Original research article

Effectiveness of early medical abortion using low-dose mifepristone and buccal misoprostol in women with no defined intrauterine gestational sac

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Abstract

Background: The study was conducted to assess the effectiveness of early medical abortion (EMA) in women with early pregnancy and no defined intrauterine gestational sac (IUGS) on ultrasound.
Study Design: Retrospective, multicenter, observational study of oral mifepristone 200 mg and buccal misoprostol 800 mcg administered 24–48 h later for EMA (gestations ≤63 days). Odds ratios (ORs) [95% confidence intervals (CIs)] of EMA failure and continuing pregnancy for women with no defined IUGS vs. those with confirmed IUGS were calculated.
Results: Women with no defined IUGS were more likely to experience EMA failure [9.0% (6/67) vs. 3.5% (465/13,345); OR (95% CI)=2.72 (1.17–6.33), p=.041] and continuing pregnancy [7.5% (5/67) vs. 0.6% (83/13,345); OR (95% CI)=12.72 (4.98–32.46), p<.001].
Conclusion: EMA failure is more likely in women with early pregnancy and no defined IUGS than those with gestations ≤63 days and confirmed IUGS.
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1. Introduction

Medical abortion offers women an effective, safe and acceptable alternative to surgical intervention for terminating an early pregnancy [1]. The medical abortion regimen recommended for early pregnancy (i.e., gestations of up to 63 days) by the Royal College of Obstetricians and Gynaecologists is oral mifepristone 200 mg then vaginal, buccal or sublingual misoprostol 800 mcg 24–48 h later [2]. In randomized controlled trials, this treatment regimen has been shown to be effective with a failure rate of 2–7% for women with gestations of up to 63 days [3–10].

Early medical abortion (EMA) may be of particular benefit for women wishing to terminate a very early pregnancy. However, published evidence on the use of EMA in women before the intrauterine gestational sac (IUGS) is visible by transvaginal ultrasound is minimal [11,12]. This is because most clinical trials of EMA require confirmation of intrauterine pregnancy by ultrasound and are likely to exclude women without a visible IUGS [13]. In March 2010, the Marie Stopes International Australia (MSIA) Authorised Prescriber protocol for EMA was amended to include women with an early pregnancy and no defined IUGS, as confirmed by ultrasound. We report the outcomes of EMA with oral mifepristone 200 mg and buccal misoprostol 800 mcg administered 24–48 h later for these women.

2. Materials and methods

2.1. Design

This analysis was part of a retrospective observational study of women who had an EMA for gestations of up to 63 days between September 1, 2009 and August 31, 2011 at 15 MSIA clinics in Australia. Data from these EMAs were collated, and the overall findings have been reported [14]. For this analysis, women with no defined IUGS who had an EMA between March 1 and December 31, 2010 were

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identified and their data were extracted. The study was conducted in accordance with the Declaration of Helsinki. All women provided written informed consent for EMA. Women with no defined IUGS provided additional informed consent because of their "uncertain" pregnancy status. The Queensland Clinical Trials Network Inc. Human Research Ethics Committee approved the Authorised Prescriber protocol and, retrospectively, publication of the data. The Australian New Zealand Clinical Trials Registry number is ACTRN12611001051932 (registered retrospectively).

2.2. EMA eligibility criteria

Before March 2010, women who had gestations of up to 63 days, as confirmed by ultrasound, were eligible for EMA as per the MSIA Authorised Prescriber protocol for EMA. From March 2010, the protocol for EMA was amended to include women with a positive urine pregnancy test, but without a defined IUGS (i.e., those who on transvaginal ultrasound had no visible gestational sac or the presence of an intrauterine anechoic structure without defining features of a gestation, such as a yolk sac or a double decidual ring). Women with no defined IUGS were eligible for EMA if their history suggested early pregnancy. Those whose history suggested ectopic pregnancy (i.e., last normal menstrual period >6 weeks ago or pain and bleeding) were further assessed to exclude this possibility. All women were required to meet the legal requirements for pregnancy termination in the Australian state or territory in which the service was provided. Women were not eligible for EMA if they had a known or suspected ectopic pregnancy; concomitant anticoagulants or corticosteroids; adrenal failure, inherited porphyria or a hemorrhagic disorder; allergy to mifepristone and/or misoprostol; intrauterine device in situ or pelvic infection. Unless they declined, all women were screened for *Chlamydia trachomatis* and, based on a risk assessment, other sexually transmitted infections. Proximity to emergency care was not an exclusion criterion.

2.3. Treatment regimen

Women were strongly encouraged to have a support person present during EMA. All women consenting to EMA were given (1) oral mifepristone 200 mg (Linepharma, Paris, France) administered at the clinic, then (2) buccal misoprostol 800 mcg (Pfizer Australia Pty Ltd., West Ryde, Australia) self-administered at home 24–48 h later, placing four 200-mcg tablets between the cheek and gum for at least 30 min before swallowing any undissolved residue. Women were instructed to contact the clinic if they had no bleeding within 24 h of taking misoprostol and were asked to return to the clinic for assessment to exclude ectopic pregnancy. The signs and symptoms of possible complications, and what to do if they occurred, were discussed with the women. All women had access to a 24-h aftercare telephone service provided by nurses employed by MSIA. Prophylactic antibiotics were prescribed only to women considered to be at high risk of infection. Rhesus-negative women (status determined before treatment) were given Rhesus D immunoglobulin (250 IU) at the time of mifepristone administration. Oral analgesics (e.g., paracetamol with codeine or ibuprofen with or without codeine) were recommended.

2.4. Assessment of pregnancy termination and complications

For women with no defined IUGS, pregnancy termination and exclusion of ectopic pregnancy were primarily confirmed by a >50% decrease in serum beta human chorionic gonadotropin (βhCG) concentration after EMA. Serum was collected from women at the clinic on the day mifepristone was administered and at their local pathology center 5–7 days after EMA. Women with an initial βhCG concentration of ≥2000 IU/L were contacted immediately and warned of the potential for ectopic pregnancy. On receipt of the second βhCG test result by the clinic, both βhCG test results were reviewed. Women were then contacted by telephone and advised whether pregnancy termination was successful or whether further investigations (e.g., ultrasound, urine pregnancy test, serum βhCG tests) were required. Women who did not have a second serum βhCG test within 5–7 days of EMA were contacted and requested to do so. All women were asked to return to the clinic about 2 weeks after EMA for assessment to exclude complications. Outcomes and any complications (e.g., continuing pregnancy, incomplete abortion requiring surgical intervention, bleeding, infection) resulting from EMA were recorded.

2.5. Data analysis

Continuous [mean, standard deviation (S.D.), range] or categorical (frequencies, percentages) variables are reported. The EMA failure rate was defined as the percentage of women with continuing pregnancy *or* incomplete abortion requiring surgical intervention. A log-linear model [odds ratios with 95% confidence intervals (CIs)] was used to compare the EMA failure rate and continuing pregnancy rate for women with no defined IUGS with those for women with a confirmed IUGS (up to 63 days gestation). $p<.05$ was considered to be significant. Statistical analyses were conducted using TIBCO Spotfire S-plus Version 8.2 (TIBCO Software Inc., Palo Alto, CA, USA).

3. Results

3.1. Patient disposition and follow-up

Between March 1 and December 31, 2010, 68 women with early pregnancy and no defined IUGS [mean±S.D. (range) years=30.0±6.5 (14, 43) years] underwent an EMA. These women had no visible gestational sac (82.4%, 56/68) or anechoic structures of 2–4 mm, without defining features of a gestation (17.6%, 12/68). One woman was subsequently diagnosed with an ectopic pregnancy and was excluded from

further analyses. The mean±S.D. (range) gestation age was 5.39±0.79 (4, 7.5) weeks (n=65; calculated from the first day of the last normal menstrual period), and initial serum βhCG concentration mean±S.D. (range) was 1215±1389 (47, 9050) IU/L (n=65). Most (92.5%, 62/67) women had follow-up assessment to confirm pregnancy termination. The comparator group comprised 13,345 EMAs (from September 1, 2009 to August 31, 2011) with a mean±S.D. (range) gestation age of 6.3±0.93 (5, 9) weeks (calculated from ultrasound assessment) [14]. Follow-up to confirm pregnancy termination was obtained for most of these EMAs (83.4%; 11,155/13,376).

3.2. EMA: failure rate and complications

Women with no defined IUGS were more likely to experience EMA failure (9.0%, 6/67) because of continuing pregnancy (7.5%, 5/67) or incomplete abortion (1.5%, 1/67). For women with no defined IUGS, the odds of EMA failure were 2.72 (95% CI=1.17–6.33) times greater than that for the comparator group (3.5%, 465/13,345; p=.041). In addition, their odds of continuing pregnancy were 12.72 (95% CI=4.98–32.46) times greater than that for the comparator group (0.6%, 83/13,345; p<.001). Those women who experienced EMA failure had an initial βhCG concentration of <870 IU/L. Other than continuing pregnancy and incomplete abortion, both of which required surgical intervention, no other complications were reported for women with no defined IUGS.

3.3. Serum βhCG concentrations

Serum βhCG concentrations measured on the day of mifepristone administration and 3–19 days after EMA were available for 56 of the 67 women with no defined IUGS. Of these 56 women, 45 (80.4%) had a >50% decrease in serum βhCG concentrations and 11 (19.6%) had a <50% decrease in serum βhCG concentrations; 6 (10.7%) due to EMA failure and 5 (8.9%) having complete abortion confirmed by ultrasound despite a <50% decrease in serum βhCG concentrations. (Of these 5 women, 2 had their second serum βhCG test within 5 days after EMA, while 1 woman had serum collected 24 h prior to mifepristone administration.)

4. Discussion

This is one of a few studies [11,12] to report findings on EMA in women with early pregnancy and no defined IUGS. In this retrospective observational study, women with early pregnancy and no defined IUGS had an EMA failure rate of 9.0% and they had a significantly greater likelihood of EMA failure and continuing pregnancy than the comparator group (confirmed IUGS up to 63 days gestation). Our findings suggest that EMA may still be an option for women with very early pregnancy and no defined IUGS who would like to proceed with pregnancy termination. However, these

women should be informed of the increased possibility of EMA failure and may therefore choose to defer treatment.

The EMA failure rate in our analysis of women with no defined IUGS (9.0%) was higher than that of the comparator group (3.5%) and those reported in other studies (2–7%) [3–10,15,16]. Higher incidences of EMA failure for women in very early pregnancy with no gestational sac on sonogram have been described [11,12]. Schaff et al. [11] reported an EMA failure rate of 7.4% (2/27) with oral mifepristone 200 mg and vaginal misoprostol 800 mcg administered 48 h later; EMA failure was because of continuing pregnancy and required surgical intervention. This was also the case for 5 of the 6 women in our study who experienced EMA failure. Although our findings and those of Schaff et al. are limited by small sample sizes, they highlight the increased potential for EMA failure in women with no defined IUGS.

Our observational study design allowed assessment of EMA in a "real world" clinical setting. Although the EMA failure rate for women with no defined IUGS was <10%, the failure rate maybe an underestimate because the outcomes of women lost to follow-up were not known. Loss to follow-up is not uncommon in routine clinical practice [2] even though follow-up provides the opportunity to confirm pregnancy termination and to detect and treat complications quickly. Women may not attend follow-up visits because they have not experienced any of the symptoms or signs indicative of an unsuccessful abortion or complications following EMA [17]. This may have been the case for the 5 women lost to follow-up in our study.

One particular benefit of EMA for very early pregnancies is the opportunity for health care providers to screen for, detect and treat ectopic pregnancy early in gestation. In a literature review, the diagnosis of ectopic pregnancy after medical abortion was rare (0.02%) [18]. In our analysis, one woman was found to have an ectopic pregnancy after EMA. Her initial serum βhCG concentration was 11,185 IU; however, attempts to contact her were unsuccessful. She developed pain on Day 5 and was subsequently referred to hospital and treated with a salpingectomy. Because of the increased potential for ectopic pregnancy in women with no defined IUGS, a shorter interval between serum βhCG concentration measurements is necessary even though longer intervals between measurements maybe more reliable for confirming pregnancy termination [19]. The slower decline in serum βhCG concentration seen in a small number of women may be explained by delayed abortion following misoprostol administration [20].

In conclusion, our findings suggest that EMA is effective for terminating very early pregnancies in women with no defined IUGS. However, these women are significantly more likely to have EMA failure or continuing pregnancy after EMA than women with a confirmed IUGS (up to 63 days gestation). Because of these risks, some women may choose to defer EMA or have additional investigations before proceeding, especially if the viability of the pregnancy is uncertain. At our clinics, we offer women with early

pregnancy and no defined IUGS the option to defer treatment by 1–2 weeks; however, we continue to provide EMA to those women who prefer not to defer treatment. As such, we have updated our EMA information and consent form to highlight the increased possibility of EMA failure in these circumstances.

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