



PRACTICE

UNCERTAINTIES

What is the best method for managing early miscarriage?

Justin Chu, *sub-specialist trainee in reproductive medicine and national clinical coordinator (MifeMiso)*,^{1 2} Adam J Devall, *senior clinical trial fellow and centre manager/team leader for miscarriage research*^{2 3}, Pollyanna Hardy *statistics lead*⁴, Leanne Beeson *senior trial manager (MifeMiso)*⁴, Arri Coomarasamy *professor of gynaecology and director of Tommy's National Centre for Miscarriage Research*³

¹Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK; ²University of Birmingham, Institute of Metabolism and Systems Research, Birmingham, UK; ³Tommy's Centre for Miscarriage Research, Birmingham, UK; ⁴University of Birmingham, Birmingham Clinical Trials Unit, Birmingham, UK

What you need to know

- Guidelines from the National Institute for Health and Care Excellence recommend expectant management, ie, waiting for spontaneous miscarriage, for 7-14 days after early miscarriage is diagnosed if there are no complications
- Medical management with misoprostol has comparable success rates to surgery but there is uncertainty about the appropriate dosing regimen, the route of administration, and the role of mifepristone
- Evidence is limited on outcomes such as women's preferences, satisfaction, and subsequent fertility

An early miscarriage is the loss of pregnancy at ≤ 13 weeks' gestation.¹ It is a major life event and can have a potentially devastating psychological impact on the woman in addition to the physical effects such as bleeding and pain.² About one in four pregnancies, where a woman has missed a menstrual period and has a positive pregnancy test, ends in early miscarriage.³ Nearly 125 000 early miscarriages occur annually in the UK, accounting for 50 000 hospital admissions.⁴

Early miscarriage is usually diagnosed by pelvic ultrasound after a woman has experienced vaginal bleeding or abdominal pain. Women with a complete miscarriage, where expulsion of pregnancy tissue is complete, are managed conservatively without further intervention. Women with a missed or incomplete miscarriage (box 1) may require further intervention.

Box 1: Categories of early miscarriage

- Missed miscarriage—pregnancy tissue is complete inside the uterus without fetal heart activity. The woman may have minimal symptoms
- Incomplete miscarriage—ultrasound imaging shows that some but not all of the pregnancy tissue has passed.⁵ Women have usually had pain and bleeding

Surgery under general anaesthesia used to be the standard treatment for miscarriage,⁶ but a wider choice of management options is now available (fig 1).³ Over the past two decades there has been a shift towards individualised care and shared decision making between clinician and patient. Up to 70% of women with miscarriage opted for expectant management, ie, waiting for spontaneous miscarriage, in a prospective cohort study (312 women).⁷ Women may have preferences around how promptly they want the miscarriage managed, or they may have concerns about surgery and future fertility.

Uncertainty exists about the preferred option in a given situation and there is a lack of clarity about the most meaningful outcomes, particularly from a woman's perspective.

What is the evidence of uncertainty?

Risks and benefits of different options

We found three Cochrane reviews comparing two or more management approaches for early miscarriage. Overall, surgical management has higher rates of miscarriage resolution in comparison with medical and expectant management (fig 2). The relative success rates, defined as complete miscarriage, are 58% with expectant management, 81% with medical management, and 96% with surgery, as per the most recent Cochrane review (24 studies, 5577 women).⁶ We found no important difference in subsequent fertility,⁶ women's satisfaction,⁶ or psychological wellbeing⁸ with medical, surgical, or expectant management, although the evidence is limited and of very low quality.⁶ A network meta-analysis concluded that medical treatments for first trimester miscarriage have similar effectiveness to surgery in achieving complete evacuation of

the uterus and severity of side effects (nausea, vomiting, and diarrhoea).⁹

Systematic reviews and randomised controlled trials have focused on complete emptying of the uterus and the lack of need for unplanned surgery as definitions of success. Many women want timely resolution of miscarriage.¹⁰ The definition and time interval used to assess complete emptying of the uterus varies across studies. Importantly, the longer the time interval used, the higher the chance of success of expectant and medical management. Considerable variation exists in the reporting of primary and secondary outcomes in miscarriage studies along with the measures used to assess them.¹¹

Moderate to high quality evidence shows that expectant management has a higher risk of incomplete miscarriage at 2 weeks and 6-8 weeks, with a higher need for unplanned surgical evacuation, more bleeding, and higher blood transfusion rates compared with surgery, as per a Cochrane review (seven randomised controlled trials, 1521 women).¹² The costs are lower for expectant management. A subsequent randomised controlled trial (360 participants), however, reported no statistically significant difference in complete uterine evacuation at 6 weeks.¹³

Expectant management

There is uncertainty regarding the length of time that women should try expectant management. Guidance from the National Institute for Health and Care Excellence (NICE) recommends expectant management for 7-14 days once miscarriage is confirmed on ultrasound.¹ An exception is women with excessive bleeding in whom emergency surgery may be needed. Guidance from the American College of Obstetricians and Gynaecologists (ACOG) suggests up to 8 weeks of expectant management to achieve approximately an 80% success rate.¹⁴ If expectant management is unsuccessful, the woman is offered medical or surgical management.¹

Medical management

The Cochrane review found no evidence of a difference in the effectiveness of different misoprostol regimens in the completion of miscarriage.⁶ There is uncertainty around the optimal route of administration (vaginal or oral), and the additional value of mifepristone.¹⁵ The PreFaiR trial (300 participants) found a higher likelihood of expulsion of the gestational sac when mifepristone (200 mg orally) was used before misoprostol administration (800 µg vaginally) compared with misoprostol alone.¹⁶ NICE and ACOG guidance currently recommend an 800 µg dose of misoprostol given vaginally for missed miscarriage with a repeat dose of 600 or 800 µg for incomplete miscarriage.¹⁴ Following publication of the PreFaiR trial, ACOG also advises the administration of 200 mg oral mifepristone, if available, 24 hours before misoprostol.¹⁴

Surgical management

Surgical uterine evacuation methods include suction curettage performed under general anaesthetic or a manual vacuum aspiration performed under local anaesthetic in an outpatient setting. Trials have compared costs, safety, and effectiveness of both surgical approaches but data to draw firm conclusions is lacking,¹⁷⁻¹⁹ and either approach appears to be equally effective in achieving complete uterine evacuation. Complications and need for further surgery are rare, although these can be serious (bleeding, infection, and uterine perforation).¹⁷

Is ongoing research likely to provide relevant evidence?

We searched the World Health Organisation International Clinical Trials Registry Platform and the clinicaltrials.gov website using the term “miscarriage management” and identified five ongoing trials.²⁰⁻²⁴ Three of these trials investigate different regimens and routes of administration used in medical management. We are leading one of these trials (the MIFEMISO trial with a target of 710 participants; ISRCTN: 17405024) in the UK. One trial investigates the time to next pregnancy after medical versus surgical management. The last trial compares the use of topical lignocaine with placebo gel in manual vacuum aspiration.

We expect these trials will add to the evidence base to help women and clinicians choose the most suitable management option.

What should we do in the light of the uncertainty?

For women with abdominal pain or vaginal bleeding in early pregnancy, NICE guidance recommends prompt referral to the local early pregnancy clinic for ultrasound assessment of the pregnancy.¹

The choice of treatment depends on individual preferences as well as the clinical situation. Emergency surgery with suction curettage remains the treatment of choice in women who have excessive bleeding or who are haemodynamically unstable. Expectant management is advised for 7-14 days as per NICE guidance, except if the woman is bleeding or is at an increased risk of haemorrhage, has previously had a traumatic experience in early pregnancy, or if there is evidence of infection.¹

Recognise that this can be a difficult time for the woman and be sensitive to her needs and preferences. Provide accurate and consistent information regarding what each management option entails and the duration of each option to resolve the early miscarriage.

Most women will have a preference as to how they would like their miscarriage to be managed.¹ For some women, the process of experiencing pain and bleeding is important in acknowledging their miscarriage and beginning the grieving process. Some women may have fears of medical or surgical intervention and therefore may wish to pursue expectant management. Others will wish to have an expedited process but want to avoid surgery, and therefore medical management could be the right option. Conversely, some women will want to manage their miscarriage as quickly as possible and would prefer surgery.³ The patient should be fully informed about the risks of surgery and general anaesthesia.

Respect a woman's decision and explain the selected management processes clearly, offering support where required. You may wish to signpost the woman and her family to charities such as the Miscarriage Association (box ‘Information resources for patients’). Women undergoing early miscarriage may require an extended period to consider their choice of management, and may benefit from written information. If the woman expresses concern about future pregnancy, explain that miscarriage management rarely affects a woman's chances of further conception. Some women wish to know how soon they can start trying for another pregnancy after miscarriage management. Let her know that she can start trying to conceive once she has been discharged from the early pregnancy clinic.

Search strategy and study selection

We searched the Cochrane library for systematic reviews on management of "early miscarriage" and "early pregnancy loss." If no Cochrane review was available we searched PubMed for other systematic reviews and individual randomised controlled trials of commonly used treatments. We preferentially selected studies that were published most recently.

How patients were involved in the creation of this article

At a large teaching hospital outpatient clinic, we asked 10 women who have had recurrent miscarriages what they felt were the biggest uncertainties surrounding how they had their miscarriages managed. Their answers revealed that patient choice regarding the management option selected for their miscarriages was what mattered most to these patients. As such, we ensured that patient choice was a central theme for this article.

Recommendations for future research

Large, robustly conducted randomised controlled trials should compare different forms of the same management options. For example, comparing different durations for expectant management and different medical regimens for the medical management of miscarriage.

- **Population:** Women with early miscarriage (≤ 13 weeks' gestation)
- **Intervention:** Expectant, medical or surgical management of miscarriage
- **Comparator:** Other forms of medical or surgical management of miscarriage (such as mifepristone and misoprostol versus misoprostol alone in the medical management of miscarriage or manual vacuum aspiration versus surgical aspiration under general anaesthesia)
- **Outcome:** Standardised outcome measures such as complete evacuation of the uterus at seven days post-randomisation or requirement for unplanned surgery

In addition, there is a need for standardised patient centred clinical outcomes through the development of a core outcome set.

Education into practice

- Based on reading this article, how would you discuss the management options for early miscarriage with women in your care?
- What options are available for miscarriage management at your local early pregnancy clinic? And what are the processes that are involved in each management option?

What patients need to know

- Miscarriages affect roughly one in every four pregnancies
- Most women will have a healthy pregnancy after a miscarriage
- Your doctor will be able to discuss your management options with you, including the risks and benefits of each option
- Broadly, you have three options if you have been diagnosed with a miscarriage:
 1. Expectant management—waiting for spontaneous miscarriage
 2. Medical management—using tablets to expedite the miscarriage
 3. Surgical management—undergoing a short surgical procedure, which can be done under local or general anaesthetic
- Current guidelines recommend expectant management for anywhere between 1 and 8 weeks after early miscarriage is diagnosed if there are no associated complications
- Surgery leads to more prompt resolution of miscarriage compared with other approaches, but it can have rare and sometimes serious risks. Expectant and medical management have comparable rates of complete miscarriage though these may take longer, and may sometimes require surgery later
- Discuss your preferences with your doctor to decide on the most suitable option

Information resources for patients

NHS: <https://www.nhs.uk/conditions/miscarriage>
Overview, symptoms, causes, diagnosis, what happens, aftercare, and prevention information

NICE: <https://www.nice.org.uk/guidance/cg154/ifp/chapter/About-this-information>
Information regarding miscarriage and its management

Miscarriage Association: <https://www.miscarriageassociation.org.uk/>
Support and information for anyone affected by the loss of a baby in pregnancy

Competing interests We have read and understood The BMJ policy on declaration of interests and declare the following interests: AC is chief investigator for the MIFEMISO trial, JJC is the National Clinical Coordinator for the MIFEMISO trial and declares receiving honorarium to attend conferences from Gedeon Richter and Pharmasure, which produce infertility treatments. AD is a member of the MIFEMISO Trial Management Group, LB is the MIFEMISO trial coordinator, and PAH is the senior statistician for the MIFEMISO trial.

Contributorship statement and guarantor JJC, AD, PAH, LB, and AC developed the outline of the manuscript and outline of the uncertainties. JJC drafted the first and revised versions of the manuscript. All authors contributed to writing and critically reviewing the manuscript. JJC is guarantor.

Funding The authors had no support from any organisations for the submitted work. The MifeMiso trial is funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (Ref: 15/160/02). AC is an NIHR Senior Investigator. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

Provenance and peer review: commissioned; externally peer reviewed.

- 1 National Institute for Health and Care Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management. NG126. 2019. <https://www.nice.org.uk/guidance/ng126>
- 2 Radford EJ, Hughes M. Women's experiences of early miscarriage: implications for nursing care. *J Clin Nurs* 2015;24:1457-65. 10.1111/joon.12781 25662397
- 3 Jurkovic D, Overton C, Bender-Atik R. Diagnosis and management of first trimester miscarriage. *BMJ* 2013;346:f3676. 10.1136/bmj.f3676 23783355
- 4 Health and Social Care Information Centre. Hospital episode statistics. NHS maternity statistics 2017-18. <https://files.digital.nhs.uk/C3/47466E/hosp-epis-stat-mat-summary-report%202017-18.pdf>
- 5 Doubilet PM, Benson CB, Bourne T, et al. Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med* 2013;369:1443-51. 10.1056/NEJMra1302417 24106937
- 6 Kim C, Barnard S, Neilson JP, Hickey M, Vazquez JC, Dou L. Medical treatments for incomplete miscarriage. *Cochrane Database Syst Rev* 2017;1:CD007223.28138973
- 7 Luise C, Jerry K, Collons WP, Bourne TH, Collins WP, Bourne TH. Expectant management of incomplete, spontaneous first-trimester miscarriage: outcome according to initial ultrasound criteria and value of follow-up visits. *Ultrasound Obstet Gynecol* 2002;19:580-2. 10.1046/j.1469-0705.2002.00662.x 12099260
- 8 Kong GW, Lok IH, Yiu AK, Hui AS, Lai BP, Chung TK. Clinical and psychological impact after surgical, medical or expectant management of first-trimester miscarriage—a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2013;53:170-7. 10.1111/ajo.12064 23488984
- 9 H Al Wattar B, Murugesu N, Tobias A, Zamora J, Khan KS. Management of first-trimester miscarriage: a systematic review and network meta-analysis. *Hum Reprod Update* 2019;25:362-74. 10.1093/humupd/dmz002 30753490
- 10 Evans L, Lloyd D, Considine R, Hancock L. Contrasting views of staff and patients regarding psychosocial care for Australian women who miscarry: a hospital based study. *Aust N Z J Obstet Gynaecol* 2002;42:155-60. 10.1111/j.0004-8666.2002.00155.x 12069141
- 11 Smith PP, Dhillion-Smith RK, O'Toole E, Cooper N, Coomarasamy A, Clark TJ. Outcomes in prevention and management of miscarriage trials: a systematic review. *BJOG* 2019;126:176-89. 10.1111/1471-0528.15528 30461160
- 12 Nanda K, Lopez LM, Grimes DA, Peloggia A, Nanda G. Expectant care versus surgical treatment for miscarriage. *Cochrane Database Syst Rev* 2012;3:CD003518. 10.1002/14651858.CD003518.pub3 22419288
- 13 Nadarajah R, Quek YS, Kuppannan K, Woon SY, Jegannathan R. A randomised controlled trial of expectant management versus surgical evacuation of early pregnancy loss. *Eur J Obstet Gynecol Reprod Biol* 2014;178:35-41. 10.1016/j.ejogrb.2014.02.021 24813099
- 14 ACOG Practice Bulletin No. 200 Summary: Early Pregnancy Loss. (2018). *Obstet Gynecol* 2018;132:1311-310.1097/AOG.0000000000002900.
- 15 Neilson JP, Hickey M, Vazquez J. Medical treatment for early fetal death (less than 24 weeks). *Cochrane Database Syst Rev* 2006;3:CD002253. 10.1002/14651858.CD002253.pub3 16855990
- 16 Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone pretreatment for the medical management of early pregnancy loss. *N Engl J Med* 2018;378:2161-70. 10.1056/NEJMoa1715726 29874535
- 17 Tunçalp O, Gülmezoglu AM, Souza JP. Surgical procedures for evacuating incomplete miscarriage. *Cochrane Database Syst Rev* 2010;9:CD001993.20824830

- 18 Tasnim N, Mahmud G, Fatima S, Sultana M. Manual vacuum aspiration: a safe and cost-effective substitute of electric vacuum aspiration for the surgical management of early pregnancy loss. *J Pak Med Assoc* 2011;61:149-53.21375164
- 19 Rausch M, Lorch S, Chung K, Frederick M, Zhang J, Barnhart K. A cost-effectiveness analysis of surgical versus medical management of early pregnancy loss. *Fertil Steril* 2012;97:355-60. 10.1016/j.fertnstert.2011.11.044 22192348
- 20 World Health Organization International Trials Registry Platform search portal. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT03628625>
- 21 World Health Organization International Trials Registry Platform search portal. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN17405024>
- 22 World Health Organization International Trials Registry Platform search portal. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT02957305>
- 23 World Health Organization International Trials Registry Platform search portal. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=PACTR201803003216942>
- 24 World Health Organization International Trials Registry Platform search portal. <http://apps.who.int/trialsearch/Trial2.aspx?TrialID=SLCTR/2017/014>

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

Figures

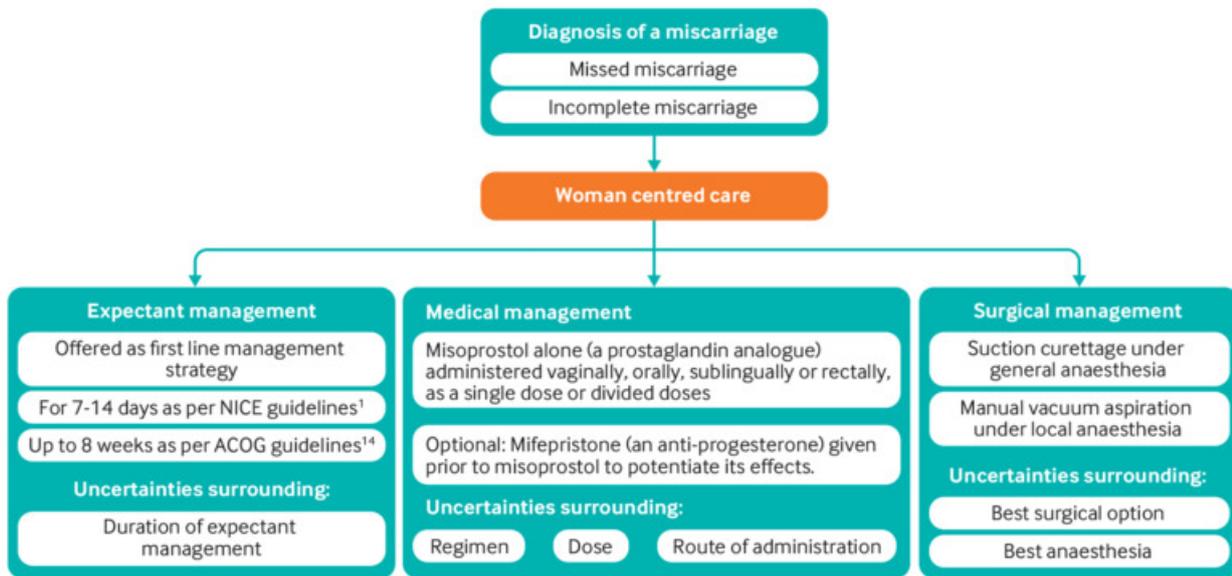


Fig 1 Management options for miscarriage

Visual Summary GOFER diagram (Graphical Overview for Evidence Reviews)

Summarising systematic reviews and randomised controlled trials of early miscarriage management

RR = Relative risk, RD = Relative difference, 95% confidence interval, GRADE scores: Very low, Low, Moderate, High

Systematic reviews	Participants	Interventions	Comparisons	Outcomes	Adverse events	Other	Evidence quality
Reh 2017	1577	Misoprostol (vaginal, oral or sublingual)	Expectant care	Complete miscarriage or procedure success: RR 1.23 (0.72 to 2.10)	Need for evacuation: RR 1.23 (0.72 to 2.10)	Adverse events: RR 2.95 (0.12 to 70.05)	Uncertainty: Evidence of very low/low quality for primary outcomes
Nanda 2012	1021	Sharp curettage, suction curettage, manual vacuum aspiration	Expectant management	Expectant management had a higher rate of incomplete miscarriage: RR 3.06 (2.14 to 4.38)	Localised pelvic infection: RR 0.53 (0.34 to 1.0)	Intensive care unit admission: RR 4.45 (1.21 to 16.42)	Outcomes were better with surgical management, but costs were higher
Turnip 2016	550	Vacuum aspiration	Vacuum aspiration	No significant difference observed	Uterine perforation: RR 0.27 (0.07 to 2.76)	No significant difference in duration of procedures: RR 7.20 (-1.04 to 6.87)	No firm conclusions made due to the paucity of data
Nelson 2006	1088	Misoprostol, methotrexate, laminaria tents, mifepristone, gemeprost	Medical management (other management)	Complete miscarriage was more common with misoprostol than with placebo: RR 4.75 (2.50 to 8.26)	Need for surgical evacuation lower in misoprostol group than placebo: RR 0.40 (0.26 to 0.60)	Uterine perforation: RR 7.20 (-1.04 to 6.87)	Further research required to ascertain effectiveness
Fernund 2016	169	Misoprostol 800mcg, vaginally	Expectant management	Complete miscarriage: 65.9% vs 43.3% (Difference 22.6%, 7.5% to 36.5%)	Expectant management was less painful: RR 0.81 (0.51 to 1.25)	Intensive care unit admission: RR 7.20 (-1.04 to 6.87)	Misoprostol was more effective
Schreiber 2018	300	Misoprostol 800mcg + Mifepristone 200mcg, vaginally	Misoprostol alone 800mcg, vaginally	Complete miscarriage without evacuation and evacuation within 10 days: RR 1.25 (0.89 to 1.83)	Participants' satisfaction was not measured		
Niedergang 2014	360	Surgical management	Expectant management	Success rate: 84% vs 74% (P=0.081)	No statistically significant difference in the success rate		
Kung 2013	180	Medical management	Expectant management	Complete miscarriage rate at Day 14: 98.1% vs 70.0% (79.3%)	Cost of providing treatment: \$563.4 USD vs \$899.4 USD		No significant differences in psychological well-being, depression scores, or anxiety levels
Rauch 2012	403	Medical management	Surgical management	Efficacy: 0.844 vs 0.968	No statistically significant difference in the success rate		
Tasman 2011	176	Manual vacuum aspiration	Electrical vacuum aspiration	Success rate: 89.6% vs 91.4% (P=0.891)	No statistically significant difference in the success rate		
Buohm 2005	126	Misoprostol 800mcg, vaginally	Placebo	Complete miscarriage without evacuation and evacuation within 10 days: 65.9% vs 43.3% (Difference 22.6%, 7.5% to 36.5%)	More pain experienced and more analgesics required with misoprostol	Uterine perforation: RR 7.20 (-1.04 to 6.87)	Misoprostol increased the rate of resolution

Fig 2 Graphical overview summarising systematic reviews and randomised controlled trials of early miscarriage management