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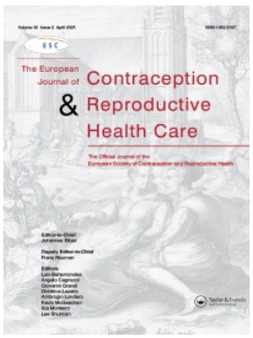

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RESEARCH ARTICLE

Depomedroxyprogesterone acetate impact on mifepristone action during medication abortion

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ABSTRACT

Purpose: To evaluate outcomes by gestational duration in patients who did and did not receive depomedroxyprogesterone acetate (DMPA) concurrently with mifepristone for mifepristone-misoprostol medication abortion and estimate the impact of DMPA on mifepristone action.

Materials and methods: In this secondary analysis of a retrospective study, we analysed treatment failure and continuing pregnancy as a reason for failure both overall and by gestational duration group. We assessed available literature to estimate that misoprostol alone would result in abortion in approximately 74% of pregnancies without mifepristone and calculated the impact of adding mifepristone to the treatment regimen and of DMPA on these outcomes.

Results: More than half of the patients in each group had pregnancies ≤49 days gestation (no DMPA: 432/704 [61.4%]; DMPA 73/141 [51.8%], $p=0.04$). Ongoing pregnancy rates increased with advancing gestational duration both with ($p=0.0005$) and without ($p=0.04$) concomitant DMPA administration. No individual gestational duration group demonstrated a significant difference in outcomes between patients that did and did not receive DMPA, likely because of small numbers in each group. Overall, concomitant DMPA with mifepristone increased the likelihood of an ongoing pregnancy by 25.3% of the expected rate if DMPA completely blocked all mifepristone action but only by 16.1% for patients with pregnancies ≤49 days gestation.

Conclusion: Ongoing pregnancy as the reason for medication abortion failure occurs more frequently with advancing gestation in patients that do and do not receive DMPA concurrently with mifepristone. DMPA may impact mifepristone variably by gestational duration, but larger studies are needed.

SHORT CONDENSATION

Outcome differences between patients that did and did not receive DMPA at the same time as mifepristone for medication abortion are notable although less than expected if DMPA fully blocked mifepristone action. Studies with large numbers within each gestational duration group are needed to more fully understand this practice.

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Abortion reversal; depomedroxyprogesterone acetate; medication abortion; mifepristone

Introduction

Two studies have evaluated the impact of depomedroxyprogesterone acetate (DMPA) on medication abortion with mifepristone and misoprostol when DMPA is administered at the same time as mifepristone [1,2]. The first, a randomised, controlled trial with results for 446 participants with pregnancies through 75 days gestation (87% at ≤63 days gestation) who received mifepristone followed by misoprostol 800 mcg buccally found no difference in overall efficacy between participants who did and did not receive DMPA at the same time as mifepristone, with failure rates of approximately 11–12% [1]. Although ongoing pregnancy as a reason for failure occurred more frequently among those receiving DMPA (3.6% vs. 0.9%, $p=0.06$); the lack of statistical significance likely reflected a small sample size for this outcome. The second study, a retrospective study of patients who used mifepristone followed by misoprostol 800 mcg buccally and attended follow-up, had different findings [2]. This study compared patients who opted to receive DMPA ($n=141$) or an etonogestrel implant ($n=200$) at the same time as mifepristone versus a random sample of patients treated during the same time frame who did not receive these methods ($n=704$). Both failure rates (9.9% vs. 2.1%, $p<0.0001$) and ongoing pregnancy as a reason for failure (6.4% vs. 1.4%, $p=0.002$) were higher for those who received DMPA at the time of mifepristone compared to the random sample. Patients who chose immediate or delayed implant placement did not have different outcomes.

These studies, together, show that simultaneous use of mifepristone and DMPA, a non-natural highly potent progestogen, may impact medication abortion outcomes. This information has been interpreted by proponents of so-called 'abortion pill reversal' as an indication that progesterone, a natural progestogen, should be effective to antagonise mifepristone actions when taken for abortion [3]. Although mifepristone-misoprostol treatment clearly has increasing

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Table 1. Misoprostol-alone efficacy for medication abortion.

First author	Publication Year	Gestational duration limit	Misoprostol dosing	Complete abortion rate	Ongoing pregnancy rate
Jain [6]	2002	56 days	800 mcg vaginally, one dose	90/125 (72.0%)	NR
Dahiya [7]	2012	56 days	800 mcg buccally, one dose	37/50 (74.0%)	2/50 (4.0%)
Ngoc [8]	2011	63 days	800 mcg buccally, repeat dose 24 h later	147/193 (76.2%)	32/193 (16.6%)
		≤49 days		121/148 (81.8%)	18/148 (12.2%)
		50-56 days		21/34 (61.8%)	10/34 (29.4%)
		57-63 days		5/11 (45.5%)	4/11 (36.4%)
Raymond [9]	2019	>71 days (93% ≤70 days)	Various (78% 800 mcg vaginally)	2221/3232 (68.7%) one dose 2343/3156 (74.2%) two doses	*

NR: not reported.
*Only reported in 50% of studies as indication for failure.

failure rates, and ongoing pregnancy as a reason for failure, with increasing gestational duration [4], both DMPA-medication abortion studies did not report efficacy outcomes by gestational duration groups [5]. Thus, we lack a full understanding of the potential impact of DMPA throughout the medication abortion gestational duration range. To provide this missing information, we reanalysed data from the retrospective study [2] to better understand the outcomes and to allow calculations that could better estimate of the impact of DMPA on mifepristone.

Materials and methods

We performed a secondary analysis of data from this retrospective study for which the methods, including entry criteria and primary outcomes, have been previously reported [2]. Briefly, the study evaluated patients with pregnancies up to 70 days gestation who received medication abortion care at a single outpatient facility from 1 January 2017 to 31 December 2019. All patients had sonographic confirmation of intrauterine pregnancy and gestational duration, received mifepristone 200 mg in clinic, were instructed to use misoprostol 800 mcg buccally 24–48 h later, and had sonographic or laboratory confirmation of outcome. The study investigators reviewed all charts by hand to confirm DMPA or etonogestrel implant placement at the time of mifepristone administration. The comparison group consisted of 1000 random patients treated during the same time period who did not start DMPA or implant use the time of mifepristone administration. The investigators only included patients that completed follow-up in their analysis (comparison group: 71.1%; DMPA: 62.9%; implant: 64.7%) and defined treatment failure as any medication or procedure used to empty the uterus after initial treatment using mifepristone and one dose of misoprostol.

For this secondary analysis, we included only those patients who received or planned to receive DMPA, and not those in the initial study who received or planned to receive a contraceptive implant. We evaluated failure and continuing pregnancy rates both overall and by gestational duration per MARE guidelines, which includes presentation of efficacy outcomes by gestational duration groups [5]. Because patients lost to follow-up were unlikely to have a continuing pregnancy, we performed a sensitivity analysis in which we included all patients lost to follow-up as not having continuing pregnancies. We performed *t*-tests, Fisher exact tests, and *chi*-square tests, as appropriate, with a $p \leq 0.05$ considered significant. The University of Minnesota Institutional Review Board approved this secondary analysis.

To understand the impact of DMPA on mifepristone action, we first evaluated existing literature to estimate medication abortion efficacy of misoprostol alone when used buccally (Table 1) [6–9]. Misoprostol-alone for medication abortion is about 74.0% effective with a single misoprostol buccal dose [7]. When considering all possible data, the effectiveness likely falls within a range of 68.7–76.2%; the range varies by misoprostol route, whether repeat dosing is routine, and by gestational duration. Using the misoprostol-alone data, we estimate the impact of DMPA on mifepristone when used simultaneously in the study cohort. We assumed that any ongoing pregnancy occurring after combined mifepristone-misoprostol use would have been continuing with misoprostol-alone use holding misoprostol dose and route of administration steady.

Results

Medication abortion outcomes

Outcomes by gestational duration are reported in Table 2. More than half of the patients in each treatment group had pregnancies ≤49 days gestation (no DMPA: 432/704 [61.4%]; DMPA 73/141 [51.8%], $p = 0.04$); patients who chose DMPA were more likely to have pregnancies >49 days gestation.

Our study cohort demonstrated significantly higher ongoing pregnancy rates with advancing gestation whether or not DMPA was administered (Table 2). However, the numbers in each gestational duration cohort were relatively small such that no individual gestational duration group demonstrated a significant difference between patients that did and did not receive DMPA. Because most patients had pregnancies ≤49 days gestation, we further evaluated ongoing pregnancy rates in those ≤49 days vs. >49 days gestation. Without concomitant DMPA administration, ongoing pregnancy rates were 3/432 (0.69% [95% CI 0–1.48%]) vs. 7/272 (2.57% [95% CI 0.69–4.46%]), respectively, $p = 0.051$. With concomitant DMPA administration, ongoing pregnancy rates were 2/73 (2.74% [95% CI 0–6.48%]) vs. 7/68 (10.29% [95% CI [3.07–17.52%]), respectively, $p = 0.089$.

Calculating impact of DMPA on mifepristone

The overall efficacy of the study cohort when no DMPA administered was 97.9%, meaning mifepristone added 23.9% (sensitivity range 22.5–29.2%) efficacy when combined with misoprostol 800 mcg buccally above what would

Table 2. Treatment failure overall and by gestational duration in mifepristone-misoprostol medication abortion patients in Minnesota (2017–2019) who did and did not receive DMPA at time of mifepristone administration.

	Any treatment failure			Treatment failure, longoing pregnancy			Treatment failure, lnot ongoing pregnancy		
Gestational duration	No DMPA In = 704	DMPA In = 141	*p*-Value*	No DMPA In = 704	DMPA In = 141	*p*-Value*	No DMPA In = 704	DMPA In = 141	*p*-Value*
All	15/704 (2.13% [1.06–3.20%])	14/141 (9.93% [4.99–14.87%])	<0.0001	10/704 (1.42% [0.55–2.29%])	9/141 (6.38% [2.35–10.42%])	0.002	5/704 (0.71% [0.09–1.33%])	5/141 (3.55% [0.49–6.60%])	0.015
≤49 day	5/432 (1.16% [0.15–2.17%])	5/73 (6.85% [1.05–12.64%])	0.008	3/432 (0.69% [0–1.48%])	2/73 (2.74% [0–6.48%])	0.154	2/432 (0.46% [0–1.10%)	3/73 (4.11% [0–8.66%])	0.023
50–56 days	3/150 (2.00% [0–4.24%])	2/24 (8.33% [0–19.39%])	0.141	1/150 (0.67% [0–1.97%])	2/24 (8.33% [0–19.39%])	0.050	2/150 (1.33% [0–3.17%])	0/24 (0% [0–0.13%])	>0.99
57–63 days	4/83 (4.82% [0.21–9.43%])	3/24 (12.50% [0–25.73%])	0.186	3/83 (3.61% [0–7.63%])	2/24 (8.33% [0–19.39%])	0.312	1/83 (1.20% [0–3.55%])	1/24 (4.17% [0–12.16%])	0.400
64–70 days	3/39 (7.69% [0–16.06])	4/20 (20.0% [2.47–37.53])	0.213	3/39 (7.69% [0–16.06%])	3/20 (15.0% [0–30.65%])	0.398	0/39 (0% [0–0.08%])	1/20 (5.0% [0–14.55%])	0.339
p-value†	0.002	0.071		0.0005	0.043		0.644	0.975	

DMPA: depomedroxyprogesterone acetate.
Data presented as outcome/group size (%, 95% confidence interval).
*Fisher exact tests.
†Chi-square test for trend.

be achieved with misoprostol-alone. The ongoing pregnancy rate in patients who did not receive DMPA was 1.4%; thus, if DMPA completely blocked the ability of mifepristone to result in an ongoing pregnancy, we would have expected ongoing pregnancy rates of 25.3% (range 23.9–30.6%) in the DMPA group. The actual ongoing pregnancy rate was 6.4%, which is 25.3% (range 20.9 to 26.8%) of the calculated expected rate. Because most patients had pregnancies ≤49 days, we similarly calculated the impact of DMPA solely within that gestational duration range; the ongoing pregnancy rate of 4.1% is 16.1% (range 13.6–18.1%) of the calculated expected rate. These calculations are fully explained in Appendix 1.

Discussion

Findings and interpretation

In this secondary analysis, we found that as gestational duration advanced, more medication abortion failures due to ongoing pregnancy occurred whether or not patients received DMPA concomitantly with mifepristone. More patients with pregnancies >49 days chose DMPA use at the time of mifepristone administration compared to those ≤49 days gestation; however, the number of patients in each gestational week subgroup were too small to effectively evaluate statistical differences in outcomes.

Administering DMPA at the same time as mifepristone for medication abortion may increase the ongoing pregnancy rate by about 25% of what would be expected if DMPA had an absolute effect (100% block) on mifepristone action. Because we did not find a significant difference in ongoing pregnancy rates within each gestational duration range between those who did and did not receive DMPA (Table 2), we did not perform this same calculation for each gestational duration week. Our estimates for the gestational duration range with the largest number of patients (≤49 days) are that concomitant DMPA may only increase the continuing pregnancy rate by about 16% of what would be expected if DMPA had an absolute effect on mifepristone action.

Results in the context of what is known

In humans, mifepristone binds to the progesterone receptor approximately 2.5 times more strongly than progesterone itself [10]. Medroxyprogesterone acetate binds to the progesterone receptor with similar affinity as progesterone itself [11]. However, when evaluating direct organ effects, the oral dose of medroxyprogesterone acetate to inhibit ovulation is 10 mg daily [12]. For comparison, the oral dose of progesterone required to inhibit ovulation is 300 mg daily [13]. When administered intramuscularly, medroxyprogesterone acetate is rapidly absorbed with detection in the systemic circulation within 30 min [14,15]. Mean plasma concentrations peak at 72 h and levels at 24 h exceed levels observed at 240 h and beyond (through and beyond 12 weeks) [15]. Recent pharmacokinetic (PK) modelling demonstrates a biphasic absorption model with 25% absorbed rapidly and 75% absorbed slowly over multiple weeks [16], consistent with early studies of DMPA PK [14]. The generally rapid absorption and significant plasma concentrations achieved over the first 24 h after DMPA administration are very different than using a natural, oral progestogen after some time has elapsed following mifepristone administration. As such, none of the outcomes from either of the DMPA medication abortion studies [1,2] is supportive of this practice ('abortion pill reversal').

Notably, the original retrospective study reported no impact of simultaneous contraceptive etonogestrel implant administration on overall abortion rates (3.0% vs. 2.1%, $p = 0.43$) or ongoing pregnancy as a reason for medication abortion failure (1.5% vs. 1.4%, $p > 0.99$) [2]. These findings are consistent with randomised trials from Europe ($n = 551$) [17] and the U.S. and Mexico ($n = 476$) [18]. Etonogestrel is absorbed rapidly after implant placement [19] and is nearly 100% bioavailable but does not reach peak until approximately 4 days after placement [20]. Etonogestrel (3-ketodesogestrel) is a testosterone derivative used in microgram dosing because of its high potency whereas medroxyprogesterone acetate, a progesterone derivative, is provided in mg doses. Thus, even though the implant provides rapid exposure to progestogen, the amount does not

impact mifepristone when used simultaneously during medication abortion.

Clinical implications

As gestational duration advanced, more medication abortion failures due to ongoing pregnancy occurred whether or not patients received DMPA concomitantly with mifepristone. Because the data within each gestational duration range in this secondary analysis is small, more data by gestational week is needed to more fully clarify the impact of DMPA use concurrently with mifepristone. Counselling when considering simultaneous use of DMPA and mifepristone in patients planning medication abortion should consider gestational duration.

Advocates of abortion pill reversal claim efficacy rates of 50% for progesterone therapy started some time after mifepristone administration with rates as high as 68% with high dose oral progesterone based in a flawed report [21,22]. Our analysis shows that, at most, with simultaneous administration of a high dose of progestogen, the effect is only 25% and even lower for pregnancies ≤49 days. The differences in the impact of DMPA and etonogestrel implants on mifepristone-misoprostol medication abortion outcomes demonstrate the we cannot make any assumptions about any how any specific progestogen will impact mifepristone without appropriate clinical trials. This data does not support that another progestogen, including high dose oral progesterone, will significantly impact continuing pregnancy rates after mifepristone administration.

Research implications

The differences in outcomes between patients that did and did not receive DMPA concurrently with mifepristone are notable although not statistically significant, demonstrating that studies with larger numbers of participants within each gestational duration group are needed to provide more clarity about the impact of concurrent DMPA and mifepristone administration, especially with increasing gestational duration. Additionally, actual use studies with a comparator group are required to establish the true impact of any progestogen on mifepristone action, especially if the progestogen is administered at various time points after mifepristone.

Strengths and limitations

This analysis is limited by retrospective nature that may alter true proportions and generalisability. As reported in the original publication, lost to follow-up rates were high and differed between treatment groups: 83/224 (37.0%) in the DMPA group and 286/990 (29.9%) in the comparison group ($p = 0.02$) [2].

Conclusions

Overall, this secondary analysis demonstrates that an increase in ongoing pregnancy as the reason for medication abortion failure is observed with advancing gestational duration for patients that receive DMPA at the time of mifepristone administration. When considering whether the effects of DMPA on mifepristone support any concept of abortion pill reversal, we estimated that DMPA, when administered simultaneously with mifepristone, increases ongoing pregnancy rates by only an estimated 25% of the predicted effect it would have if it prevented all actions of mifepristone. Thus, the likelihood that administering progesterone orally sometime after mifepristone (e.g. 24 h or more) will have any substantial effect on mifepristone clinical action is likely low.

Ethical approval

The University of Minnesota Institutional Review Board approved this secondary analysis.

Author contributions

CRediT: **Mitchell D. Creinin**: Conceptualization, Methodology, Writing – original draft, Writing – review & editing; **Christy M. Boraas**: Data curation, Writing – review & editing.

Disclosure statement

MDC has received speaking honoraria from Gedeon Richter, Mayne, and Organon, has stock options with Femasys, and has consulted for Curai, Danco, Estetra SRL, Gedeon Richter, Merck Sharpe Dohme, Medicines360, and Organon. The Department of Obstetrics and Gynaecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Chemo Research SL, Femasys, Medicines360, Merck, Sebela, and Sumitomo Pharma.

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The findings and conclusions in this article are those of the authors and do not necessarily reflect the views of Planned Parenthood Federation of America, Inc.

Data availability statement

All data generated or analysed during this study are included in this published article.

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Appendix 1. Calculation of DMPA effects on mifepristone action in patients who received mifepristone and misoprostol for medication abortion

Misoprostol efficacy when used alone for abortion (Table 1): 74.0%, range of 68.7–76.2%

Mifepristone-misoprostol outcomes when no DMPA used, total study population (efficacy 97.9%).

	With Misoprostol Efficacy 74.0%	Range of Misoprostol Efficacy	
Misoprostol action	74.0%	76.2%	68.7%
Mifepristone action	23.9% (= 97.9 − 74.0%)	22.5% (= 97.9 − 76.2%)	29.2% (= 97.9 − 68.7%)
Ongoing pregnancy (mifepristone did not stop pregnancy from continuing)	1.4%	1.4%	1.4%
Aspiration for other reasons	0.7%	0.7%	0.7%
TOTAL	100%	100%	100%

If DMPA completely blocked the expected action of mifepristone, the continuing pregnancy rate would be 25.3% (23.9 + 1.4%), not just 1.4%. This 25.3% represents the potential 'efficacy' of DMPA to fully antagonise mifepristone and result in ongoing pregnancy.

Patients that received DMPA had a 6.4% continuing pregnancy rate, which is (6.4/25.3) 25.3% of the expected proportion if DMPA fully blocked mifepristone actions (the impact for resulting in an ongoing pregnancy).

The same calculations using the range of misoprostol action provide a range of DMPA effects of 26.8% (6.4/23.9) and 20.9% (6.4/30.6%).

Mifepristone-misoprostol outcomes when no DMPA used, ≤49 days gestation (efficacy 98.8%).

	With Misoprostol Efficacy 74.0%	Range of Misoprostol Efficacy	
Misoprostol action	74.0%	76.2%	68.7%
Mifepristone action	24.8% (= 98.8 − 74.0%)	22.6% (= 98.8 − 76.2%)	30.1% (= 98.8 − 68.7%)
Ongoing pregnancy (mifepristone did not stop pregnancy from continuing)	0.7%	0.7%	0.7%
Aspiration for other reasons	0.5%	0.5%	0.5%
TOTAL	100%	100%	100%

If DMPA completely blocked the expected action of mifepristone, the continuing pregnancy rate would be 25.5% (24.8 + 0.7%), not just 0.7%. This 25.5% represents the potential 'efficacy' of DMPA to fully antagonise mifepristone and result in ongoing pregnancy.

Patients that received DMPA had a 4.1% continuing pregnancy rate, which is (4.1/25.5) 16.1% of the expected proportion if DMPA fully blocked mifepristone actions (the impact for resulting in an ongoing pregnancy).

The same calculations using the range of misoprostol action provide a range of DMPA effects of 18.1% (4.1/22.6) and 13.6% (4.1/30.1%).