Mifepristone and misoprostol versus placebo and misoprostol for resolution of miscarriage in women diagnosed with missed miscarriage: the MifeMiso RCT

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Declared competing interests of authors: Andrew Horne reports having served as a consultant for AbbVie (Lake Bluff, IL, USA), Roche Diagnostics (Roche Holding AG, Basel, Switzerland), Ferring Controlled Therapeutics (Glasgow, UK) and Nordic Pharma Ltd (Berkshire, UK), and has received research support from the Medical Research Council (MRC), National Institute for Health Research (NIHR), Chief Scientist's Office, Wellbeing of Women, Roche Diagnostics, AstraZeneca (Cambridge, UK) and Ferring Controlled Therapeutics outside the submitted work. Pollyanna Hardy reports membership of the NIHR Health Technology Assessment (HTA) Commissioning Committee (2020–present). Meenakshi Choudhary reports membership of the NIHR HTA Maternal, Neonatal and Child Health Panel Panel (2017–18), NIHR HTA Prioritisation Committee C (Mental Health, Women and Children's Health) (2017–20) and the NIHR HTA Prioritisation Committee B (In Hospital) (2017–21). Arri Coomarasamy reports membership of the NIHR Efficacy and Mechanism Evaluation (EME) programme (2019–present) outside the submitted work.

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published November 2021
DOI: 10.3310/hta25680

Scientific summary

The MifeMiso RCT

Health Technology Assessment 2021; Vol. 25: No. 68
DOI: 10.3310/hta25680

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Miscarriage is the most common complication of pregnancy. As many as 15–25% of pregnancies end in a miscarriage, and the number of miscarriages in England is estimated to be approximately 125,000 per year. Management of miscarriage can be expectant (i.e. waiting for natural miscarriage), medical (i.e. with drugs) or surgical. About 25% of women opt for medical management; however, there is uncertainty about the optimal drug regimens for medical management.

Before National Institute for Health and Care Excellence (NICE) guideline CG154 was published in 2012, it was common practice to use a combination of mifepristone (Mifegyne®, Exelgyn, Paris, France) and misoprostol. The 2012 guideline, however, recommended that misoprostol alone should be given to women having medical management. This recommendation was based on very limited evidence, from one study of 115 women, which found no difference between a combination of mifepristone and misoprostol and misoprostol alone. Recognising the limited available evidence, NICE and the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) called for a trial.

Objectives

The primary objective was to test the hypothesis that treatment with mifepristone plus misoprostol is superior to treatment with misoprostol alone for the resolution of miscarriage within 7 days in women diagnosed by pelvic ultrasound scan with a missed miscarriage in the first 14 weeks of pregnancy.

The key secondary objective aimed to test the hypothesis that the addition of mifepristone reduces the need for surgical intervention to resolve the miscarriage.

Other secondary objectives aimed to evaluate if the addition of mifepristone reduces the need for further doses of misoprostol, to evaluate if the addition of mifepristone improves other clinical outcomes [including surgical intervention up to and including 7 days post randomisation and after 7 days post randomisation, duration of bleeding, infection, negative pregnancy test at 21 days post randomisation, time from randomisation to discharge from early pregnancy unit (EPU) care, side effects and complications], to evaluate if the addition of mifepristone improves patient satisfaction and acceptability of management and to assess the cost-effectiveness of the combination of mifepristone and misoprostol in the medical management of missed miscarriage.

Methods

Participants were randomised online in a 1 : 1 ratio via a secure internet facility through an Integrated Trial Management System. Minimisation was implemented for maternal age (< 30 or ≥ 30 years), body mass index (< 35 or ≥ 35 kg/m^2), previous parity (nulliparous or parous women), gestational age (< 70 or ≥ 70 days), amount of bleeding (Pictorial Blood loss Assessment Chart score; ≤ 2 or ≥ 3) and randomising centre.

Clinical data were collected up to discharge from EPU care. Participants who agreed to participate in the qualitative study were interviewed by telephone or videoconference or face to face within approximately 6 weeks of their discharge date. The primary analysis was by intention to treat. A within-trial cost-effectiveness study and a nested qualitative study were also conducted as part of the trial.

Results

A total of 711 women, from 28 hospitals in the UK, received either mifepristone plus misoprostol (357 women) or placebo plus misoprostol (354 women). The follow-up rate for the primary outcome was 98% (696 of 711 women). The risk of failure to pass the gestational sac within 7 days was 17% (59 of 348 women) in the mifepristone plus misoprostol group, compared with 24% (82 out of 348 women) in the placebo plus misoprostol group [risk ratio (RR) 0.73, 95% confidence interval (CI) 0.54 to 0.98; $p = 0.04$]. Surgical intervention to resolve the miscarriage was needed in 17% (62 out of 355 women) in the mifepristone plus misoprostol group, compared with 25% (87 out of 353 women) in the placebo plus misoprostol group (RR 0.70, 95% CI 0.52 to 0.94; $p = 0.02$). There was no evidence of a difference in the incidence of adverse events between the two groups. A total of 42 women, 19 in the mifepristone plus misoprostol group and 23 in the placebo plus misoprostol group, took part in an interview. Women appeared to have a preference for active management of their miscarriage, to help bring a timely resolution to the physical process. Overall, when women experienced care that supported their psychological well-being throughout the care pathway, and information was delivered in a skilled and sensitive manner such that women felt informed and in control, they were more likely to express satisfaction with medical management.

The within-trial cost-effectiveness analysis found that the use of mifepristone and misoprostol resulted in an absolute effect difference of 6.6% (95% CI 0.7% to 12.5%). The average cost per woman was lower in the mifepristone and misoprostol (MifeMiso) group than in the placebo and misoprostol group, with a cost saving of £182 (95% CI £26 to £338). Hence the use of mifepristone and misoprostol for the medical management of a missed miscarriage dominated the use of misoprostol alone. The model-based analysis, that compared the trial intervention with other existing possible interventions for the management of miscarriage not analysed in the trial, showed that the MifeMiso intervention is dominant when compared with expectant management and the current medical management strategy. However, the intervention is a less effective, although less costly, strategy than surgical management.

Conclusions

Our trial showed that pre-treatment with mifepristone followed by misoprostol resulted in a higher rate of resolution of missed miscarriage than misoprostol treatment alone. Women were largely satisfied with medical management of missed miscarriage and would choose it again.

Registration

This trial is registered as ISRCTN17405024.

Funding

This project was funded by the NIHR HTA programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 68. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 15/160/02. The contractual start date was in February 2017. The draft report began editorial review in August 2020 and was accepted for publication in April 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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