



Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Fertility and obstetric outcomes after curettage versus expectant management in randomised and non-randomised women with an incomplete evacuation of the uterus after misoprostol treatment for miscarriage



M. Lemmers^{a,b,*}, M.A.C. Verschoor^a, K. Overwater^b, P.M. Bossuyt^c, D. Hendriks^d,
M. Hemelaar^e, J.M. Schutte^f, A.H. Adriaanse^g, W.M. Ankum^a, J.A.F. Huirne^b, B.W.J. Mol^h

^a Department of Obstetrics and Gynaecology, Academic Medical Centre, P.O. Box 22770, 1100 DE, Amsterdam, The Netherlands

^b Department of Obstetrics and Gynaecology, VU Medical Centre, P.O. Box 7057, 1007 MB, Amsterdam, The Netherlands

^c Clinical Research Unit, University of Amsterdam, Academic Medical Centre, P.O. Box 22770, 1100 DE, Amsterdam, The Netherlands

^d Department of Obstetrics and Gynaecology, Amphia Ziekenhuis, P.O. Box 90158, 4800 RK, Breda, The Netherlands

^e Department of Obstetrics and Gynaecology, Westfriesgasthuis, P.O. Box 600, 1620AR, Hoorn, The Netherlands

^f Department of Obstetrics and Gynaecology, Isala Kliniek, P.O. Box 10400, 8000 GK, Zwolle, The Netherlands

^g Department of Obstetrics and Gynaecology, Noordwest Ziekenhuisgroep, P.O. Box 501, 1800 AM, Alkmaar, The Netherlands

^h The Robinson Research Institute|School of Medicine, University of Adelaide, The South Australian Health and Medical Research Institute, Adelaide, Australia

ARTICLE INFO

Keywords:
Misoprostol
Curettage
Miscarriage
Incomplete evacuation
Fertility
Obstetric outcome

ABSTRACT

Objective: To assess fertility and obstetric outcomes in women treated with curettage or undergoing expectant management for an incomplete miscarriage after misoprostol treatment.

Study

Design: Between June 2012 and July 2014, we conducted a multicentre randomised clinical trial (RCT) with a parallel cohort study for non-randomised women, treated according to their preference. In the RCT 30 women were allocated curettage and 29 expectant management. In the cohort 197 women participated; 65 underwent curettage and 132 women underwent expectant management. Primary outcome was curettage, defined as either an empty uterus on sonography at six weeks or an uneventful clinical follow-up. We used questionnaires to assess fertility and obstetric outcome of the first new pregnancy subsequent to study enrolment.

Results: Curettage was seen in 91/95 women treated with curettage (95.8%) versus 134/161 women managed expectantly (83.2%) ($p = 0.003$). The response rate was 211/255 (82%). In 198 women pursuing a new pregnancy, conception rates were 92% (67/73) in the curettage group versus 96% (120/125) in the expectant management group (OR 0.96, 95% CI 0.89; 1.03, $p = 0.34$), with ongoing pregnancy rates of 87% (58/67) versus 78% (94/120), respectively (OR 1.12, 95% CI 0.99; 1.28, $p = 0.226$). Preterm birth rates were 1/46 in the curettage group versus 8/81 in the expectant management group (OR 0.22, 95% CI 0.03; 1.71 $P = 0.15$). Caesarean section rates were 23% and 24% for women in the curettage group and expectant management group respectively.

Conclusion: In women with an incomplete evacuation of the uterus after misoprostol treatment, curettage and expectant management does not lead to different fertility and pregnancy outcomes, as compared to expectant management.

© 2017 Elsevier B.V. All rights reserved.

Introduction

Miscarriage occurs in around 15% of all clinical pregnancies [1]. Women experiencing a miscarriage can either be managed expectantly, medically with misoprostol or surgically by performing a curettage. Since the beginning of the 20th century, curettage is performed for miscarriage and induced abortion [2,3]. Despite it

* Corresponding author at: Department of Obstetrics and Gynaecology, Academic Medical Centre, P.O. Box 22770, 1100 DE, Amsterdam, The Netherlands.
E-mail address: marike.lemmers@gmail.com (M. Lemmers).

being highly effective, curettage can lead to complications such as bleeding, perforation of the uterus, bladder or bowel, the formation of intrauterine adhesions known as Asherman's syndrome and is associated with preterm birth in future pregnancies [4–6].

More recently, treatment with misoprostol has gained popularity [7]. In the Netherlands in 2005, 50% of Dutch gynaecologists used misoprostol, while in 2014 almost all Dutch gynaecologists offered misoprostol to women as treatment for a first trimester miscarriage [8,9]. Misoprostol is a non-invasive alternative to curettage, it is cost-effective and has little adverse effects [1,3]. Although the duration of vaginal bleeding after misoprostol treatment is longer than after curettage, haemoglobin levels are similar for both treatments [10,11]. In approximately 15–50% of the women treated with misoprostol for first trimester miscarriage, sonographic examination will show signs of incomplete evacuation of the uterus. [2,3,12] This finding generally leads to additional curettage. The MisoREST trial compared the effectiveness of surgical versus expectant management in these women. In this trial, curettage was effective in 96% of the women, and expectant management was safe, and effective in over 80% [13].

Previous studies have assessed fertility after misoprostol treatment and have found no impairment of misoprostol treatment on future fertility [14,15]. It is unknown whether in women with an incomplete evacuation of the uterus, curettage leads to differences in fertility rates and obstetric outcomes in the subsequent pregnancy, compared to expectant management. The present study explores these questions.

Methods

Study design

In the MisoREST trial 256 patients participated, originating from over 27 hospitals in The Netherlands; 59 women were randomly assigned curettage (N=30), or expectant management (n=29) while 197 women declining randomization received the treatment of their own choice (65 curettage, 132 expectant management). Women were included in the study between June

2012 and June 2014. For details regarding the design of the study we refer to the original publication of the MisoREST trial [13].

All participating women were sent two questionnaires regarding their fertility (one year after participation in the MisoREST trial) and obstetric outcome of any pregnancy subsequent to participation in the MisoREST trial (2.5–4.5 years after participation in the MisoREST trial). In order to increase the response rate up to three reminder emails were sent. If women, in spite of these efforts, did not respond, we contacted their hospitals to ascertain if a pregnancy had occurred and if so, we asked for the outcome.

Outcome

The fertility related questions regarded; conception since study participation, planning thereof, time to conception and details of any pregnancy: miscarriage, ectopic, termination, pregnancy outcomes (miscarriage, intra-uterine death, EUG, delivery), gestational age at time of delivery, type of delivery (i.e. caesarean or vaginal) and baby's general health after birth.

Statistical analysis

We compared the survey outcomes for the two treatments, and analysed the data using independent T-tests or Mann-Whitney U tests for continuous variables and Pearson's chi-square tests or Fisher's exact test for categorical variables. A Kaplan Meier curve was constructed to report time to conception and log rank to determine significance. P-values less than 0.05 were considered to indicate statistical significance. All tests were executed two-sided using SPSS version 22.

Results

Baseline characteristics were comparable among both groups, with the exception AP diameter of the uterine cavity and empty uterus six weeks after study inclusion. Since the interaction term of group allocation and treatment preference between the

Table 1
Baseline characteristics.

Baseline Characteristics	Treatment		p-Value
	Curettage N = 95	Expectant N = 161	
Age in years, mean (SD)	31.5 (±5.4)	32.6 (±4.7)	0.10
Nulliparous, n (%)	50 (52.6)	75 (46.6)	0.35
Obstetric History, n (%)			
Previous miscarriage	33 (34.7)	67 (41.6)	0.28
Previous curettage	13 (13.7)	22 (13.7)	0.93
Number of previous curettages:			
0	82 (86.3)	130 (86.3)	1.0
1	8 (8.4)	17 (10.6)	0.58
≥2	5 (5.3)	5 (3.1)	0.39
Previous misoprostol treatment	10 (10.5)	20 (12.4)	0.70
GA at misoprostol use in weeks, mean (SD)	10.5 (±1.8)	10.6 (±1.5)	0.40
AP diameter uterine cavity in mm, median (IQR)	17 (14,25)	15 (12,17.5)	0.001
Ethnicity, n (%)			
Caucasian	79 (83.2)	128 (79.5)	0.47
Middle-Eastern/North African	4 (4.2)	15 (9.3)	Ns
Afro-Caribbean	6 (6.3)	5 (3.1)	Ns
African (Sub-Sahara)	2 (2.1)	3 (1.9)	Ns
Other	1 (1.0)	7 (4.3)	Ns
Unknown	3 (3.2)	3 (1.9)	Ns
MisoREST outcomes, n (%)			
Empty uterine cavity six weeks after randomization	91 (95.8)	134 (83.2)	0.003

Means ± SDs are presented for Age, BMI and GA.

GA = gestational age, AP = anteroposterior, Ns = not significant.

	Total	Curettage	Expectant	p-value
Response rate	211/256 (82%)	76/95 (80%)	135/161 (84%)	0.497
Wish to conceive	198/211 (94%)	73/76 (96%)	125/135 (93%)	0.385
Conceived	187/198 (95%)	67/73 (92%)	120/125 (96%)	0.218
Ongoing pregnancy	152/186 (82%)	58/67 (87%)	94/120 (78%)	0.117

Fig. 1. flow chart.

randomised and non-randomised women was not statistically significant ($p > 0.05$) we combined these groups. Curation defined as an empty uterine cavity six weeks after study inclusion or uneventful clinical course was found in 91/95 (95%) women treated with curettage 95% versus 134/161 (83%) women managed expectantly (RR 1.15, 95% CI 1.06–1.25). Baseline characteristics are shown in Table 1.

Fertility outcome was available for 82% of the women. The flowchart describes the response rate to the questionnaire, wish to conceive, conception rate and ongoing pregnancy rate (Fig. 1).

Of these 211 women, a total of 198 women tried to conceive, and 13 did not. Of the 198 women, 73 had had curettage and 125 had been managed expectantly. In the curettage group 67/73 (92%) of the women conceived versus 120/125 (96%) of the women in the expectant management group (OR 0.96, 95% CI 0.89;1.03, $p = 0.34$). Consequently, six women in the curettage group and five women in the expectant management group did not conceive. Conception rates did not differ statistically between both groups ($p = 0.22$). The mean time to pregnancy was 32 weeks for women in the curettage group versus 29 weeks for women who underwent expectant management (mean difference 3.15 weeks 95% CI –4.60;10.91). Time to pregnancy and cumulative time to pregnancy are displayed in Table 2. The Kaplan-Meier curve illustrates the time to pregnancy for women treated with curettage and expectant management. (Fig. 2) The overall time to pregnancy did not differ significantly ($p = 0.209$).

The number of ongoing pregnancies was 58/67 (87%) in the curettage group versus 94/120 (78%) in the expectant management group (OR 1.12, 95% CI 0.99;1.28, $p = 0.226$). Spontaneous miscarriage before 16 weeks of gestation, termination of pregnancy or ectopic pregnancy occurred in 8/67 (12%) of the women in the curettage group, versus 26/120 (22%) of the women in the expectant management group. For one woman in the curettage group it was unknown if the pregnancy was ongoing or not. One woman in the expectant management group underwent a termination of pregnancy because of multiple congenital malformations suspected for trisomy 18.

Obstetric outcomes were available for 127/152 women. The mean gestational age at delivery was 39 weeks and 5 days in the curettage group versus 38 weeks and 6 days in the expectant management group. Two women, both managed expectantly, delivered before 32 weeks of gestation at 26 weeks and 27 weeks of gestation respectively. There was one preterm birth before 37 weeks of gestation in the curettage group versus 8 women in the

expectant management group (including the two women who delivered <32 weeks of gestation) (OR 0.22, 95% CI 0.03;1.71 $P = 0.15$).

Caesarean section rate was 22% (10/46) in women who underwent curettage, versus 26% (21/81) in women who underwent expectant management ($p = 0.67$). In the curettage group three out of ten caesarean sections planned in pregnancy, and six out of ten were secondary caesarean sections while for one caesarean section the indication was unknown. In the expectant management group, ten out of 19 caesarean sections were planned in pregnancy and six out of 19 caesarean sections were unscheduled. For the remaining three caesarean sections planning thereof was unclear.

Mean birth weights were 3640 g (± 610) in the curettage group and 3438 g (± 590) in the expectantly managed group ($p = 0.673$). There was one neonatal death which occurred in a woman that had undergone expectant when she had an incomplete evacuation. This child, born at 26 weeks of gestation, died from the effects of extreme prematurity.

Discussion

Main findings

In women with an incomplete evacuation of the uterus, curettage and expectant management lead to similar fertility rates, time to pregnancy and ongoing pregnancy rates. Occurrence of pregnancy complications was comparable, as were caesarean section rates.

Strengths and limitations

To our knowledge this is the first partly randomised trial to assess fertility rates and obstetric outcome in women treated with either curettage or expectant management in case of an incomplete evacuation of the uterus after misoprostol treatment for first trimester miscarriage. The follow-up was 2.5–4.5 years, and therefore long enough to reliably assess fertility and the outcomes of subsequent pregnancy. Although the time between the event of a pregnancy and the questionnaire could have been substantial we judge recall bias to be relatively low, since the occurrence of a pregnancy is a major life event which most women remember well.

Table 2
Time to first conception.

Time between misoprostol treatment and subsequent conception (months)	Pregnancy rate		Cumulative pregnancy rate		p-Value for cumulative rates
	Curettage (N = 73)	Expectant management (N = 125)	Curettage (N = 73)	Expectant management (N = 125)	
0–3	12 (16%)	27 (22%)	12 (16%)	27 (22%)	0.460
3–6	23 (32%)	32 (26%)	33 (48%)	59 (47%)	1.00
6–12	19 (26%)	44 (35%)	54 (74%)	103 (82%)	0.203
>12	6 (8%)	9 (7%)	60 (82%)	112 (90%)	0.190
Not pregnant	6 (8%)	5 (4%)			
Unknown time to pregnancy	7 (10%)	8 (6%)			

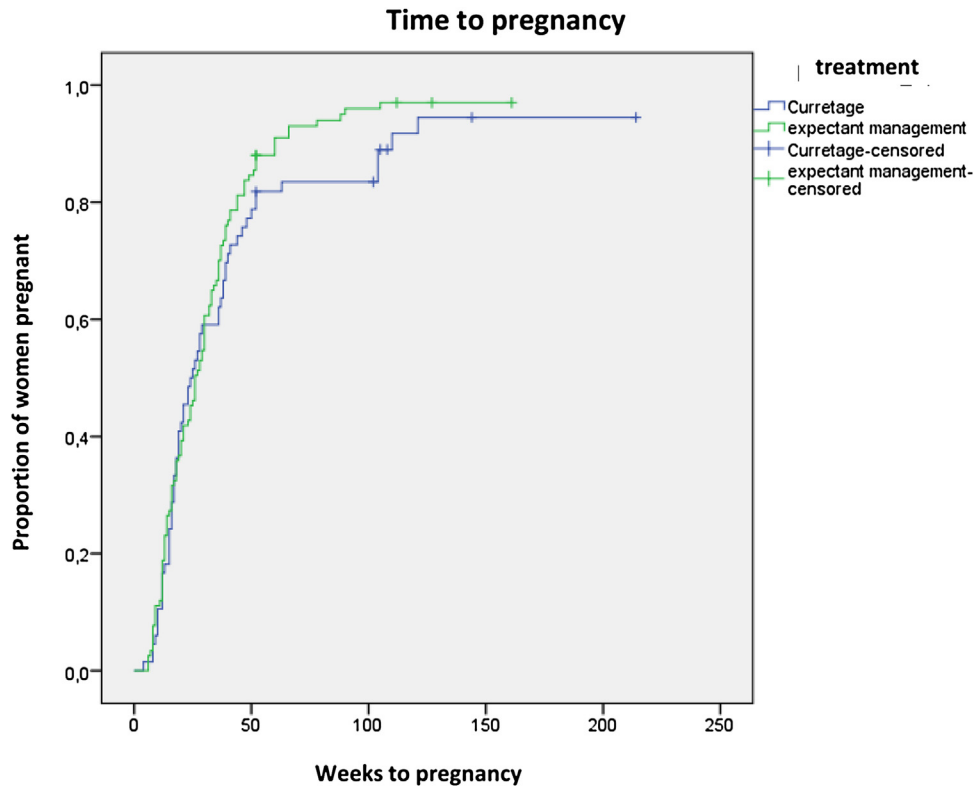


Fig. 2. Time (weeks) to first conception after index misoprostol treatment, classified by treatment.

For the original MisoREST trial, power analysis was performed for the main outcome (empty uterus or uneventful clinical course) and not for the secondary outcomes such as fertility and obstetric outcomes which are discussed in the present study. A type two error therefore cannot be ruled out. We intended to randomise 162 women, but were able to randomize only 59. Due to a strong preference of the participating women for either curettage or expectant management the trial was held prematurely.

Clinical implications

In the present study at least 74% of the responding women, with a wish to conceive, who underwent curettage, conceived within one year following study participation. For women managed expectantly at least 82% of the women conceived within the first year after study participation. In the study by Blohm et al., 75% for women treated with curettage and 78% for women managed expectantly for a first trimester miscarriage conceived within one year after the miscarriage [16]. Kaplan et al. report a 73% conception rate in the first year in women managed expectantly for a first trimester miscarriage [17]. Although we studied women with an incomplete miscarriage after initial misoprostol treatment, conception rates were in the same range, or slightly higher. Apparently, the incomplete miscarriage which was the reason for inclusion in our trial, did not impair future fertility, without obvious impact of its surgical or expectant management.

Around 22–26% of the pregnancies ended in caesarean section in this study. This percentage is probably similar to the caesarean section rate in the general Dutch population. Caesarean section rate was 15.1% in 2007 and 16.4% in 2013 and still rising (www.perinatreg.nl).

Preterm birth <37 weeks of gestation, occurred in 7% of the women in this study. The proportion of women delivering preterm is consistent with the literature [18,19]. We expected a higher

incidence of preterm birth in women with a previous curettage as we identified a previous curettage to be a risk factor for subsequent preterm birth in a previous systematic review [6]. In the current study we did not find any difference in premature delivery in both groups. This may be explained by the fact that cervical dilatation is unnecessary in typical cases of incomplete miscarriage after primary misoprostol treatment or expectant management, as opposed to the situation where curettage is being used as a primary treatment.

Conclusion

In women with an incomplete evacuation of the uterus after misoprostol treatment, expectant management is a safe alternative to curettage with regard to long term fertility and pregnancy outcome.

Contributors

MV, ML, PB, JH, 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. ML and MV performed the trial, collected the data and performed statistical analyses. JH, DH, MH, JS and AA were local investigators. ML and KO performed the analyses. ML and KO wrote the first draft of the report and ML revised subsequent draft. All authors contributed to and approved the final report. WA is guarantor.

Funding

This study was funded by ZonMw, a Dutch organization for Health Research and Development, project number 80-82310-97-12066. The views expressed in this article are those of the authors and not necessarily those of ZonMW.

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.

Trial registration number

Dutch Trial Register NTR3310, <http://www.trialregister.nl>.

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.

References

- [1] Neilson JP, Gyte GM, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. *Cochrane Database Syst Rev* 2013;3:CD007223.
- [2] Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM, et al. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med* 2005;353(8):761–9.
- [3] Ankum WM. Management of first trimester miscarriage. *Br J Hosp Med (Lond)* 2008;69(7):380–3.
- [4] Gilman Barber AR, Rhone SA, Fluker MR. Curettage and Asherman's syndrome—lessons to (re-) learn? *J Obstet Gynaecol Can* 2014;36(11):997–1001.
- [5] Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brolmann HA, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. *Hum Reprod Update* 2014;20(2):262–78.
- [6] Lemmers M, Verschoor MA, Hooker AB, Opmeer BC, Limpens J, Huirne JA, et al. Dilatation and curettage increases the risk of subsequent preterm birth: a systematic review and meta-analysis. *Hum Reprod* 2016;31(1):34–45.
- [7] Creinin MD, Schwartz JL, Guido RS, Pymar HC. Early pregnancy failure—current management concepts. *Obstet Gynecol Surv* 2001;56(2):105–13.
- [8] Verschoor MA, Lemmers M, Wekrow AL, Huirne JA, Goddijn M, Mol BW, et al. Practice variation in the management of first trimester miscarriage in the Netherlands: a nationwide survey. *Obstet Gynecol Int* 2014;2014:387860.
- [9] Brouns JF, Burger MP, van Wijngaarden WJ. Evaluation of the introduction of a new treatment for the termination of pregnancy in The Netherlands. *Acta Obstet Gynecol Scand* 2010;89(9):1210–3.
- [10] Davis AR, Hendlish SK, Westhoff C, Frederick MM, Zhang J, Gilles JM, et al. Bleeding patterns after misoprostol vs surgical treatment of early pregnancy failure: results from a randomized trial. *Am J Obstet Gynecol* 2007;196(1):e1–7 31.
- [11] Sahin HG, Sahin HA, Kocer M. Randomized outpatient clinical trial of medical evacuation and surgical curettage in incomplete miscarriage. *Eur J Contracept Reprod Health Care* 2001;6(3):141–4.
- [12] Creinin MD, Harwood B, Guido RS, Fox MC, Zhang J. Trial NMoEPF. Endometrial thickness after misoprostol use for early pregnancy failure. *Int J Gynaecol Obstet* 2004;86(1):22–6.
- [13] Lemmers M, Verschoor MA, Oude Rengerink K, Naaktgeboren C, Opmeer BC, Bossuyt PM, 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):2421–7.
- [14] Bord I, Gdalevich M, Nahum R, Meltzer S, Anteby EY, Orvieto R. Misoprostol treatment for early pregnancy failure does not impair future fertility. *Gynecol Endocrinol* 2014;30(4):316–9.
- [15] Graziosi GC, Bruinse HW, Reuwer PJ, Teteringen O, Mol BW. Fertility outcome after a randomized trial comparing curettage with misoprostol for treatment of early pregnancy failure. *Hum Reprod* 2005;20(6):1749–50.
- [16] Blohm F, Hahlin M, Nielsen S, Milsom I. Fertility after a randomised trial of spontaneous abortion managed by surgical evacuation or expectant treatment. *Lancet (London, England)* 1997;349(9057):995.
- [17] Kaplan B, Pardo J, Rabinerson D, Fisch B, Neri A. Future fertility following conservative management of complete abortion. *Hum Reprod* 1996;11(1):92–4.
- [18] Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ* 2010;88(1):31–8.
- [19] Tielsch JM. Global incidence of preterm birth. *Nestle Nutr Inst Workshop Ser* 2015;81:9–15.