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Reversal of medication abortion with progesterone: a systematic review

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjsrh-2023-201875).

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Received 22 March 2023
Accepted 15 September 2023
Published Online First 20 October 2023

To cite: Stifani BM, Lavelanet AF. *BMJ Sex Reprod Health* 2024;**50**:43–52.

ABSTRACT

Background We sought to determine whether there is evidence to recommend progesterone for individuals not wishing to complete a medication abortion after taking mifepristone.

Methods We undertook an updated systematic review including a primary search for studies in which individuals received progesterone to reverse the effects of mifepristone, and a secondary search for studies in which individuals received mifepristone alone. We searched PubMed, Embase, Cochrane, CINAHL and grey literature up to December 2022. We used the Joanna Briggs Institute critical appraisal tools for risk of bias assessment. We compared ongoing pregnancy rates among individuals treated with progesterone to those managed expectantly.

Results We did not find new studies in our secondary search. For the main search, we included three case series and one randomised controlled trial. Data were available for 561 individuals who received progesterone after mifepristone, of whom 271 (48%) had ongoing pregnancies. The quality of the evidence in the case series was low due to methodological and ethical issues. Enrollment in the randomised trial stopped early due to bleeding events in both arms. The ongoing pregnancy rate for individuals ≤7 weeks who received progesterone was 42% (95% CI 37-48) compared with 22% (95% CI 11-39) for mifepristone alone. At 7–8 weeks, the ongoing pregnancy rate was 62% (95% CI 52-71) in the progesterone group and 50% (95% CI 15- 85) in the mifepristone alone group.

Conclusion Based mostly on poor-quality data, it appears the ongoing pregnancy rate in individuals treated with progesterone after mifepristone is not significantly higher compared to that of individuals receiving mifepristone alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A 2015 systematic review of progesterone to reverse the effects of mifepristone found one study that met inclusion criteria and concluded that there is insufficient evidence to recommend this treatment. Since then, new studies have been published and more practitioners around the world have started offering progesterone to individuals no longer wishing to complete a medication abortion after taking mifepristone.

WHAT THIS STUDY ADDS

⇒ We undertook a review of the three new studies published on this topic and conclude that there remains insufficient evidence to recommend progesterone for individuals no longer wishing to complete the medication abortion process. Further, one of the new studies was halted due to bleeding events, highlighting safety concerns with not taking misoprostol after mifepristone.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Practitioners should be aware that there is insufficient evidence to recommend progesterone treatment to reverse the effects of mifepristone, and potential risk to not taking misoprostol after mifepristone. Any further studies on this topic should be conducted in a controlled setting given the potential safety risks.

INTRODUCTION

Medication abortion accounts for an increasing proportion of abortions.[1] Medication management using mifepristone followed by misoprostol is highly effective and safe.[2–4] Most individuals who have medication abortions are highly satisfied with their experience,[5] as individuals are often sure of their decision[6] and feel relief rather than regret after the abortion.[7] Rarely, some pregnant individuals who take mifepristone to terminate a pregnancy choose not to complete the abortion process.[8]

Mifepristone is a progesterone receptor antagonist that blocks the progesterone receptor with a higher affinity than progesterone itself,[9] and it has a half-life of 25–30 hours.[10] A 200 mg dose of mifepristone is undetectable in humans 10 days after ingestion.[11] It disrupts pregnancy by promoting decidual necrosis; it also softens the cervix and increases uterine contractility and sensitivity to prostaglandins.[3] Some have hypothesised that when individuals no longer desire abortion after ingestion of mifepristone, administering high doses of progesterone increases the rates of ongoing pregnancy compared with expectant management.[12] However, it is unclear whether progesterone can counteract the effects of mifepristone. Data show that high-dose progestogens can decrease the efficacy of medication abortion. In a randomised trial, the ongoing pregnancy rate after medication abortion was 3.6% in the group that received depot medroxyprogesterone acetate at the same time as mifepristone, compared with 0.9% in the group that received it at a later time.[13] Administration of lower doses such as those delivered by the etonogestrel implant, on the other hand, do not seem to impact medication abortion success rates.[14]

Several states in the United States require that medication abortion users be informed about the potential of reversing the effects of mifepristone should they change their mind about the abortion.[15] Further, some groups that advocate for decreased access to abortion advertise "abortion pill reversal" on the internet.[16] Recently, these groups have gained traction globally, partnering with local activists and practitioners in Europe, Latin America and elsewhere to provide what they promote as "abortion reversal" regimens.[17 18] However, this practice is not included in any national or international guideline on medication abortion.[2 3] The American College of Obstetricians and Gynecologists states that "[c]laims regarding abortion 'reversal' treatment are not based on science and do not meet clinical standards".[19] The Royal College of Obstetricians and Gynaecologists along with other professional organisations in the UK issued a similar statement in 2022.[20]

The authors of a 2015 systematic review on the reversal of medication abortion using progesterone found only one study that met inclusion criteria for review.[21] They also reviewed the existing literature on ongoing pregnancy rates among individuals who took mifepristone alone in trials of medication abortion and reported rates ranging from 8% to 46% with different mifepristone regimens. The authors concluded that there was insufficient evidence to recommend progesterone treatment to reverse the effects of mifepristone. Since then, new studies have been published on this topic, and discussion, as well as promotion, of abortion reversal is increasing in certain parts of the world.[22 23] We therefore undertook an updated systematic review of the literature around use of progesterone after mifepristone. The objective of this review is to determine whether there is new sufficient evidence to recommend treatment with progesterone for pregnant individuals who took mifepristone and no longer wish to complete the medication abortion process.

METHODS

Search strategy

We conducted two systematic searches: one for studies of abortion reversal with progesterone (main search), and another for studies documenting ongoing pregnancy rates after mifepristone alone (secondary search). We performed the searches in December 2021, then again in December 2022. For the main search, we searched PubMed, Embase, Cochrane and CINAHL. We also searched Google Scholar and Greylit.org for grey literature sources and searched the reference lists of existing publications. With the help of a librarian, we built search constructs appropriate for each database. We uploaded all citations to Mendeley and then to Covidence, where we removed all duplicates. The two researchers performed title and abstract screening of all studies and full-text screening of studies that initially appeared to meet eligibility criteria. We resolved any conflicts via discussion. We report our methods and findings in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[24] Refer to the online supplemental file for details on the search strategies.

Of note, we recognise that the term "antagonisation" would be more scientifically accurate than "reversal" since the perceived action of progesterone would be at the receptor level. However, we chose to use the term "reversal" for simplicity because it has been most often used both in the scientific literature and by individuals who promote this practice.

For the secondary search, we focused on studies that reported continuing pregnancy rates after use of mifepristone alone, as the authors of the 2015 systematic review had done.[21] We searched PubMed using the same search strategy as mentioned earlier without the reversal term. We only searched for studies published after March 2015, as those published earlier were included in the previous systematic review.

Study selection

For the main search, we included studies in which pregnant individuals took mifepristone to induce abortion but did not take misoprostol, and in which at least one study arm received progesterone, or any other pharmacological intervention administered in any dosage or form for the purpose of reversing the effects of mifepristone. Because we anticipated few if any randomised trials, we included all types of primary studies with and without comparison groups, even case series. We defined case series as "a group or series of case reports involving patients who were given similar treatment".[25] Included studies had to report

on our primary outcome, which was the proportion of participants with ongoing pregnancy after treatment with progesterone or any other pharmacological intervention for abortion reversal. The secondary outcomes were treatment side effects or complications, and the incidence of birth defects. We included any listed complications or side effects including bleeding, surgical intervention and gastrointestinal side effects. We included studies even if they did not include any of our predetermined secondary outcomes. We excluded review articles, editorials, letters, advisories, unpublished manuscripts and commentaries.

For the secondary search, we included cohort studies and randomised controlled trials in which pregnant individuals took mifepristone; did not take misoprostol; and did not receive progesterone or any other pharmacological intervention to reverse the effects of mifepristone. The primary and secondary outcomes were the same as those for the primary search.

Study synthesis and assessment

The two authors extracted data on the predefined primary outcome, reporting on the number of participants enrolled in each study or included in each case series, and the number of continuing pregnancies. We also extracted data on the secondary outcomes for the studies which reported on them. For the primary analysis we calculated the overall proportion (and 95% Wilson Score Confidence Interval, CI) of ongoing pregnancies following treatment with progesterone, compared with the overall proportion (and 95% Wilson Score CI) of ongoing pregnancies following mifepristone alone. For this analysis, we included studies in which participants had received 200 mg mifepristone in the mifepristone alone group, as that is the regimen currently used in clinical practice.[2 3] In this group, we considered data from studies that were published prior to 2015 and included in the 2015 systematic review[21] but were not part of the results of our secondary search beginning after March of 2015. We also analysed data according to gestational age as it is a main predictor of ongoing pregnancy after mifepristone use.

The two researchers independently conducted a critical appraisal for each study, then met to discuss results and resolve conflicts. For the case series, we used the Case Series Critical Appraisal Tool developed by the Joanna Briggs Institute (JBI).[26] For the randomised controlled trial, we used the JBI Checklist for Randomised Controlled Trials.[27] We chose the JBI institute tools because they are the only ones we are aware of that include a tool for case studies.

RESULTS

Characteristics of included studies

For the main search, we identified 1284 references through database and grey literature searches. We removed 337 duplicates and screened 947 references. Of these, we excluded 932 irrelevant references based on title and abstract screening and selected 15 for full-text screening. We excluded 11, which were the wrong study design (primarily commentaries) and included a total of four studies in the review (see figure 1, PRISMA flow diagram). In the secondary search, we screened 443 references and did not find any new studies that reported on continuing pregnancies after use of mifepristone alone.

We included four studies from our main search in this review. Three studies were case series and did not have comparison groups.[28–30] Of these, only one had been included in the 2015 systematic review of abortion reversal.[21 28] The fourth study is a double-blind, randomised, placebo-controlled trial.[31] Table 1 shows the characteristics of the included studies.

The first study was a case series of seven patients who took mifepristone for medication abortion and then changed their mind and attempted reversal with progesterone.[28] Their gestational ages ranged from 7 to 11 weeks and the treatment with progesterone was started at 7–72 hours after mifepristone ingestion. Progesterone regimens varied (see table 2 for details). Timing of progesterone initiation also varied. Although the article included few details, it appears that gestational cardiac activity was documented on ultrasound prior to initiating progesterone in at least five of the cases. Pregnancy outcomes were available for six of the seven patients and were assessed via patient history. One patient was lost to follow-up. The study did not report on any of our predetermined secondary outcomes.

The second study was a case series of three patients selected among women who contacted an Australian pregnancy support service via the internet and who received a 2-week vaginal progesterone course for abortion reversal.[30] Timing of progesterone initiation varied. Pregnancy outcomes were assessed via ultrasound at varying timepoints and/or patient history. The study did not report on any of our predetermined secondary outcomes.

The third study was a larger case series of patients selected among women from "several different countries" who called a hotline for abortion reversal.[29] A total of 325 different healthcare providers treated them with various progesterone regimens. The maximum interval between mifepristone and initiation of progesterone was 72 hours. A total of 1668 women called the hotline expressing interest in progesterone, but only 754 initiated progesterone therapy. It is unclear why the remaining 954 did not initiate therapy. The authors excluded an additional 207/754 women from the analysis because they later chose to complete the abortion, were >72 hours after taking mifepristone, or were lost to follow-up. Pregnancy outcomes were available for 547 women and were assessed via patient history. It appears that gestational cardiac activity was documented prior to initiation of progesterone treatment in some cases and not others. The study did not report on

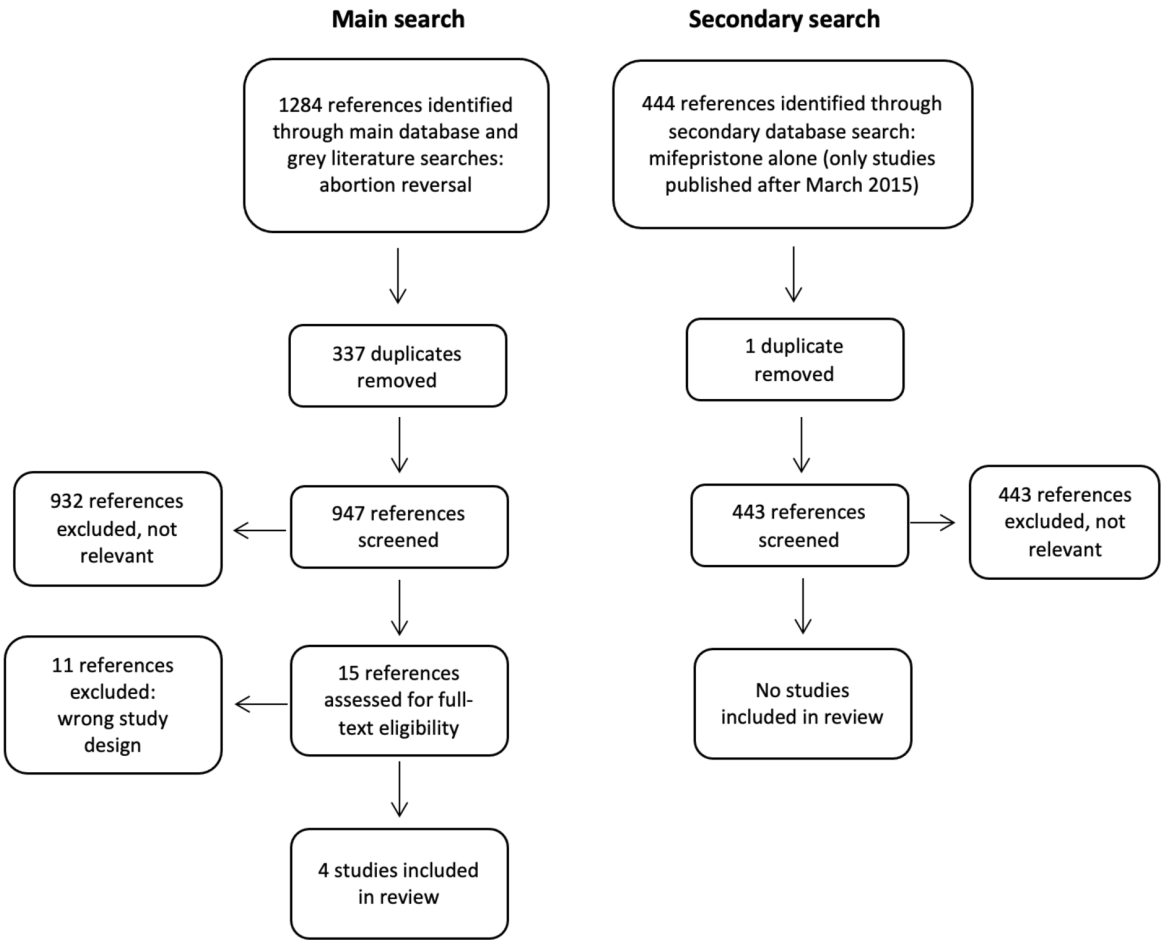

Figure 1 Summary of study selection process for inclusion in the systematic review of ongoing pregnancies after mifepristone and either treatment with progesterone (main search) or expectant management (secondary search).

any of our predetermined secondary outcomes, other than the incidence of birth defects.

Of note, we strongly considered excluding this publication from the primary review because it does not contain detailed follow-up information for all patients. However, we chose to include it because the guidelines for case series are not well established. According to the National Cancer Institute, "reports of case series usually contain detailed information about the individual patients, (including) demographic information (for example, age, gender, ethnic origin) and information on diagnosis, treatment, response to treatment, and follow-up after treatment".[25] However, case series are not mentioned in the STROBE guidelines for observational studies, so there are no clear elements that must be reported for a study to qualify as a case series.[32] As some epidemiologists have noted, "a case series can be incomplete; completeness would contribute to the reliability of the study, but the study remains a case series" even if it is incomplete.[33]

None of the case series included here specify the dose of mifepristone individuals ingested, but 200 mg was the dose recommended by international guidelines at the time the studies were conducted.[34]

The fourth study was a randomised, double-blind, placebo-controlled trial in which individuals at 44–63 days of pregnancy who were awaiting surgical abortions agreed to take mifepristone and were randomised to receiving high-dose oral progesterone or placebo 24 hours after mifepristone ingestion.[31] The primary outcome was continued gestational cardiac activity at 2 weeks as determined via ultrasound. This was the only study which also reported on our predetermined secondary outcomes of treatment side effects and complications. It is important to note that although researchers planned to include 20 patients in each arm, enrollment stopped early due to bleeding events in both arms.

Synthesis of results

The four selected studies included a total of 561 individuals who received progesterone treatment after taking mifepristone, and for whom the primary outcome of ongoing pregnancy could be assessed. Of these, a total of 271 (48%) had ongoing pregnancies. Only one study[31] had a control group, and 2/6 patients in that group had ongoing pregnancies. The same study was also the only one to report on treatment side effects

Table 1 Characteristics of studies included in a systematic review of abortion reversal

Authors (year)	Study type	Population	Intervention	Comparison	Outcome
Delgado & Davenport[28] (2012)	Case series	US women who took mifepristone for abortion and were interested in reversing effect; pelvic ultrasound performed prior to initiating treatment in at least 5/7; mifepristone dose unspecified	Treatment with progesterone (various regimens)*	None	Proportion of ongoing pregnancies – assessed via patient history (timing of assessment not specified) †Secondary outcomes: none
Garratt & Turner[30] (2017)	Case series	Women in Australia who took mifepristone and were interested in reversing effect; pelvic ultrasound not performed prior to initiating treatment; mifepristone dose unspecified	Vaginal progesterone for 2 weeks: 400 mg twice daily for 3 days, then 400 mg nightly for 6 days, then 200 mg nightly for 6 days	None	Proportion of ongoing pregnancies – assessed via ultrasound and patient history (timing of assessment varied) †Secondary outcomes: none
Delgado *et al*[29] (2018)	Case series	Pregnant women in US and several other countries who had taken mifepristone but not misoprostol and were interested in reversing effects; 72 hours or less after taking mifepristone; mifepristone dose unspecified	Various progesterone dosing/ formulations: high-dose oral, intramuscular (various doses and frequencies), oral caps, vaginal suppository	None	Proportion of ongoing pregnancies – assessed via patient history (timing of assessment not specified) †Secondary outcomes: incidence of birth defects
Creinin *et al*[31] (2020)	Double-blind, randomised, placebo-controlled trial	Patients at 44–63 days of gestation with confirmed cardiac activity who were planning surgical abortion	Mifepristone 200 mg, followed 24 hours later by oral progesterone 400 mg - twice daily for 3 days, then once daily until planned surgical abortion 14–16 days after enrollment	Mifepristone 200 mg followed by placebo	Proportion of ongoing pregnancies at 2 weeks – assessed via ultrasonography †Secondary outcomes: complications and side effects

*See individual cases in table 2 for details on treatment regimens.
†Secondary outcomes: our secondary outcomes of interest were treatment side effects and complications (including bleeding, surgical intervention and gastrointestinal side effects) and birth defects.

and complications. Of the 12 patients included in that study (six in the treatment arm and six in the control arm), five patients experienced complications (two in the treatment arm and three in the placebo arm). Table 2 shows the primary and secondary outcomes for all included studies.

The larger case series[29] reported ongoing pregnancy rates according to gestational age at which mifepristone was ingested. They were 25% at 5 weeks, 46% at 6 weeks, 49% at 7 weeks, 61% at 8 weeks and 77% at 9 weeks (table 2).

Pooled analysis of ongoing pregnancy rates

For the planned analysis of ongoing pregnancy rates, we included data from two studies in the mifepristone alone group: data from the control group of the 2020 Creinin *et al*[31] study, and data from a 1988 study by Maria *et al*.[35] We included data from the Maria *et al* study (which was also included in the 2015 systematic review) because it is the only study of mifepristone alone in which participants received 200 mg of mifepristone. Because this study only included participants who were 7 weeks pregnant or less, we applied the same criterion to the progesterone group and excluded from this analysis participants who were more than 7 weeks pregnant at the time of mifepristone ingestion. We also compared ongoing pregnancy rates for pregnancies of 7–8 weeks by comparing those treated with progesterone to the control group of the Creinin *et al* study only.[31]

Table 3 shows the ongoing pregnancy rate for all pregnancies 7 weeks or less in the four included studies, which was 42% (95% CI 37 to 48). In comparison, the ongoing pregnancy rate at 7 weeks or less after mifepristone alone based on the Maria *et al* study and the Creinin *et al* study's control group was 22% (95% CI 11 to 39). For pregnancies of 7–8 weeks, the ongoing pregnancy rate after progesterone treatment was 62% (95% CI 52 to 71) compared with 50% (15–85%) in the Creinin *et al* control group.

Quality of the evidence

For the three case series we rated the quality of the evidence as low, but we chose to include them in this review as there is very limited evidence available on this topic. online supplemental table 1 shows our critical appraisal of these studies, and online supplemental table 2 shows a detailed explanation of our ratings. For two of the studies it was unclear how many individuals had presented seeking medication abortion reversal, whether any of those who had presented were not offered progesterone, and whether all of the women treated with progesterone were included in the case series.[28 30] For the two case series published by Delgado and colleagues[28 29] it was unclear whether the pregnancy outcomes were assessed in a standardised way (eg, ultrasound vs chart review vs patient report). Also, some but not all participants had

Table 2 Characteristics and pregnancy outcomes of individuals treated with progesterone or placebo for abortion reversal in the four studies included in this review

Case	GA (days or weeks)	Treatment initiation time	Regimen	Outcomes (pregnancy outcome, complications or side effects)
Delgado & Davenport[28] (2012)				
1	8 weeks	30–40 hours	200 mg in oil, IM, daily x 2 days; then two doses every other day x 2; then twice weekly until 9 weeks 5 days; then restarted at 11 weeks 2 days, twice weekly; then decreased to 100 mg twice weekly until 29 weeks 5 days	Viable infant at 37 weeks
2	11 weeks	72 hours	200 mg in oil, IM; continued for 2 weeks (unknown frequency); then PO micronised progesterone for 5 months (unknown frequency and dosage)	Viable infant
3	7 weeks	36–48 hours	200 mg in oil, IM; then two more times the first week, then weekly for 5–6 weeks, then 200 mg in oil twice weekly for 2 weeks, then micronised progesterone orally for 5 months	Viable infant at 39 weeks
4	7 weeks 4 days	46 hours	200 mg in oil, IM, twice weekly for 19 weeks	Viable infant at 40 weeks
5	Unknown	Unknown	200 mg in oil, route and frequency unknown	Abortion soon after injection
6	7 weeks	7 hours	200 mg PV; followed by IM 200 mg after 11 hours; then 2 days later	Abortion complete 3 days after mifepristone
7	Lost to follow-up; no information available			
Garratt & Turner[30] (2107)				
N	43 days	28 hours	Vaginal progesterone: 400 mg twice daily for 3 days, then 400 mg nightly for 6 days, then 200 mg nightly for 6 days; routine antenatal care after 2 weeks of progesterone	Viable pregnancy at 8 weeks 4 days on ultrasound at 2 weeks; viable infant at 39 weeks
T	61 days	3.5 hours	Same as above	LTFU at 2-week follow-up ultrasound; reported delivery of live infant "7 months later, likely at term"
O	7.5 weeks	31 hours	One dose of vaginal progesterone 400 mg; discontinued as experienced heavy vaginal bleeding soon after treatment initiation	Heavy vaginal bleeding soon after starting progesterone; follow-up US at 1 week showed empty uterus, completed abortion
Delgado *et al*[29]				
N/A	754 treated 5 weeks: 19 6 weeks: 113 7 weeks: 102 8 weeks: 88 9 weeks: 30 Unknown: 138	Variable (72 hours or less)	High-dose oral progesterone: 31 IM progesterone: 125 Oral, all groups: 119* Vaginal caps: 156 Vaginal suppository: 34 Unknown: 82	Outcomes available for 547: Births: 257 LTFU before 20 weeks: 112 LTFU after 20 weeks: 4 Excluded because chose to complete abortion: 57 Excluded because wrong time interval: 38 Ongoing pregnancies by progesterone regimen: High-dose oral: 21/31 (68%) IM progesterone all groups: 80/125 (64%) Oral, all groups: 64/119 (54%) Vaginal caps: 61/156 (39%) Vaginal suppository: 11/34 (32%) Ongoing pregnancies by gestational age: 5 weeks: 19/76 (25%) 6 weeks: 61/113 (46%) 7 weeks: 50/102 (49%) 8 weeks: 54/88 (61%) 9 weeks: 23/30 (77%) Birth defects: 6 (2 absent digits; 1 choroid plexus cyst, 1 cystic kidney, 1 failed hearing test, 1 heart murmur)
Creinin *et al*[31] (2020)				
1	53 days	24 hours	Mifepristone 200 mg, followed by oral progesterone 400 mg 24 hours later - twice daily for 3 days, then once daily until planned surgical abortion 14–16 days after enrollment	Continuing GCA at 17 days
2	50 days	24 hours	Same as above	Continuing GCA at 16 days
5	49 days	24 hours	Same as above	Continuing GCA at 16 days
8	56 days	24 hours	Same as above	Expelled pregnancy, haemorrhage not requiring transfusion or uterine aspiration at day 3

Continued

Table 2 Continued

Case	GA (days or weeks)	Treatment initiation time	Regimen	Outcomes (pregnancy outcome, complications or side effects)
9	47 days	24 hours	Same as above	Nausea, vomiting, dehydration; requested aspiration at day 3
12	48 days	24 hours	Same as above	Continuing GCA at 15 days
3	50 days	24 hours	Placebo	Continuing GCA at 16 days
4	48 days	24 hours	Placebo	No GCA at 4 days
6	61 days	24 hours	Placebo	Continuing GCA at 16 days
7	48 days	24 hours	Placebo	D&C requested (bleeding, anxiety) at day 4
10	60 days	24 hours	Placebo	Expelled pregnancy, incomplete, emergent D&C at day 5
11	60 days	24 hours	Placebo	Expelled pregnancy, incomplete, emergent D&C, transfusion at day 6

*Unclear if this group includes the individuals treated with high-dose oral progesterone.
D&C, dilation and curettage; GA, gestational age; GCA, gestational cardiac activity; IM, intramuscular; LTFU, lost to follow-up; N/A, not available; PO, per os; PV, per vagina; US, ultrasound.

ultrasounds to confirm gestational cardiac activity prior to initiating progesterone, and there were no stated criteria for ultrasound use.[28 29] For the 2018 Delgado *et al* case series less than one-third (547/1668) of the women who initially expressed interest in progesterone treatment were included in the analysis. While the reasons for exclusion are clear for 207 of these women, they are not for the remaining 914 women. It is possible that some of the latter women may have been excluded because of embryonic demise at the time of presentation, or because they were experiencing bleeding or pain. For the Creinin study we rated the quality of the evidence as high given the randomised, double-blind study design (online supplemental table 3). However, the study did not reach the intended sample size as researchers stopped enrollment early due to safety concerns.

DISCUSSION

Our review of the use of progesterone to reverse the effect of mifepristone found that ongoing pregnancy rates are not significantly different for individuals treated with progesterone compared with those managed expectantly. Also, individuals who do not receive misoprostol after mifepristone may be at increased risk of bleeding.

We found few studies investigating the effect of progesterone treatment to reverse the effects of mifepristone. Only one study was rigorously designed but did not reach its intended sample size due to safety concerns. The remainder were case series with serious ethical and methodological concerns. We compared the ongoing pregnancy rate at 7 weeks or less and 7–8 weeks for individuals treated with progesterone after mifepristone compared with those who were managed expectantly, pooling data from the four studies in

Table 3 Proportion of pregnant individuals with continuing pregnancies after taking mifepristone at 7 weeks' gestation or less, and at 7–8 weeks' gestation, with or without progesterone

	7 weeks of pregnancy or less			7–8 weeks of pregnancy		
Authors (year)	Total pregnancies (n)	Ongoing pregnancies (n)	Percentage ongoing pregnancies (95% CI) (%)	Total pregnancies (n)	Ongoing pregnancies (n)	Percentage ongoing pregnancies (95% CI) (%)
Mifepristone 200 mg + progesterone (any dose)						
Delgado & Davenport[28] (2012)	2	1		2	2	
Garratt & Turner[30] (2017)	1	1		2	1	
Delgado *et al*[29] (2018)	291	121		88	54	
Creinin *et al*[31] (2020)	3	2		3	2	
Total	**297**	**125**	**42% (37–48%)**	**95**	**59**	**62% (52–71%)**
Mifepristone 200 mg alone						
Maria *et al*[35] (1998)*	30	7		–	–	
Creinin *et al*[31] (2020)	2	0		4	2	
Total	**32**	**7**	**22% (11–39%)**	**4**	**2**	**50% (15–85%)**

CIs are calculated 95% Wilson Score CIs.
*All participants in this study were at 49 days of gestation or less.

this review and the only prior study which examined ongoing pregnancy rates after a 200 mg dose of mifepristone. Even including all the data from the poorly conducted case series, ongoing pregnancy rates are not significantly higher for individuals treated with progesterone compared with those managed expectantly.

Most of the data in this analysis were collected as part of a large case series[29] with ethical and methodological issues. While we considered excluding it from the analysis, we ultimately included it because it did meet our definition of case series, though its lack of completeness and inclusiveness of cases over time limits its reliability.[25 33] This case series by Delgado *et al* reported a success rate of progesterone treatment of up to 68%.[29] As was also highlighted by authors who conducted a partial reanalysis of those findings,[36] this success rate was likely inflated by two factors. While some participants had gestational cardiac activity confirmed by ultrasonography prior to initiating progesterone, it is unclear how many individuals in total had ultrasound examinations and how many were excluded from the study because they already had an embryonic demise prior to initiating progesterone. Only selecting individuals who had gestational cardiac activity at the time they sought abortion reversal would falsely inflate progesterone's success rate because mifepristone alone does not always cause embryonic demise, particularly at higher gestational ages.[21 37] Also, the authors excluded from the analysis individuals who were lost to follow-up before 20 weeks, many of whom may have experienced embryonic demise.

Both the 2012 and 2018 case series[28 29] we included in the review also raise ethical concerns. First, investigators and their associated institutions have a responsibility to ensure that research is conducted ethically.[38] The 2012 case series does not mention obtaining informed consent, nor does it mention institutional review board (IRB) approval or review, which is inappropriate as the authors report giving an experimental treatment and following patients prospectively.[28] In the 2018 case series, in which more than 700 women received an experimental treatment, the authors obtained "written informed consent that included permission to track [the individuals'] data" and claim that the study received an "institutional review board waiver".[29] However, this study was temporarily retracted due to ethical concerns as the authors initially failed to provide information about IRB approvals.[29 39]

Second, journals and publishers have a role in promoting ethical conduct in research and publishing.[40] The 2018 case series was published in the journal *Issues in Law & Medicine*. This journal consistently publishes articles written by individuals and funded by sources which openly oppose access to abortion, without disclosing its ties to this movement, potentially biasing the results. While location of publication was not a criterion for inclusion in this review, it is important to raise the possibility that the peer review process in such journals may not have been as transparent as in other scientific journals.

Another limitation of the studies included in this analysis is that only one study[31] reported treatment side effects and complications. The 2018 case series included information about birth defects but nothing about side effects or complications experienced by the women treated with progesterone.[29] In the Creinin *et al* study,[31] a concerning number of participants experienced complications in both arms of the study. In the six-patient treatment group, one patient had a haemorrhage not requiring a blood transfusion. In the six-patient control group, two had haemorrhages requiring uterine aspiration, one of which also required transfusion. Similar events may have arisen in the other case series but were not reported. These findings suggest that when individuals change their mind after ingesting mifepristone for medication abortion, both expectant management and treatment with progesterone may be associated with a higher risk of bleeding than continuing the abortion with misoprostol, where complications requiring emergency department visits are rare.[4]

In conclusion, based on data from poorly conducted studies that may not have undergone rigorous peer review, there is insufficient evidence to recommend progesterone for individuals who change their minds after initiating the medication abortion process. Only one study included was of high quality, but we cannot draw conclusions related to effectiveness as it was stopped due to safety concerns. Given these concerns, any further studies of this topic should be conducted in a controlled environment, and they should be rigorously designed and ethically conducted.

Ultimately, obtaining high-quality evidence on whether progesterone can reverse the effects of mifepristone could help provide patient-centred care for the small minority of individuals who do change their minds after starting the medication abortion process. The WHO defines people-centred care as an approach to care in which "people have the education and support they need to make decisions and participate in their own care".[41] Providing accurate information to those who are interested in reversing the effects of mifepristone would be in line with these principles. Similarly, obtaining additional data about the efficacy and safety of these treatment options would enable policymakers to meet their international human rights law obligations to ensure that individuals have access to accurate and evidence-based information to inform their decision-making.[2] However, until such evidence is available, clinicians who seek to support patients in this way should be cautious about providing high-dose progesterone off-label given the lack of evidence of benefit and the potential safety concerns. Clinicians should also counsel patients that expectant management may be less safe than completing the medication abortion process with misoprostol.

Registration

We did not register this review. The review protocol was not published but is available on request.

Acknowledgements The UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction(HRP) funded this work. The named authors alone are responsible for the views expressed in this publication and do not necessarily represent the decisions or the policies of the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction(HRP) or the World Health Organization(WHO).

Contributors AFL had the idea for this systematic review. AFL and BMS designed the systematic review protocol and decided on search strategies. AFL and BMS conducted abstract and full-text screening. BMS extracted data and wrote the first draft of the manuscript. AFL and BMS revised the manuscript and approved the final version. AFL and BMS accept full responsibility as guarantors.

Funding The UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) funded this work.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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