Initiating intramuscular depot medroxyprogesterone acetate 24–48 hours after mifepristone administration does not affect success of early medical abortion

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ABSTRACT

Objectives The primary objective of this study was to determine whether intramuscular depot medroxyprogesterone acetate (IM DMPA) given at the time of misoprostol administration, 24–48 hours after mifepristone, affects the rate of continuing pregnancy. In addition, the study explored factors predictive of continuing pregnancy.

Design Case-control study based on database review of women who underwent early medical abortion (EMA) over a 4-year period.

Setting Single abortion service in Scotland.

Participants 5122 women who underwent an EMA within the timeframe of this study.

Main outcome measures Continuing pregnancies among women receiving IM DMPA were compared with those choosing other hormonal methods of contraception, non-hormonal contraception or no contraception at the time of misoprostol administration. Logistic regression was performed to assess the effects of demographic characteristics, gestation at presentation and method of contraception provided, on outcome of pregnancy.

Results A total of 4838 women with complete data were included, of which there were 20 continuing pregnancies (0.4%); 284 women were excluded due to missing data. There was no increased risk of a continuing pregnancy among women who initiated IM DMPA at the time of misoprostol administration (24–48 hours after mifepristone) compared with women who initiated no hormonal contraception at this time (RR 0.48; 95% CI 0.06 to 3.81). Gestation ≥8 weeks and previous terminations were factors associated with increased likelihood of continuing pregnancy.

Conclusions Women choosing IM DMPA after EMA can be reassured that IM DMPA can be safely initiated at the time of misoprostol administration 24–48 hours after mifepristone without an increase in the risk of a continuing pregnancy. Both increasing gestation and previous termination were factors associated with an increased likelihood of continuing pregnancy following an EMA.

Key messages

- Early medical abortion (EMA) is a highly efficacious method of abortion with a low risk of continuing pregnancy.
- Administering intramuscular depot medroxyprogesterone acetate (IM DMPA) 24–48 hours after mifepristone does not increase risk of a continuing pregnancy after EMA.
- Previous termination and increasing gestational age are associated with an increased likelihood of a continuing pregnancy following an EMA.

INTRODUCTION

Research indicates that most women ovulate in the first cycle after early medical abortion (EMA) (gestation up to 9 weeks)[1] and that as many as 15% have resumed sexual intercourse within 1 week of EMA.[2] These figures illustrate the importance of initiating an effective method of contraception immediately after EMA if women wish to avoid a subsequent unintended pregnancy, as recommended by UK national and international guidelines.[3 4]

Guidelines advise that following an EMA all hormonal methods of contraception can be initiated.[3 4] In countries where

women can self-administer misoprostol at home, it may be more convenient for them to start the contraceptive method on the day of intake of mifepristone.[2] However, women having the recommended regimen of EMA in the UK (ie, mifepristone followed 24–48 hours later by misoprostol) need to make an additional clinic visit to receive misoprostol as it is not currently permitted to take this at home in parts of the UK.[5] In October 2017, the Scottish Government approved home administration of misoprostol[6] but this currently does not apply to England. In many UK services, therefore, hormonal contraception is often initiated at the return visit for misoprostol (i.e. 24–48 hours after mifepristone).[4]

There have been theoretical concerns that initiating progestogen-containing contraceptives such as progestogen-only implants (IMP) and intramuscular depot medroxyprogesterone acetate (IM DMPA) at the time of EMA may affect the efficacy of EMA in view of potential competition between mifepristone and progestogen at the progesterone receptor.[7] In spite of these concerns, there is now good evidence that commencing IMP at the time of mifepristone does not affect efficacy of EMA.[2] However, a recent study reported that the risk of continuing pregnancy (failed EMA) was higher when IM DMPA was given on the day of mifepristone intake compared with after the abortion was complete (continuing pregnancy rate of 3.6% vs 0.9%, respectively; 95% CI 0.4 to 5.6).[8] Considering this research, updated Faculty of Sexual & Reproductive Healthcare guidelines now recommend that women be advised that IM DMPA can be safely initiated at the time of mifepristone administration but that there may be a slightly higher risk of continuing pregnancy if IM DMPA is initiated at this time.[4]

There are no data available regarding the success rate of the recommended EMA regimen[5] when DMPA is administered 24–48 hours after mifepristone intake, at the time of misoprostol administration.[4] Pharmacokinetics studies indicate that mifepristone is rapidly absorbed, reaching maximal serum concentrations within 1–2 hours of administration and remaining in the micromolar range up to 48 hours after oral intake.[9] DMPA can be detected as early as 20 min after intramuscular injection, with serum levels steadily increasing to effective concentrations within 24 hours.[9] Therefore, in theory a delay of at least 24 hours following mifepristone administration should be sufficient to prevent potential competition between mifepristone and DMPA. However, research investigating the effect of this time delay on the efficacy of EMA is required to establish whether this assumption is correct.

The primary objective of this study was to determine whether initiation of IM DMPA at the time of misoprostol administration (24–48 hours after mifepristone) affects the rate of continuing pregnancy compared with the initiation of other hormonal methods or no hormonal methods of contraception at this time. In addition, the study also explored other factors that may be predictive of continuing pregnancy.

METHODS

A review of the computerised database of women who underwent an EMA at home in the Lothian region was conducted. A case-control design was used to determine whether the methods of contraception provided at the time of misoprostol administration impacted on the outcome of the EMA.

NHS Lothian (Edinburgh and surrounding region) provides abortion services for over 2000 women per year.[10 11] Women receive advice about contraception at their initial assessment visit, and those having an EMA receive a method of contraception (pills, patches, rings, IM DMPA, IMP or condoms) on the day of administration of misoprostol, which is 24–48 hours after mifepristone administration. For women choosing intrauterine contraception (IUC), a 'fast-track' appointment is made for this to be inserted at a specialist clinic within 2 weeks of the procedure.[11] All DMPA used in this study was nurse-administered and was the intramuscular 150 mg preparation (IM DMPA).

The criteria for women having EMA at home in the NHS Lothian Abortion Service have been reported previously.[12] To be eligible for home EMA, women must be aged 16 years or over, have adult support, live within reasonable travelling distance from the abortion service, have no requirement for an interpreter, and have no causes for concern such as gender-based violence.[12]

The EMA drug regimen used consists of a single oral dose of mifepristone 200 mg followed 24–48 hours later by misoprostol 800 µg, self-administered vaginally or sublingually. Women confirm the success of EMA by performing a low-sensitivity urinary pregnancy test (LSPT) (detection limit 1000 IU)[13] at home 2 weeks after the abortion, and contact the service if the LSPT is positive or if there are signs or symptoms of continuing pregnancy.[12]

The computerised database of the abortion service was utilised specifically to identify EMAs over a 4-year period between 1 April 2012 and 31 March 2016. The database recorded information on women including demographics (age, body mass index, smoking status, reproductive history), gestation at presentation, outcome of pregnancy, and method of contraception provided by the service. The databases were compiled prospectively by research nurses and adhered to data protection standards for National Health Service (NHS) databases. Continuing pregnancies were determined by checking regional hospital and abortion service computerised databases for women who made a subsequent visit to the abortion services or another hospital in the region with an ongoing pregnancy or who were booked for maternity care with an ongoing pregnancy.

The NHS Lothian Quality Improvement Team for sexual and reproductive health approved the project. Ethical committee approval was deemed not to be required by the NHS Lothian Research Governance Office.

Patient involvement

There was no patient involvement in this database review study.

Analysis

Statistical analysis was performed on coded data using an Excel database. Excel was used to perform descriptive statistics and SPSS IBM software (Version 22.0. Armonk, NY: IBM Corp.) used for all other analysis. Women with missing data on the database were excluded from analysis. A case is defined as a woman who had a continuing pregnancy following an EMA; women with pregnancies that did not continue following an EMA acted as controls. Relative risk (RR) was used to examine the efficacy of EMA following different methods of hormonal contraception at the time of misoprostol administration in comparison to non-hormonal contraception. Logistic regression was used to examine whether women's characteristics (smoking, previous births and abortions, gestation at presentation (<8 weeks or ≥8 weeks) and the time interval between mifepristone and misoprostol) were associated with an increased likelihood of continuing pregnancy following an EMA. All variables included in the models are adjusted for one another. The adjusted odds ratios (aOR) and 95% CIs were used to interpret this model. Statistical significance was defined as $P<0.05$.

RESULTS

Characteristics of women

Over the 4-year period, 5122 women chose to have EMA at home. Some 284 women who had missing data were excluded from analysis; all women who had continuing pregnancies were included in the analysis. Of the 4838 women included in analysis there were 20 (0.4%) continuing pregnancies. The demographics of women and their gestation (assessed by ultrasound) in the case and control groups are shown in table 1.

Uptake of contraception and its effect on efficacy of EMA

Of the 4838 women who underwent an EMA, 3862 (79.8%) received contraception at the time of misoprostol administration. A total of 1674 (34.6%) women chose long-acting reversible contraception (LARC) (IM DMPA, IMP and IUC), 1753 (36.2%) chose a short-acting contraceptive (oral contraceptive pills, patches and rings) and 435 (9%) opted for a supply of non-hormonal (barrier) contraception. The proportion of women ≥8 weeks' gestation in each contraception method group was about the same (mean 18.5%); similarly, the proportions of women with previous abortion in each contraception method group were similar (mean 29.9%)

The RR of a continuing pregnancy in women receiving each method of contraception (or none) is shown in table 2. The risk of continuing pregnancy among women choosing IM DMPA was half that of women not using hormonal methods, but this was not statistically significant. Of the 475 women who received IM DMPA, 203 (42.7%) received this at 24 hours after mifepristone and there were no continuing pregnancies in this group.

Table 1 Characteristics of women undergoing early medical abortion

Characteristics*	Number of women (n=4838)	Continuing pregnancy (n=20)	Not continuing pregnancy (n=4818)
Age (years)	27 (17–46)	27 (18–40)	27 (17–46)
Body mass index (BMI) (kg/m^2)	23.6 (14.4–64.4)	23.4 (19–29)	23.7 (14.4–64.4)
Current smoker	1861 (39)	9 (45)	1852 (38)
Had previous birth	2126 (44)	10 (50)	2116 (44)
Had previous miscarriage	564 (12)	1 (5)	563 (12)
Had previous ectopic pregnancy	83 (1.7)	0	83 (2)
Had previous abortion	1486 (31)	13 (65)	1473 (31)
Gestation at presentation (weeks)			
<8	3952 (82)	10 (50)	3942 (82)
≥8	886 (18)†	10 (50)	876 (18)
Time from mifepristone to misoprostol (hours)			
24	2271 (47)	6 (30)	2265 (47)
48	67 (53)	14 (70)	2553 (53)

*Figures shown are number (%) except age and BMI, which are median (range).
†A small number of women had an early medical abortion at >9 weeks' gestation (maximum gestation 9^{+5}).

Table 2 Relative risk of continuing pregnancy following early medical abortion with different forms of contraception provided at the time of misoprostol administration (n=4838)

Method of contraception	Number of women (%) (n=4838)	Number of women using method with gestation at presentation ≥8 weeks (%)	Number of women using method who had previous abortion (%)	Number of continuing pregnancies (n=20)	Relative risk (RR) of continuing (95% CI)
Combined contraceptive*	1268 (26.2)	229 (18.1)	382 (30.1)	5	0.90 (0.29 to 2.73)
Progestogen-only pills	485 (10.0)	90 (18.6)	146 (30.1)	3	1.40 (0.37 to 5.26)
Progestogen-only implant	797 (16.5)	125 (15.7)	225 (28.2)	3	0.85 (0.23 to 3.21)
Depot medroxyprogesterone acetate	475 (9.8)	102 (21.5)	141 (29.7)	1	0.48 (0.06 to 3.81)
None/barrier method/fast track*†	1813 (37.5)	328 (18.1)	570 (31.4)	8	1.00 (Ref.)

*Number of women using the following methods: combined oral contraception=1182 (pill=1181, patch=79 and ring=8); none=976; condoms=433; diaphragm=2; copper intrauterine device=185; levonorgestrel intrauterine system=215; laparoscopic sterilisation=2.
†Women receiving fast-track service for intrauterine device/system (2-week appointment) were not given an interim method by the abortion services therefore they can be grouped with 'no hormonal contraception'.
Ref., reference.

Association of patient characteristics with continuing pregnancy

Of the characteristics investigated, previous abortion and gestation ≥8 weeks at presentation showed a significant association with continuing pregnancy (table 3). Women who presented at ≥8 weeks' gestation were 3.8 times more likely to have continuing pregnancy than those who presented at earlier gestations. Compared with women who did not have a previous abortion, women who did had a 5.2 times increased likelihood of having a continuing pregnancy after EMA. Time from mifepristone to misoprostol, women's smoking status and experience of previous births were not found to be associated with EMA outcome.

Table 3 Outcome of early medical abortion in relation to women's characteristics, gestation at presentation and time from mifepristone to misoprostol (n=4838)*

	Continuing pregnancy (n=20)	Not continuing pregnancy (n=4818)	Adjusted odds ratio (aOR)	95% CI	P values
Current smoker					
Yes	9	1861	0.97	0.4 to 2.4	0.95
No	11	2957	Ref.		
Previous birth					
Yes	10	2126	0.63	0.2 to 1.6	0.33
No	10	2692	Ref.		
Previous abortion					
Yes	13	1486	5.23	1.9 to 14.1	0.001
No	7	3332	Ref.		
Gestation at presentation (weeks)					
<8	10	3952	Ref.		
≥8	10	886	3.8	1.5 to 9.5	0.004
Time from mifepristone to misoprostol (hours)					
24	6	2271	Ref.		
48	14	2567	1.85	0.7 to 4.9	0.21

*All factors included in the logistic regression models are adjusted for one another.
Ref., reference.

DISCUSSION

Main findings

Our study confirms a low rate of continuing pregnancy in keeping with the high efficacy of EMA as previously reported.[14] We have provided evidence that giving IM DMPA at the time of misoprostol administration (24–48 hours after mifepristone) does not appear to impact the efficacy of EMA. In addition, the efficacy of EMA was not significantly affected by any of the other hormonal methods of contraception (pill, patch, ring or implant). Our study also shows that high numbers (nearly 70%) of women attending our abortion services left with an effective form of hormonal contraception.

The concern about IM DMPA use and efficacy of EMA if DMPA if given at the time of mifepristone administration arose from a randomised controlled trial (RCT) by Raymond et al[8] in which women were randomised to either IM DMPA given at the time of mifepristone (Quickstart) or at a follow-up visit weeks later (Afterstart). That study reported that the estimate of the difference between the continuing pregnancies in the two groups was imprecise, with their data showing only a very small (0.4%) increase resulting from giving IM DMPA at the time of mifepristone.[8] However, it should be recognised that participants in that study strongly preferred the Quickstart regimen, with 88% of women saying they were pleased with the timing of IM DMPA in comparison to 23% in the Afterstart group.[8]

All DMPA used in the present study was nurse-administered and was intramuscular 150 mg. However, there is growing use of the subcutaneous (SC) preparation of DMPA (Sayana Press 104 mg SC) in the UK and other countries. The subcutaneous preparation (SC DMPA) is

absorbed more slowly and produces a lower peak serum hormone level in comparison to the intramuscular preparation.[15] It is unknown whether SC DMPA affects the success of EMA if given at the time of mifepristone. The significance of these pharmacokinetic differences on any interaction with either mifepristone or misoprostol is currently unknown.[8]

The success of EMA has been associated with various factors, including age, gestational age and parity.[15] In concordance with previous research, we have shown that both previous termination and increasing gestation are factors associated with failure of EMA.[16 17] Previous studies have reported that EMA failure rate and subsequent requirement for surgical intervention was higher in women who were parous compared with those who were nulliparous.[16] In the present study, we have not shown any significant association between parity and success of EMA.

Limitations and strengths

This large case-control study represents the largest study (n=475) to examine the relationship between IM DMPA initiation at EMA and abortion outcome. However, the study did not allow for control of all possible confounding factors, being limited by available variables from the database. Continuing pregnancy following EMA is an uncommon event (0.4% in this study), and as such the case-control design was appropriate in identifying the risk factors associated with this outcome.

A key strength of the study is the robust follow-up processes in place to ensure that continuing pregnancies are recorded, including checking regional computer systems that record attendances at all hospitals in the region, including maternity records, databases and telephone registers to maximise the accuracy of capturing any continuing pregnancies. Therefore, the likelihood of missing a continuing pregnancy after EMA is low.

What this study adds

As the service delivery model in the UK has been that women receive misoprostol on licensed premises, this has meant an additional visit for misoprostol if it is to be taken as recommended at least 24 hours after mifepristone.[4] Therefore, this study gives reassurance that initiating IM DMPA at this visit 24–48 hours after mifepristone does not affect the outcome of EMA. However, in settings where women can self-administer misoprostol at home, or where regimens for EMA are used with simultaneous administration of mifepristone and misoprostol,[18 19] then an alternative option could be that women could self-administer SC DMPA at home after ensuring that there is a delay of at least 24 hours after mifepristone. Given the data available to date, any location or timing of DMPA administration would seem reasonable based on the woman's informed choice.

In conclusion, this study provides evidence that giving IM DMPA at the time of misoprostol administration, with at least a 24 hours' delay after mifepristone, does not appear to increase the risk of a continuing pregnancy after EMA.

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