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Authors

Hsia, Jennifer K
Lohr, Patricia A
Taylor, Jeanette
et al.

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Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation☆,☆☆

Jennifer K Hsia [a,1], Patricia A Lohr [b], Jeanette Taylor [b], Mitchell D Creinin [a,*]

[a] Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, CA, USA
[b] British Pregnancy Advisory Service, Stratford Upon Avon, UK

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ABSTRACT

Objective: To evaluate outcomes with mifepristone 200 mg orally followed 24–48 h later by misoprostol 800 mcg vaginally for medical abortion at 64–70 days of gestation.

Study design: We reviewed electronic databases and medical records for medical abortion cases at 64–70 days' gestation at British Pregnancy Advisory Service clinics in England and Wales from May 2015 through October 2016. Women selected in-office follow-up or self-evaluation of abortion outcome using a checklist along with low-sensitivity urine pregnancy testing. We excluded cases in which we could not locate records and when women did not proceed with medical abortion, did not use misoprostol following mifepristone if abortion had not occurred and did not attend a scheduled follow-up assessment. We analyzed demographic characteristics, treatment outcomes and significant adverse events. We defined treatment success as complete abortion without surgical evacuation and without continuing pregnancy.

Results: Of 2743 cases identified, we could not locate 40 charts and excluded 30 cases, leaving a final sample of 2673. Overall, 2538 (94.9%, 95% CI 94.1–95.8) women had a successful medical abortion. Reasons for failure included continuing pregnancy (n=90, 3.4%, 95% CI 2.7–4.1), retained nonviable pregnancy (n=2, 0.1%, 95% CI 0–0.2) and incomplete abortion (n=43, 1.6%, 95% CI 1.1–2.1). Of those with continuing pregnancies, 81 underwent a uterine aspiration and 9 opted to continue the pregnancy. Thirty-five (1.3%, 95% CI 0.9–1.7) women had significant adverse events; 16 (0.6%, 95% CI 0.3–0.9) underwent an in-hospital aspiration. Pelvic infection (n=4, 0.2%) and transfusion (n=1, 0.03%) occurred rarely.

Conclusion: Medical abortion from 64 to 70 days with mifepristone and vaginal misoprostol is effective with a low rate of serious adverse events.

Implications: Medical abortion between 64 and 70 days of gestation may be offered on an outpatient basis using mifepristone and vaginal misoprostol. Service provision without an in-person follow-up is feasible. Not all women with a continuing pregnancy after medical abortion treatment opt to have an aspiration procedure.

1. Introduction

Medical abortion with mifepristone 200 mg orally and misoprostol 800 mcg vaginally [1–3] or buccally [4] is highly effective through 63 days of gestation [1–4]. In many countries, women use these medications on an outpatient basis and expel the pregnancy at home. A home-based model of medical abortion is as safe, effective and acceptable to women as in-clinic care [5]. In countries like Britain and the United States, where this model predominates, abortions in the first 9 weeks of gestation are now induced more frequently with mifepristone and misoprostol than by surgical evacuation [6–8].

Recent research shows that the upper gestational age limit for outpatient regimens using mifepristone and buccal [9,10] misoprostol may be extended to 70 days of gestation without a clinically significant reduction in effectiveness compared to 57–63 days of gestation [9–11]. Similar efficacy is reported in a small number of cases with sublingual misoprostol [12]. Few data are available to evaluate outcomes with mifepristone and a single dose of misoprostol vaginally beyond 63 days of gestation. One prospective cohort study of women treated as inpatients reported a complete abortion rate of 94.5% in 253 cases treated at 63–83 days of gestation, [13] a rate similar to the 92.5% rate reported with buccal misoprostol at 64–70 days of gestation [11].

In 2015, British Pregnancy Advisory Service (BPAS), the largest non-profit provider of abortion services in the United Kingdom, extended

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* Corresponding author. Tel.:+1 916 734 6670.
E-mail address: mdcreinin@ucdavis.edu (M.D. Creinin).
[1] Dr. Hsia's current affiliation is Department of Obstetrics and Gynecology, Palo Alto Medical Foundation, Mountain View, CA, USA.

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the upper gestational age limit for outpatient medical abortion from 63 to 70 days of gestation using the regimen recommended in national guidance: mifepristone 200 mg orally followed in 24–48 h by misoprostol 800 mcg vaginally [14]. Prior to this date, BPAS only offered this care with admission to a treatment unit. Because only one BPAS unit in the country offered in-clinic medical abortion care, this pathway created a significant burden for women who needed to travel a long distance to reach the clinic and often resulted in an overnight stay. This report describes an evaluation of the effectiveness and safety of the outpatient regimen during the first 18 months of the service.

2. Material and methods

2.1. Medical abortion protocol

Women desiring an abortion had an initial consultation, which included gestational age dating by vaginal or abdominal ultrasound using dating criteria of Hadlock et al. [15]. Those eligible for and requesting a medical abortion swallowed mifepristone 200 mg in the clinic. Due to legal restrictions on the home use of misoprostol in Britain during the evaluation period [16], women returned to the clinic in 24–48 h for misoprostol 800 mcg vaginal insertion either self-administered or by a nurse, depending on the woman's preference. Women then went home to complete the abortion. Women chose between a follow-up visit with a clinical assessment and ultrasound scan 1–2 weeks after mifepristone administration or a self-assessment using a low-sensitivity pregnancy test (1000 IU) and a symptom checklist 2 weeks after treatment [17]. Clinicians instructed those choosing self-assessment to contact the clinic if they had one or more triggers on the checklist or a positive or indeterminate urine pregnancy test; clinic staff scheduled these women for an in-person clinical assessment that included an ultrasound scan. Clinicians offered surgical evacuation to women with ongoing pregnancies. For those diagnosed with an incomplete abortion (persistent heavy bleeding or cramping with heterogenous intrauterine contents) or a retained nonviable gestational sac, clinicians offered the choice of an additional dose of misoprostol, expectant management or a surgical evacuation. Surgical evacuation may also have been performed for other indications such as brisk bleeding, hemodynamic instability, infected retained tissue or patient request.

2.2. Data abstraction and analysis

We identified all women scheduled for a medical abortion from 64–70 days of gestation from May 1, 2015, to 31 October 31, 2016, using BPAS' electronic Booking and Invoicing System. BPAS has 63 clinics in England and Wales of which 55 clinics provided medical abortion from 64 to 70 days of gestation. We performed a chart review and excluded cases with no locatable records and when women did not proceed with medical abortion or did not use misoprostol following mifepristone if abortion had not occurred. We also excluded women who scheduled in-person follow-up and did not return or who contacted the clinic due to a self-assessment trigger but did not attend a scheduled appointment. A research nurse and research assistant extracted demographic characteristics, treatment and follow-up details, and outcomes (including reasons for failure and any complications) onto an anonymized data collection form and then entered the findings into a secure database for analysis. The medical record did not include a distinct variable documenting intended follow-up method, so this exact information could not be ascertained. We cross-referenced BPAS' electronic adverse events database to capture any other incidents reported by clinical staff or received from external providers (e.g., general practitioners) and reviewed any discharge summaries from hospitals or doctors received to accurately record any diagnoses or interventions. We defined significant adverse events as emergency department presentation or inpatient hospitalization (further categorized by whether the clinician performed an aspiration), transfusion and pelvic infection.

We defined the primary outcome, treatment success, as complete abortion without surgical intervention and without continuing pregnancy. Secondary outcomes included indications for surgical evacuation and significant adverse events.

We also evaluated the total number of women who received medical and surgical abortion services at 64–70 days gestation for the 18 months prior to and during this analysis. We used these outcomes to determine the proportion of women in each time period who obtained medical abortion.

We used Fisher's Exact Testing for statistical evaluations with a $p<.05$ considered significant. The funding source had no involvement is study design, data analysis and interpretation, or preparation of the manuscript. The BPAS Research and Ethics Committee and the Institutional Review Board at the University of California, Davis, approved and exempted the study from full human subjects review.

3. Results

Of the 2743 scheduled medical abortion cases at 64–70 days of gestation during the 18-month study period, we could not locate 40 (1.5%) medical records and excluded 30 (1.1%) women, including 21 who used mifepristone alone but did not abort, 6 who did not proceed with a medical abortion and 3 who did not follow up to assess outcome when clinically indicated. We describe the demographic characteristics of the final sample of 2673 women in Table 1.

Treatment outcomes are summarized in Table 2. Of the 2538 (94.9%, 94.1–95.8) with a complete abortion, 9 (0.4%, 95% CI 0.1–0.6) expelled the pregnancy with mifepristone treatment only. Overall, 287 (10.7%) women had an in-person follow-up evaluation as intended, due to a need for further assessment or due to a complication. Of the 90 cases of continuing pregnancy, 81 (90%, 95% CI 83.8–96.2) chose a uterine aspiration. Overall, 126 (4.7%) women had a uterine aspiration for continuing pregnancy, incomplete abortion or retained sac.

Thirty-five (1.3%, 95% CI 0.9–1.7) women experienced 37 significant adverse events; no deaths occurred. The majority of the adverse events included presentation to an emergency department or inpatient admission ($n=32$, 1.2%, 95% CI 0.8–1.6). Women who visited a hospital related to the medical abortion did so most commonly for a bleeding-related complaint ($n=28$, 1.0%, 95% CI 0.7–1.4). However, only 12 (0.4%, 95% CI 0.2–0.7) required an aspiration during that visit; one (0.04%, 95% CI 0–0.1) of these women also received a blood transfusion. Infections included three (0.1%, 95% CI 0–0.2) women diagnosed as outpatients with pelvic infection and one woman admitted to the hospital with sepsis. This latter patient had an ongoing pregnancy that she opted to continue; she presented approximately 8 months later in sepsis having delivered a macerated fetus and subsequently required a hysterectomy due to the infection.

In the 18 months prior to the outpatient service initiation, 6 of 5479 (0.1%) eligible women at 64–70 days of gestation opted for medical

Table 1
Descriptive characteristics of women undergoing medical abortion at 64–70 days of gestation at BPAS from 1 May 2015 to 31 October 2016 ($N=2673$)

Characteristic	*n* (%) or median (range)
Age (years)	25 (13–49)
Gravidity	2 (1–16)
Parity	1 (0–8)
Prior abortion	903 (33.8%)
Prior cesarean delivery	283 (10.6%)
Race	
White	2159 (80.8%)
Black	209 (7.8%)
Asian	215 (8.0%)
Other	90 (3.4%)
Gestational age (days)	67 (64–70)

Table 2
Medical abortion outcomes in cases at 64–70 days of gestation at BPAS from 1 May 2015 to 31 October 2016 (*N*=2673)

Outcome	*n* (%, 95% CI)
Success	2538 (94.9%, 94.1%–95.8%)
Failure: overall	135 (5.1%, 4.2%–5.9%)
Continuing pregnancy	90 (3.4%, 2.7%–4.1%)
Incomplete abortion	43 (1.6%, 1.1%–2.1%)
Retained nonviable sac	2 (0.1%, 0%–0.2%)

abortion. During the first 18 months of the outpatient service, 2743/6762 (40.6%) chose medical abortion (p<.001).

4. Discussion

This analysis in more than 2600 women who received mifepristone 200 mg orally followed 24–48 h later by misoprostol 800 mcg vaginally for abortion from 64 to 70 days of gestation provides a large dataset within this gestational age range and demonstrates that the regimen is effective with a low incidence of significant adverse events. These findings confirm those of an earlier, smaller study of women managed with this regimen at 63–83 days of gestation [13] and are comparable to other reports of medical abortion at 64–70 days of gestation with buccal and sublingual misoprostol (Table 3). These outcome rates are similar to those reported in the U.S. Food and Drug Administration label for mifepristone in the United States based on two studies as shown in Table 3 [11]. Of note, the continuing pregnancy rate appears to be about the same whether vaginal or buccal misoprostol is used. However, the overall treatment success rate is slightly higher with vaginal compared to buccal misoprostol (Table 3). Given the lower success rate in this gestational age range compared to earlier gestations [1–4], future research could address additional misoprostol dosing or alternative regimens.

Providers may be concerned about a higher incidence of other adverse events with outpatient medical abortion as gestational age advances, in particular, the risk of hemorrhage and need for acute intervention or blood transfusion. In our study, 1.2% of women presented to hospital for assessment related to the medical abortion. Although the main complaint in about half of cases was heavy bleeding, reassuringly, only 6 (0.2%) women needed emergency aspiration and only 1 (0.04%) needed a transfusion. This transfusion rate is lower than the 0.5% reported in a study using misoprostol buccally at 57–70 days gestation and in line with the overall rates for women of all gestational ages through 70 days in the U.S. mifepristone label [11]. A U.S. study representing 54,911 medical and surgical abortions in California during 2009–10 reported a similar emergency department visit rate of 0.9% [19]. The medical abortions in the California study only included women through 9 weeks of gestation for whom the significant adverse event rate was 0.31%, lower than our rate of 1.3%. This difference may be related to gestational age of our cohort or differential use of hospital services in the U.K. where access is free.

The relatively large sample size of this study compared to other evaluations of single-dose outpatient medical abortion regimens at 64–70 days of gestation is a strength. Weaknesses include the retrospective nature of the review and our inability to know the exact proportion of women who planned self-assessment vs. in-person follow-up. A prior study in BPAS clinics demonstrated that most (87.2%) women assigned to have office follow-up reported a priori a preference for remote follow-up [20], a rate similar to the 89.3% non-in-person follow-up rate in our population. An additional weakness, the use of self-assessment for follow-up by most women in the analysis, meant that identification of treatment failures and other complications required the woman or another care provider such as a general practitioner informed BPAS of the issue or the woman returned to BPAS for assessment. We attempted to minimize missing any complications by reviewing the case notes and cross-referencing with BPAS' complications and booking databases. However, some women may have received treatment of a complication elsewhere without informing BPAS. In cases in which a woman informed BPAS of a complication, details may have been relayed inaccurately in some cases. Management of adverse events, such as the threshold for blood transfusion or choice of intravenous or oral antibiotics, can also differ between clinicians and across institutions. Additionally, despite staff training staff in the reporting and coding of incidents, there can be errors and omissions in the reporting process.

As would be expected, women infrequently chose medical abortion at 64–70 days of gestation prior to the availability of an outpatient service. Based on the initial significant increase in uptake, implementation of an outpatient regimen has successfully enhanced access to medical abortion for women at these gestational ages. In 2017 in Scotland [21] and 2018 for England [22] and Wales [23], the respective Secretaries of State approved home use of misoprostol following office mifepristone administration. Associated guidelines, and in the case of England the approval wording itself, limit home use of misoprostol to 69 days of gestation. These decisions will reduce the burden of multiple clinic visits and may further increase medical abortion uptake, including beyond 63 days of gestation. Our data support the safety and efficacy of this regimen through 70 days of gestation; these governments should consider amending guidance and approval wordings accordingly.

Our findings provide further support for the outpatient administration of mifepristone and misoprostol for medical abortion at 64–

Table 3
Outcomes of medical abortion at 64–70 days in the literature and including this report [a]

First author	Year published	Study design	Mifepristone dose	Misoprostol dose	Number of women evaluated	Successful abortion	p value compared to current study	Continuing pregnancy rate	p value compared to current study
Hsia (current study)	–	Retrospective	200 mg	800 mcg vaginally	2673	2538 (94.9%)	–	90 (3.4%)	–
Gouk [13]	1999	Prospective	200 mg	800 mcg vaginally	127	120 (94.5%)	.83	7 (5.5%)	.21
Bracken [12]	2014	Prospective	200 mg	400 mcg sublingual	321	295 (91.9%)	.03	7 (2.2%)	.32
Winikoff [10][b]	2012	Prospective	200 mg	800 mcg buccally	304	282 (92.8%)	.11	9 (3.0%)	.87
Smith [18][b]	2015	Prospective	200 mg	800 mcg buccally	147	135 (91.8%)	.12	5 (3.4%)	1.0
Total vaginal misoprostol					2800	2658 (94.9%)[c]		97 (3.5%)[d]	
Total buccal misoprostol					451	417 (92.5%)[c]		14 (3.1%)[d]	

[a] Only includes studies reporting outcomes with at least 50 women at 64–70 days.
[b] Study comprising the data used for mifepristone U.S. Food and Drug Administration label [7].
[c] p value=.04 comparing successful abortion rates of total vaginal and total buccal misoprostol groups (Fisher's Exact Test).
[d] p value=.78 comparing continuing pregnancy rates of total vaginal and total buccal misoprostol groups (Fisher's Exact Test).

70 days of gestation and add to the existing evidence that the misoprostol may be administered by the vaginal route.

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