



## Full length article

## MisoREST: Surgical versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage: A cohort study



Marieke Lemmers<sup>a,b,\*,1</sup>, Marianne A.C. Verschoor<sup>a,1</sup>, Katrien Oude Rengerink<sup>c</sup>, Christiana Naaktgeboren<sup>c</sup>, Patrick M. Bossuyt<sup>d</sup>, Judith A.F. Huirne<sup>b</sup>, Ineke A.H. Janssen<sup>e</sup>, Celine Radder<sup>f</sup>, Ellen R. Klinkert<sup>g</sup>, Josje Langenveld<sup>h</sup>, Lucet van der Voet<sup>i</sup>, F. Frederike Siemens<sup>j</sup>, Marlies Y. Bongers<sup>k</sup>, Marcel H. van Hooff<sup>l</sup>, Marinus van der Ploeg<sup>m</sup>, F.P.J. Sjors<sup>n</sup>, S.F.P.J. Coppus<sup>n</sup>, W.M. Ankum<sup>a</sup>, Ben Willem J. Mol<sup>o</sup>, on behalf of the MisoREST study group

<sup>a</sup> Department of Obstetrics and Gynaecology, Academic Medical Center, P.O. Box 22770, 1100 DE Amsterdam, The Netherlands

<sup>b</sup> Department of Obstetrics and Gynaecology, VU Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

<sup>c</sup> Julius Center for Health Sciences and Primary Care, UMC Utrecht, P.O. Box 85500, 3508 GA Utrecht, The Netherlands

<sup>d</sup> Clinical Research Unit, University of Amsterdam, Academic Medical Center, P.O. Box 22770, 1100 DE Amsterdam, The Netherlands

<sup>e</sup> Department of Obstetrics and Gynaecology, Groene Hart Ziekenhuis, P.O. Box 1098, 2800 BB Gouda, The Netherlands

<sup>f</sup> Department of Obstetrics and Gynaecology, Onze Lieve Vrouwe Gasthuis West, P.O. Box 9243, 1006 AE Amsterdam, The Netherlands

<sup>g</sup> Department of Obstetrics and Gynaecology, University Medical Center Groningen, P.O. Box 30001, 9700 RB Groningen, The Netherlands

<sup>h</sup> Department of Obstetrics and Gynaecology, Atrium Medical Center, P.O. Box 4446, 6401 CX Heerlen, The Netherlands

<sup>i</sup> Department of Obstetrics and Gynaecology, Deventer Hospital, P.O. Box 5001, 7400 GC Deventer, The Netherlands

<sup>j</sup> Department of Obstetrics and Gynaecology, Reinier de Graaf Hospital, P.O. Box 5011, 2600 GA Delft, The Netherlands

<sup>k</sup> Department of Obstetrics and Gynaecology, Maxima Medical Center, Postbus 7777, 5500 MB Veldhoven, The Netherlands

<sup>l</sup> Department of Obstetrics and Gynaecology, Sint Franciscus Gasthuis, Rotterdam, P.O. Box 10900, 3004 BA Rotterdam, The Netherlands

<sup>m</sup> Department of Obstetrics and Gynaecology, Martini ziekenhuis Groningen, P.O. Box 30033, 9700 RM Groningen, The Netherlands

<sup>n</sup> Department of Obstetrics and Gynaecology, UMC St. Radboud, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

<sup>o</sup> The Robinson Research Institute, School of Paediatrics and Reproductive Health, University of Adelaide, 55 King William Road, North Adelaide SA 5006 and The South Australian Health and Medical Research Institute, Adelaide, Australia

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## ABSTRACT

**Objective:** To assess the effectiveness of curettage versus expectant management in women with an incomplete evacuation of the uterus after misoprostol treatment for first trimester miscarriage.

**Study design:** We conducted a multicenter cohort study alongside a randomized clinical trial (RCT) between June 2012 until July 2014. 27 Dutch hospitals participated. Women with an incomplete evacuation after misoprostol treatment for first trimester miscarriage who declined to participate in the RCT, received treatment of their preference; curettage (n=65) or expectant management (n=132). A successful outcome was defined as an empty uterus on sonography at six weeks or uneventful clinical follow-up. We furthermore assessed complication rate and (re)intervention rate

**Results:** Of the 197 women who declined to participate in the RCT, 65 preferred curettage and 132 expectant management. A successful outcome was observed in 62/65 women (95%) in the surgical group versus 112/132 women (85%) in the expectant group (RR 1.1, 95% CI 1.03–1.2), with complication rates of 6.2% versus 2.3%, respectively (RR 2.7, 95% CI 0.6–12).

**Conclusion:** In women with an incomplete evacuation of the uterus after misoprostol treatment, expectant management is an effective and safe option. This finding could restrain the use of curettage in women that have used misoprostol in the treatment of first trimester miscarriage.

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\* Corresponding author at: Department of Obstetrics and Gynaecology, Academic Medical Center, P.O. Box 22770, Amsterdam, 100 DE, The Netherlands.  
E-mail address: [m.lemmers@amc.uva.nl](mailto:m.lemmers@amc.uva.nl) (M. Lemmers).

<sup>1</sup> The authors consider that the first two authors should be regarded as joint First Authors.

## Introduction

First trimester miscarriage occurs in 10–15% of pregnant women [1]. Historically, women diagnosed with a miscarriage were either managed expectantly or were offered curettage [2–4]. Misoprostol has been introduced more recently as an option for the treatment of first trimester miscarriage. Misoprostol is non-invasive, inexpensive, and easy to administer [2,5–11] and it's use results in high patient satisfaction rates. [6,12–14]

After the expulsion of the pregnancy, an ultrasound is usually performed to check if the uterus has completely emptied. In 5–50% of the women treated with misoprostol, such ultrasound indicates an incomplete evacuation of the uterus [2,3,5,8–11]. Although women generally have few symptoms, and in spite of the limited value of ultrasound in determining the presence of intra uterine pregnancy remnants, this finding often leads to an additional curettage, which reduces the initial advantage of non-invasive therapy [15,16]. This is of concern since curettage is more expensive and bears the risk of short- and long term complications such as cervical tears, uterine perforation, infection, intra-uterine adhesions (Asherman's syndrome) and an increased risk of preterm birth in the subsequent pregnancy [17,18].

While there is no doubt that curettage is an effective treatment for women who have an incomplete evacuation of the uterus, expectant management might be a safer and more cost-effective treatment option. The objective of our study was to compare the effectiveness and safety of both treatment options in a randomized clinical trial, and a parallel cohort study for women who declined randomization; these women were treated according to their preference.

The results of the RCT have been published recently [19]. Due to the fact that many eligible women expressed a preference for either expectant management or immediate curettage, the power of the RCT remained relatively small with 59 included women. The study showed that curettage was effective in 97% versus 76% of women allocated to expectant management. Here, we report on the much larger sample of women that were treated according to the same protocol according to their preference.

## Methods

### Study design

We report on a cohort of women that was approached to participate in a multicenter RCT comparing curettage and expectant management. Eligible for participation in the study were women with a first trimester miscarriage who had been treated with misoprostol and showed incomplete evacuation of the uterus at routine ultrasound scanning one to two weeks after initial misoprostol treatment. Incomplete evacuation was defined as evidence of intra-uterine remnants or an antero-posterior (AP) diameter of the uterine cavity exceeding 10 mm in ultrasound scanning. Exclusion criteria were age <18 years, severe vaginal bleeding or severe abdominal pain requiring immediate intervention, fever (>38 °C) requiring antibiotic treatment and curettage, or contraindications for curettage or a failed misoprostol-induced miscarriage as substantiated by the finding on ultrasound scanning of an intact gestational sac still being present.

Eligible women were counseled by their doctors, gynecologists or by specialized research nurses. Data of the randomized women have been published elsewhere [19]. The study was performed 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 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. Women who declined randomization were treated according to their own preference and asked for consent to take part in the observational study, which followed the same protocol for follow-up. Here, we report on the women that refused randomization and followed their preference.

### Procedures

#### Curettage

Women who preferred curettage were scheduled for this procedure within 3 workdays. Curettage was performed according to local hospital protocol. Curettage could be performed as a vacuum aspiration or by blunt or sharp curettage and anesthesia was either general, regional or local.

#### Expectant management

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

A research nurse contacted all participating women two weeks after study entry. Transvaginal ultrasound was scheduled six weeks after study entry. In all participating women a (re-)curettage was scheduled in case of persisting abnormalities at follow-up on ultrasound scanning six weeks after study entry. All out-of-protocol visits, complications and (re-)interventions were registered during a three month follow-up.

### Outcomes

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

Secondary outcomes were need for antibiotic treatment, excessive blood loss (estimated or measured  $\geq 500$ cc and/or blood transfusion needed) and the type and number of (re-)interventions ((re-)curettage, hysteroscopy, laparoscopy and laparotomy). We recorded reasons for (re-)interventions during three months of follow-up after study entry. Furthermore we recorded the histopathology of tissue obtained during (re-) intervention. During the three months follow-up, all other complications and interventions were registered.

### Statistical analysis

Data were analyzed according to the intention to treat principle. Dichotomous or categorical data were presented as numbers with percentages, and treatment successes was expressed as relative risks (RR) with corresponding 95% confidence intervals (95% CI). P-values were calculated using a  $\chi^2$  test statistic. A P-value <0.05 was supposed to indicate statistical significance. A propensity score analysis will be performed to control for potential confounding in this observational study. All baseline patient characteristics presented in Table 1 will be considered as potential confounders and used to calculate a propensity score for being in the expectant treatment group. If the propensity scores differ between groups, the propensity score will be added as a covariate to a logistic regression model and the adjusted odds ratios will be compared to the unadjusted odds ratio.

All analyses were done with the Statistical Package of the Social Sciences (SPSS, version 21.0).

**Table 1**  
Baseline characteristics.

	Preference group	
	Curettage (n = 65)	Expectant (n = 132)
Age in years, mean (SD)	31.4 (4.8)	32.7 (4.6)
Nulliparous, n (%)	34 (52.3)	65 (49.2)
Obstetric History n (%)		
Previous miscarriage	22 (33.8)	59 (44.7)
Previous curettage	11 (16.9)	17 (12.9)
Previous misoprostol treatment	5 (7.9)	18 (13.7)
GA at misoprostol use, mean (SD) <sup>a</sup>	10.7 (1.6)	10.7 (1.5)
AP diameter uterine cavity mm, median (IQR)	18. (14.0–28.0) <sup>b</sup>	15.0 (12.0–17.0)
Ethnicity n (%)		
Caucasian	55 (84.6)	109 (82.6)
Middle-Eastern/North-African	3 (4.6)	10 (7.6)
Other	4 (9.2)	11 (3.8)
Unknown	3 (1.5)	2 (10.7)

GA = gestational age; AP = antero-posterior.

<sup>a</sup> Study entry was 1–2 weeks after misoprostol use.<sup>b</sup> Curettage vs expectant management  $p = 0.04$ .

## Results

Between June 2012 and July 2014, we identified 347 women who were eligible for the study, of whom 59 women were randomized to curettage or expectant management. Results of these randomized women are reported elsewhere [19]. Women who refused to be randomized were treated according to their preference. Of the 292 non-randomized eligible women 84 women refused any study participation, three women withdrew their consent before any data were obtained; two women who chose expectant management, and one woman who chose curettage. One woman who underwent expectant management was lost to follow-up. Two women who underwent a curettage were excluded, one had never been treated with misoprostol but had a primary curettage for non-vital pregnancy, while the other woman still had a gestational sac in situ after misoprostol treatment. Since having a gestational sac present after misoprostol treatment was an exclusion criterium, this woman was wrongfully included and therefore not considered in the analysis. Here, we report on 197 women who were treated according to their preference; 65 women underwent curettage and 132 women were managed expectantly (flowchart, Fig. 1).

Baseline characteristics between women treated with curettage and those with expectant management were comparable (Table 1), except for median AP diameter of uterine contents which was 18 mm in the curettage group and 15 mm in the in the expectant management group (difference 3 mm,  $p = 0.04$ ).

There were 11 women who did not have an ultrasound scan at six weeks after study entry, four women in the curettage group and seven in the expectant management group. One woman, in the expectant management group, who did not have sonography the clinical course during the three months of follow up, had a complicated course. This woman experienced blood loss >500 ml, after which an emergency curettage had to be performed. One woman, who did not have sonography the clinical course during the three months of follow up, was complicated. This woman with an eventful clinical course, underwent expectant management and experienced blood loss >500 ml. In all other women the clinical course during three months follow-up was uneventful.

Overall, an empty uterine cavity at six weeks follow-up, or an uneventful clinical course was seen in 95% (62/65) of women in the curettage group and in 85% (112/132) of women in the expectant group (RR 1.1, 95% CI 1.03–1.2). The propensity scores differed between treatment groups (independent samples Mann Whitney  $U$  test  $p$ -value = 0.000). The moderate predictive value the

propensity score had for treatment group selection indicated that a propensity score method should be considered (AUC 0.70.) Therefore, we added the propensity score into a multivariable logistic regression model along with treatment arm and compared and the adjusted odds ratios for treatment effect obtained from this model to the unadjusted odds ratio. The adjusted odds ratio for curettage resulting in a successful outcome compared to expectant management from the model containing the propensity score (OR<sub>adjusted</sub> 3.4; 95% CI 0.9–12.9) was only slightly lower than the unadjusted odds ratio for was (OR<sub>unadjusted</sub> 3.7 (95% 1.06–12.9)). However, the treatment effect was no longer significant.

In 24 women the curettage was scheduled later than the intended 3 days. According to the intention to treat principle, these women were included in the analysis in the curettage group.

The complication rates were not significantly different between the two treatment groups 6.2% (curettage) versus 2.3% (expectant management), respectively (RR 2.7, 95% CI 0.6–12). In the curettage group three women were treated with antibiotics because of a pelvic infection or urinary tract infection, versus two women in the expectant management group. A primigravid woman without a history of uterine surgery treated with curettage was diagnosed with Asherman's syndrome within three months after study participation. (Table 2) In the curettage group, there were 11 women who had a re-intervention: two women underwent a second curettage, seven women had a hysteroscopy performed, while two women underwent both a second curettage and later an additional hysteroscopy. Reasons for interventions are summarized in Table 2. Two women had both curettage and hysteroscopy, one woman because of suspicion of intra-uterine remnants, while one other woman had fever. In one woman a second curettage was performed because of blood loss, while in the other women persisting intra uterine remnants were suspected. Two women had a hysteroscopy because of suspected Asherman's syndrome, three women had a suspected intra uterine pregnancy remnant. In two women the reason for hysteroscopy remained unknown. One woman in the curettage group underwent laparoscopy within three months of follow up because of cholecystolithiasis (Table 2).

In the women managed expectantly, an intervention within three months was performed in 24 women: 12 had a curettage, seven had a hysteroscopy while five women underwent both. Reasons for undergoing both curettage and hysteroscopy were persisting blood loss ( $n = 3$ ), pain ( $n = 1$ ), and suspected intra-uterine remnants ( $n = 1$ ). Although pain was the major complaint, the one woman experiencing pain also had irregular blood loss and a sonographic suspicion of an incomplete evacuation. In eight of

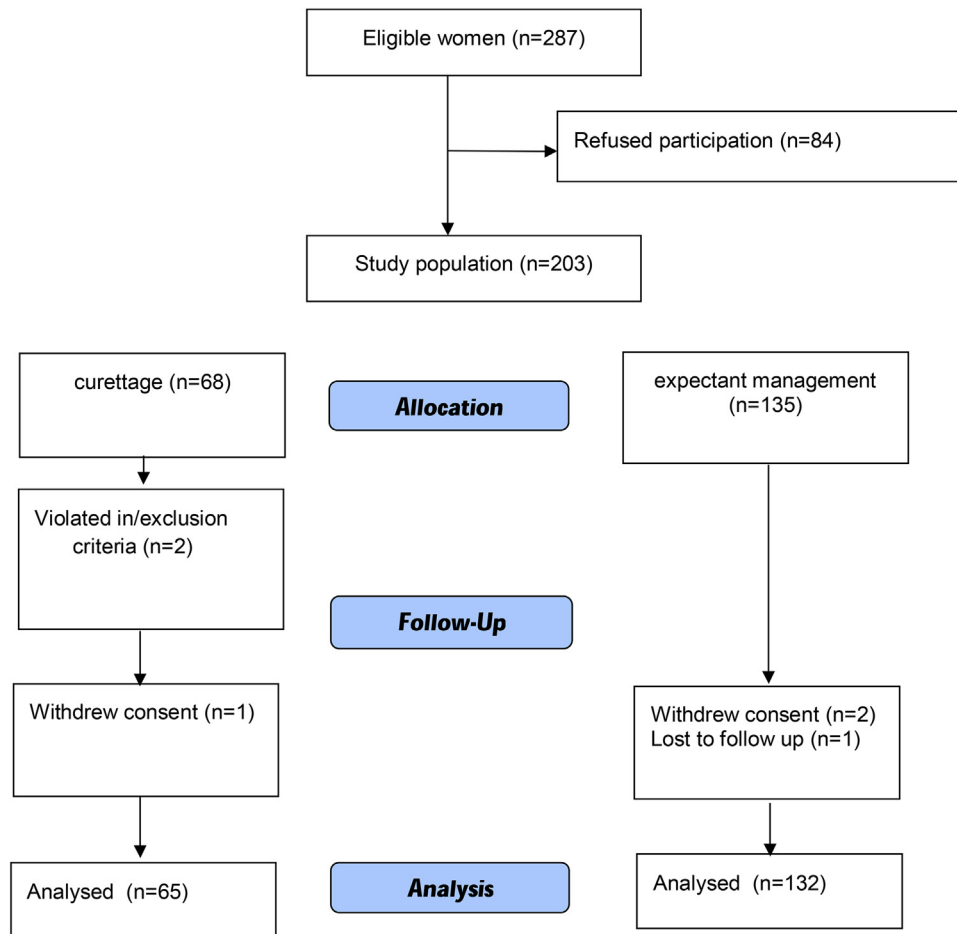


Fig. 1. Flow diagram.

Table 2  
Results.

	Preference group		
	Curettage (n = 65)	Expectant (n = 132)	RR (95% CI)
Efficacy (empty uterus at six weeks and/or uneventful clinical course for 3 months), n (%)	62 (95%)	112 (85%)	1.12 (1.03–1.23)
Secondary outcomes			
Bleeding, days (median, IQR)	11 (6–20)	8 (3–14)	p = 0.51
Pain, days (median, IQR)	2.0 (0–9.3)	0 (0–3.0)	p = 0.045
Complications			
Bleeding $\geq$ 500cc, n (%)	4 (6.2)	3 (2.3)	2.70 (0.6–11.7)
Antibiotic treatment, n (%)	0 (0.0)	1 (0.8)	N/A
Asherman syndrome, n (%)	3 (4.6)	2 (1.5)	3.0 (0.5–18)
	1 (1.5)	0 (0.0)	N/A
(Re) interventions			
(Re)curettage, n (%)	4 (6.2)	17 (12.9)	0.48 (0.2–1.4)
Hysteroscopy, n (%)	7 (10.8)	12 (9.1)	1.18 (0.5–2.9)
Reasons for (re)curettage			
Patients wish, n (%)	0 (0)	8 (47.1)	
Bleeding, n (%)	1 (25)	5 (29.4)	
Pain, n (%)	1 (25)	1 (5.9)	
Sonographic image of pregnancy tissue at follow-up n (%)	2 (50)	2 (11.9)	
Other, n (%)	0 (0)	0 [0]	
Unknown (but no complications registered), n (%)	0 (0)	1(5.9)	
Reasons for hysteroscopy			
Patients wish, n (%)	0 [0]	0 [0]	
Bleeding, n (%)	0 (0)	3(25.0)	
Pain, n (%)	0 (0)	1(8.3)	
Sonographic image of pregnancy tissue at follow-up, n (%)	3 (42.9)	6 (50.0)	
Other, n (%)	2 (28.6)	0 (0)	
Unknown (but no complications registered), n (%)	2 (28.6)	2 (16.7)	

the 12 women who underwent a curettage, the procedure was performed electively; in these women the physician judged a curettage was not medically indicated, though women wished to have this procedure performed due to for instance mild or persisting blood loss or anxiety. Two women underwent a curettage due to blood loss, in one woman there were suspected intra uterine remnants while in one woman the reason for curettage was unknown. Five out of seven women underwent hysteroscopy because of suspected intra uterine remnants. In the last two women the reason for hysteroscopy was unknown.

Histology was present for the nine women in the curettage group who underwent a second intervention (curettage and/or hysteroscopy) and for the 24 women in the expectant management group who underwent a curettage and/or hysteroscopy. In the curettage group, in eight out of nine women who underwent a second curettage and/or hysteroscopy, histology confirmed the presence of pregnancy tissue. In the remaining woman there was no tissue obtained at all. For the 24 women in the expectant management group, pregnancy tissue was present in six women who underwent an intervention, but not in the remaining 18 women. Histology in these 18 women showed blood clots ( $n=1$ ), decidual cast ( $n=4$ ), or no tissue at all ( $n=2$ ) while it was unknown in 11 women (Table 3).

## Discussion

### Main findings

We reported on the outcome of curettage versus no treatment in women with a non-empty uterus after misoprostol for curettage in women who were eligible for a RCT, but who had a clear preference on the type of treatment. In women with an incomplete evacuation of the uterus after misoprostol treatment for first trimester miscarriage, curettage was effective in 95% of the women versus 85% in women who were managed expectantly. Both complication rates and (re)intervention rates did not differ statistically significant in both treatment arms.

### Strengths and limitations

We conducted our study in 27 hospitals in a nationwide consortium. The drop-out rate was low and there were few missing data. To our knowledge this is the first study comparing curettage to expectant management for incomplete evacuation of the uterus after misoprostol treatment.

This study had various potential limitations. This study reports on women that were not randomised ( $N=197$ ) due a strong preference for either curettage or expectant management. Despite this, we found expectant management very often to be successful.

Several other studies reporting on women with miscarriages also found strong patient preferences for either curettage or expectant management [10,20–28]. Due to the fact that women chose their treatment of preference, selection bias cannot be excluded. All doctors counselling women with an incomplete evacuation for participation in the MisoREST study received instruction. This instruction was also available on the study

website. In spite of these instructions it is possible doctors counselled women differently depending on physical complaints and ultrasound findings as well as on local tradition, while women with few complaints may have been more likely to choose expectant management.

The results of this observational study are at risk of being biased due to confounding arising from differences in patient characteristics between the treatment arms. Because the sample size of this study was not large enough to control for several confounders at once, we used a propensity score method to control for this bias. Our propensity score analysis suggests that even though patients different between treatment groups, this did not likely introduce a large degree of bias.

Furthermore, in case of an inconclusive or doubtful image on ultrasound scanning during follow-up, women who underwent initial expectant management may have been submitted to a subsequent curettage more readily. The study protocol recommended ultrasound to be performed six weeks after study entry. In 11 women ultrasound was not performed. Most of these women had their curettage performed under ultrasound guidance and had an uneventful follow-up. We considered these women to have an empty uterus six weeks later. Women who were managed expectantly with uneventful follow-up, were similarly considered to have had an empty uterine cavity at six weeks after study enrolment.

### Interpretation of findings and clinical implications

In our previously published RCT, 97% of the women who underwent curettage compared to 76% of women managed expectantly had an empty uterus on sonography or uneventful clinical follow-up (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). These results are in line with the results of the present cohort study. When we combine the results of the RCT and cohort by means of a meta-analysis using an inverse variance approach, the OR for curettage versus expectant management is 4.46 (95% CI 1.43–13.87) (Fig. 2).

Leung et al. evaluated ultrasound criteria for diagnosing an 'empty uterus' in 46 women with sonographic signs of pregnancy remnants after misoprostol treatment. Short-term complications such as bleeding and infection were related to a uterine dimension  $>11\text{ mm}^2$ . Short term complications defined as vaginal bleeding or suspected intra uterine infection necessitating readmission and additional interventions occurred in 9/24 women (37.5%) allocated to expectant management versus 0% in women who underwent curettage [29].

In the present study, complication rates were not significantly different in the curettage and expectant management group, which did not depend on the size of the suspected pregnancy remnants on ultrasound scanning.

Creinin et al. reported that 4 out of 60 women (6.7%) required a curettage for incomplete evacuation of the uterus after primary misoprostol treatment. Three of these four women had clinically significant blood loss [15]. This is similar to the proportion of women documented to have had excessive blood loss in our study.

In our study, in 75% of the women who underwent a secondary curettage after initial expectant management, no pregnancy tissue was found on histopathological examination. In the curettage group, there was only one woman (11%) where pregnancy tissue could not be confirmed on histopathological examination. This finding questions the accuracy of ultrasound in the follow-up of misoprostol treatment, since sonographically suspected pregnancy remnants were not confirmed by histopathological examination in so many women. In this study we

**Table 3**  
Histology results for women with (re)interventions.

	Preference group	
	Curettage (n=9)	Expectant (n=24)
Pregnancy tissue, n (%)	8 (89%)	6 (25%)
No pregnancy tissue, n (%)	1 (11%)	7 (29%)
Unknown, n (%)	0 (0%)	11 (46%)

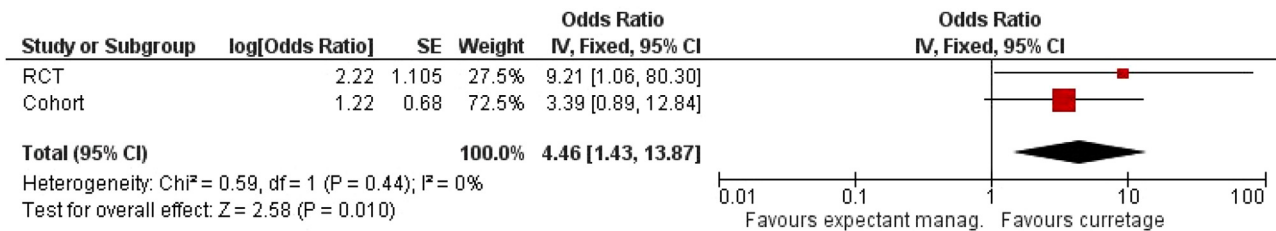


Fig. 2. Forrest plot.

included women with a sonographic suspicion of an incomplete evacuation, with an endometrial thickness of minimally 10 mm. This cut-off value since there is no consensus in literature on ultrasound criteria for the diagnosis of incomplete evacuation, and in daily practice a thickened endometrium often leads to additional curettage. Creinin et al., concluded that women who were successfully treated for a miscarriage showed a wide range of endometrial thicknesses which implies a thickened endometrial lining after miscarriage to be a physiological finding [15]. Our study confirms these findings: clinical signs and symptoms rather than mere endometrial thickness should guide treatment decisions. In fact, many of the women who had a curettage in the expectant management group might have had this intervention unnecessary from a medical point of view, as either the preference of the woman or the clinician, or a combination of both might have driven the curettage. Thus, the success rates of expectant management might be better than the 85% that we found.

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 19% of women to develop intra-uterine adhesions after undergoing curettage, which might impair future fertility [17]. Another recently performed meta-analysis demonstrated a 30% increased risk of preterm birth in subsequent pregnancies of women with a history of curettage [18]. This is of concern in view of the frequent use of curettage in daily practice. Another argument for expectant management is obviously its lower costs.

## Conclusion

We found that in women with an incomplete evacuation of the uterus after misoprostol treatment for first trimester miscarriage, curettage was more effective than expectant management. However, since expectant management was proven to be safe and effective in at least 5 out of 6 women, we feel that expectant management should be considered first line treatment in women with a suspected incomplete evacuation after misoprostol treatment for first trimester miscarriage.

## Contributors

MV, ML, PB, 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, LV, FS, MB, MH, JP, SC, were local investigators. MV and ML performed the analyses, KOR and CN supervised statistical analyses. MV and ML wrote the first draft of the report and revised subsequent draft. All authors contributed to and approved the final report. WA is guarantor.

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## Ethical approval

The study was approved by the research ethics service committee of the Academic Medical Centre (project number 2011-373); research governance approvals were granted by participating hospitals and all patients gave informed consent.

## Data sharing

Patient level data is available from the corresponding author. Consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

## Transparency declaration

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.

## Study protocol

The original study protocol was published in May 2013: 'Surgical versus expectant management in women with an incomplete evacuation of the uterus after treatment with misoprostol for miscarriage: the MisoREST trial'. Verschoor MAC et al. *BMC Pregnancy and Childbirth* 2013, 13:102 (2 May 2013). <http://www.biomedcentral.com/1471-2393/13/102>.

Furthermore the protocol is available through the study website: [www.studies-obsgyn.nl/misorest](http://www.studies-obsgyn.nl/misorest).

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