registered in the Dutch trial registry as NTR3110. The original study protocol was published in May 2013 (Verschoor et al, 2013). http://www.biomedcentral.com/1471-2393/13/102. The protocol is also available through the study website: www.studies-obsgyn.nl/misorest.

The study was approved by the research ethics committee of the Academic Medical Centre (project number 2011-373) and by the board of directors of each of the participating hospitals. All patients gave informed consent. Patient level data are available from the corresponding author. Consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.
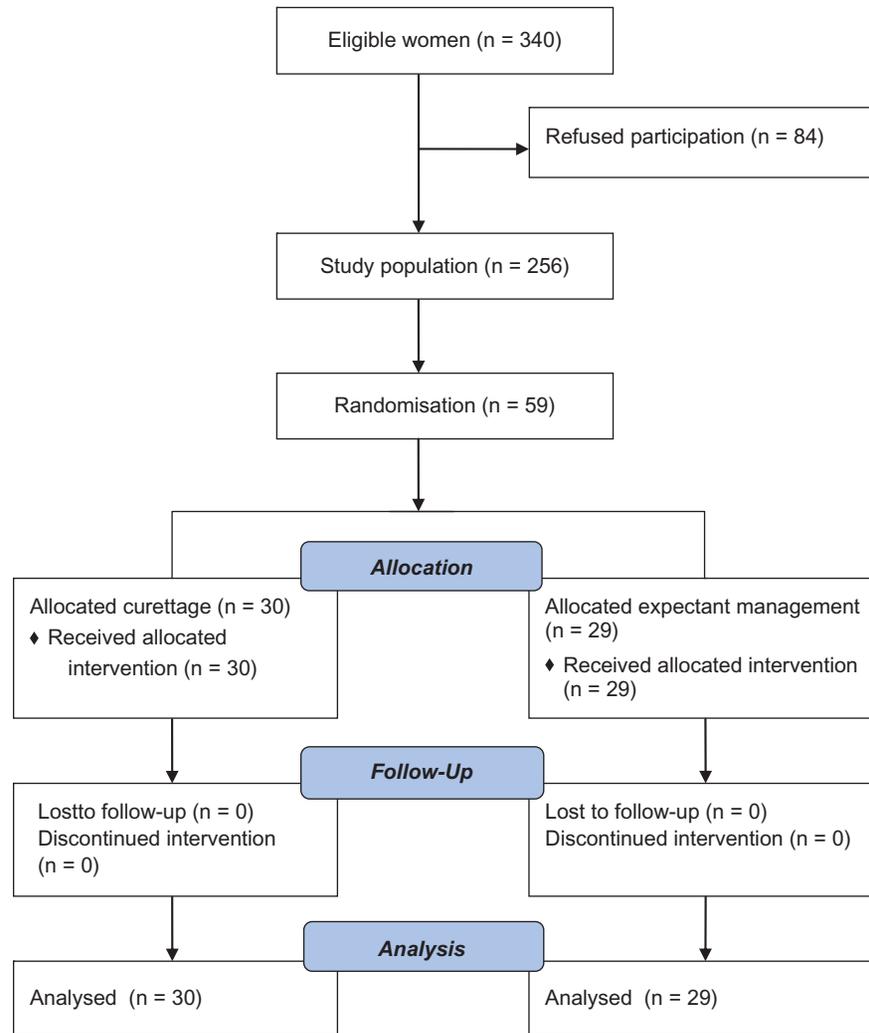
Figure 1 Flow diagram.

Eligibility criteria

Women with a first trimester miscarriage who had been treated with misoprostol and showing incomplete evacuation of the uterus at routine sonography one to 2 weeks after initial misoprostol treatment were eligible for the study. Incomplete evacuation was defined as sonographic evidence of intra-uterine remnants or an anterio–posterior (AP) diameter of the uterine cavity exceeding 10 mm. Exclusion criteria were age <18 years, severe vaginal bleeding or severe abdominal pain requiring immediate intervention, fever (>38°C) requiring antibiotic treatment and curettage, contraindications for curettage or a failed misoprostol-induced miscarriage as substantiated by the sonographic finding of an intact gestational sac still being present.

Eligible women were counselled by their doctors or by specialized research nurses. After written informed consent had been obtained, women were randomized to immediate curettage or expectant management.

Randomization procedure

We randomly assigned women to either expectant management or curettage (1:1), using the web-based application ALEA 2.0 with computer generated randomization lists. Blinding was not possible due to the nature of the intervention.

Procedures

Women allocated to curettage were scheduled for this procedure within three work days after randomization. Curettage was performed according to local hospital protocol, and could consist of a vacuum aspiration blunt curettage or sharp curettage. The procedure was performed in a daycare setting under general, regional or local anaesthesia.

Women allocated to expectant management received no further treatment. They were instructed to contact the hospital in case of excessive pain or blood loss, or fever.

All women were contacted by a research nurse 2 weeks after study entry. Transvaginal sonography was scheduled 6 weeks after study entry. In both study arms, a (re-)curettage was scheduled in cases where the sonographic follow-up 6 weeks after study was suspect for a pregnancy remnants and/or AP diameter of the uterine cavity >1 mm. During 3 months of follow-up, all out-of-protocol visits, complications and (re) interventions were registered.

Table I Baseline characteristics.

	RCT	
	Curettage (*n* = 30)	Expectant (*n* = 29)
Age in years, mean (SD)	31.8 (6.5)	32.1 (4.9)
Nulliparous, n (%)	16 (53.3)	10 (34.5)
Obstetric history, n (%)		
Previous miscarriage	11 (36.7)	8 (27.5)
Previous curettage	2 (6.7)	5 (17.2)
Previous misoprostol treatment	5 (17.2)	2 (6.9)
GA at misoprostol use, mean (SD)[a]	10.0 (2.1)	10.2 (1.4)
AP diameter uterine cavity mm, median (IQR)	15.0 (13.0–21.0)	16.0 (13.5–18.5)
Ethnicity, n (%)		
Caucasian	24 (80.0)	19 (65.5)
Middle-Eastern/North-African	1 (3.3)	5 (17.2)
Other	5 (16.7)	4 (13.8)
Unknown	0 (0.0)	1 (3.4)

GA=gestational age.
[a]Study entry was 1–2 weeks after misoprostol use.

Outcomes

A successful outcome was defined as the sonographic finding of an empty uterus (total endometrial diameter of <10 mm) at 6 weeks follow-up, or an uneventful clinical course during 3 months of follow-up without any complications or need for (re)interventions.

Secondary outcomes were excessive blood loss (estimated or measured ≥500cc and/or blood transfusion needed), antibiotic treatment, the type and number of (re)interventions (e.g. (re-)curettage, hysteroscopy, laparoscopy and laparotomy). We also recorded the reason for the (re)intervention during 3 months of follow-up after study entry and the histopathology of any tissue obtained during the (re-)intervention. All other complications and interventions were registered until 3 months after study entry.

Statistical analysis

All analyses were by intention-to-treat. We calculated the proportion of treatment success, and relative risks, with 95% confidence intervals. Dichotomous or categorical data were presented as numbers with percentages, and relative risks were presented with corresponding 95% confidence intervals. We tested differences for statistical significance using the χ^2-test statistic. Data were analysed using the Statistical Package of the Social Sciences (SPSS, version 21.0).

Sample size

Anticipating a 98% success rate with curettage, versus 85% for expectant management, we needed to randomize 130 women on a 1:1 basis to reject the null hypothesis of a no difference. Assuming a drop-out and cross-over rate of 20%, we planned to include 162 patients (81 per arm). Because of the relatively small sample size and the expected duration of inclusion, an interim analysis was not planned.

During the study, many women were found to have a strong preference for one of the treatment options. Since we randomized about 30 women per year, we anticipated that randomising 162 women would require an unacceptably long inclusion period. We therefore decided on 01/07/14 to halt the trial prematurely after randomization of 59 women. This decision was approved by the data safety monitoring board.

Results

Between June 2012 and July 2014, we identified 340 women who were eligible for the study. Of these, 59 women were randomized: 30 to curettage and 29 to expectant management. Another 197 women were managed according to their preference; treatment outcome in these preference groups will be presented elsewhere. The other 84 women declined any study participation (Fig. 1).

Baseline characteristics of both treatment arms were comparable (Table I). While the protocol recommended curettage within 3 days for women allocated to curettage, in 8 women the curettage was scheduled later, between 4 and 9 days.

Eight women did not have sonography at 6 weeks after study entry (curettage, *n* = 6; expectant management, *n* = 2). In seven of these women, the course during the 3 months follow-up was uneventful but one woman, allocated to expectant management, had an emergency curettage for heavy vaginal bleeding.

In the group allocated to curettage, an empty uterine cavity or uneventful clinical follow-up was observed in 97% (29/30) of women, compared with 76% (22/29) in the women allocated to expectant management (RR 1.27, 95% CI 1.03–1.58).

In the curettage group, 3/30 (10%) women had a complication, compared with 3/29 (10%) in the expectant management group (RR 0.97, 95% CI 0.21–4.4). One woman in the curettage group was treated for post-spinal headache with a blood patch the day after surgery. Another women allocated to curettage was diagnosed with Asherman's syndrome within 3 months of randomization. Two women in the expectant management group underwent an emergency curettage because of excessive blood loss, estimated ≥500cc. In both treatment arms, one woman received antibiotic treatment.

Two women in the curettage group underwent a hysteroscopy within 3 months after randomization. One hysteroscopy was performed for uterine cavity assessment prior to IVF treatment. For the other woman, the indication for hysteroscopy was unknown.

Seven women in the expectant management group underwent an intervention within 3 months after randomization: four women underwent a curettage and three women underwent hysteroscopy. Three curettages were performed because of persistent vaginal bleeding, while in the fourth woman the reason for curettage was unknown. All three hysteroscopies were performed because of sonographic evidence of intrauterine remnants (Table II).

In the women allocated to curettage, histology confirmed pregnancy tissue in 11/30 women (37%). In 5/30 women (17%), histology could not confirm the presence of pregnancy remains, while histology was unavailable in the remaining 14 women. Among the two women who had a hysteroscopy after initial curettage, one had histological confirmed pregnancy tissue, while in the other histology did not confirm the presence of chorionic, amnionic or foetal tissue. Of seven women with initial expectant management followed by an intervention, histology was available for six cases, of which only two samples (29%) contained pregnancy tissue remnants (Table III).

Table II Results.

	RCT		
	Curettage (n = 30)	Expectant (n = 29)	RR (95%CI)
Efficacy (empty uterus at 6 weeks and/or uneventful clinical course for 3 months), n (%)	29 (97%)	22 (76%)	1.27 (1.03–1.58)
Secondary outcomes			
Complications	3 (10.0)	3 (10.3)	1.0 (0.85–1.19)
Bleeding ≥500cc, n (%)	0 (0.0)	2 (6.9)	N/A
Antibiotic treatment, n (%)	1 (3.3)	1 (3.4)	0.97 (0.1–14.7)
Asherman syndrome, n (%)	1 (3.3)	0 (0.0)	N/A
Post-spinal headache, n (%)	1 (3.3)	0 (0.0)	N/A
Bleeding, days (median, IQR)	7 (3–14)	14 (2–42)	$P = 0.08$
Pain, days (median, IQR)	1 (0–2)	7.5 (0.8–18.8)	$P = 0.048$
(Re)interventions			
(Re)curettage, n (%)	0 (0)	4 (13.8)	N/A
Hysteroscopy, n (%)	2 (6.7)	3 (10.3)	0.64 (0.1–3.6)
Reasons for (re)curettage			
Patients wish, n (%)	0 (0)	0 (0)	
Bleeding, n (%)	0 (0)	3 (75)	
Pain, n (%)	0 (0)	0 (0)	
Sonographic image of pregnancy tissue at follow-up, n (%)	0 (0)	0 (0)	
Other, n (%)	0 (0)	0 (0)	
Unknown (but no complications registered), n (%)	0 (0)	1 (25)	
Reasons for hysteroscopy			
Patients wish, n (%)	0 (0)	0 (0)	
Bleeding, n (%)	0 (0)	0 (0)	
Pain, n (%)	0 (0)	0 (0)	
Sonographic image of pregnancy tissue at follow-up, n (%)	0 (0)	3 (100)	
Other, n (%)	1 (50)	0 (0)	
Unknown (but no complications registered), n (%)	1 (50)	0 (0)	

Table III Histology results for women with (re) interventions.

	RCT	
	Curettage (n = 2)	Expectant (n = 7)
Pregnancy tissue, n (%)	1 (50%)	2 (29%)
No pregnancy tissue, n (%)	1 (50%)	4 (57%)
Unknown, n (%)	0 (0%)	1 (14%)

Discussion

Main findings

In women allocated to curettage, an empty uterine cavity or uneventful clinical follow-up was observed in 97% of women, compared with 76% of the women allocated to expectant management. The risk of complications was comparable between the treatment groups.

Strengths and limitations

To our knowledge, this is the first randomized trial comparing curettage to expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment. Our trial was conducted in 27 hospitals in a nationwide consortium. The drop-out rate was low, and we had few missing data.

Our study had several potential limitations. Due to the strong treatment preferences of many women, we were able to randomize only 59 instead of the targeted 162 women. This is in line with previous studies reporting on women with miscarriage, where strong patient preferences were reported. In these studies on miscarriages, a significant proportion of the women wished to receive treatment of their own choice, instead of being allocated to one of these therapies (Henshaw, *et al.*, 1993, Molnar, *et al.*, 2000, Lee, *et al.*, 2001, Wieringa-de Waard, *et al.*, 2004, Shelley, *et al.*, 2005, Graziosi, *et al.*, 2006, Niinimaki, *et al.*, 2006, Smith, *et al.*, 2006, Trinder, *et al.*, 2006, Kong, *et al.*, 2013). Due to the nature of the interventions, neither the participating women nor the doctors could be blinded for the treatment allocation.

While the study protocol recommended sonography to be performed 6 weeks after study entry, in eight women this examination was not performed. Most of the women had their curettage performed under ultrasound guidance, and their course was uneventful, which is why we considered these women to have an empty uterus 6 weeks later. Similarly, women without sonography but with an uneventful follow-up were also assumed to have an empty cavity at 6 weeks follow-up.

Interpretation of findings and clinical implications

Leung *et al.* conducted a RCT and evaluated ultrasound criteria for diagnosing an 'empty uterus' in 46 women with sonographic signs of pregnancy remnants after misoprostol treatment. In women with an intrauterine dimension >11 cm^2, those managed expectantly had a higher risk on short term complications (bleeding or infection) than those treated with curettage (37.5% vs 0%) (Leung, *et al.*, 2004). In contrast, we found comparable complication rates which were independent from the AP diameter of uterine contents.

In the present study, we chose to include women with a sonographic mass exceeding 10 mm. This cut-off is arbitrary. It is known that sonography is of limited value in predicting the presence of intrauterine remnants. We do not know whether, and if so, what, thickness corresponds best to the presence of intrauterine pregnancy remnants (Fiala, *et al.*, 2003, Debby, *et al.*, 2008). This is underlined by the high success rate of expectant management in women with presumed incomplete uterine evacuations after misoprostol treatment, as found in the present study. Furthermore histology in women undergoing a (re)intervention was only confirmed in approximately one third of the cases. Obviously, this finding questions the accuracy of sonography in the follow-up after misoprostol treatment, since sonographically suspected intra uterine remnants were not confirmed by histopathological examination of removed tissue in so many women.

Creinin *et al.* concluded that women successfully treated for miscarriage showed a wide range of endometrial thicknesses which implies that a thickened endometrial lining after miscarriage is a physiological finding. Our study confirms these findings; clinical signs and symptoms rather than mere endometrial thickness should guide treatment decisions (Creinin, *et al.*, 2004).

This seems even more important in view of the long-term consequences of curettage, which were beyond the scope of our present study. An earlier meta-analysis showed that 19% of women develop intrauterine adhesions (Asherman syndrome) after undergoing curettage, which might impair future fertility in particular in case of dense adhesions (Hooker, *et al.*, 2014). Another recently performed meta-analysis demonstrated an increased risk of preterm birth in subsequent pregnancies of women with a history of curettage (OR 1.3, 95% CI 1.2–1.4). The subsequent risk of very preterm birth <28 weeks is increased even more (OR 1.7, 95% CI 1.5–1.9) and of concern in view of the frequent use of curettage in daily practice (Lemmers, *et al.*, 2015).

In designing the study, we phrased a superiority hypothesis for curettage versus expectant management, thereby evaluating whether the more invasive intervention indeed is superior to non-invasive alternatives, taking into account the potential harmful effects. Although curettage is more effective than expectant management, we have to conclude from our trial that women have a high preference for expectant management leading to a preterm termination of our trial. In addition, expectant management does not lead to significantly more (short term) complications.

For every four women who were managed expectantly in our study, 3 of them were able to avoid undergoing a surgical procedure, while in 2 out of 30 women treated with curettage, a second intervention was performed. Furthermore, since histopathology only confirmed the presence of pregnancy tissue in one third of samples, it is likely that the proportion of women with successful expectant management is higher than currently reported.

Authors' roles

MV, ML, PB, BO, JH, PG, MH, WA and BWM were responsible for drafting and revising the original protocol. WA, JH and BWM were the principal investigators, obtained funding and had overall responsibility for management of the trial. MV and ML performed the trial, collected the data and performed statistical analyses. JH, CJ, CR, EK, JL, RC, LV, FS, PG, MH, JP, and SC were local investigators. MV and ML performed the analyses; KOR and CN supervised the statistical analyses. MV and ML wrote the first draft of the report and revised the subsequent draft. All authors contributed to and approved the final report. WA is guarantor. ML and MV affirm that the manuscript is an honest, accurate and transparent account of the research findings and no important aspects of the study have been omitted

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Conflict of interest

None declared.

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