Contraception 101 (2020) 302–308

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

Original Research Article

A non-inferiority study of outpatient mifepristone-misoprostol medical abortion at 64–70 days and 71–77 days of gestation ☆,☆☆,★

Ilana G. Dzuba [a,*], Erica Chong [a], Curtiss Hannum [b], E. Steve Lichtenberg [c], Elba Margarita Lugo Hernández [d], Nguyen thi Nhu Ngoc [e], Ashlesha Patel [f], Gulnara Rzayeva [g], Patricio Sanhueza Smith [h], George Tsertsvadze [i], Beverly Winikoff [a]

[a] Gynuity Health Projects, 220 E. 42nd Street, Suite 710, New York, NY 10017, USA
[b] The Women's Centers, 777 Appletree Street, 7th Floor, Philadelphia, PA 19106, USA
[c] Family Planning Associates, 659 West Washington Blvd, Chicago, IL 60661, USA
[d] Clinica Comunitaria Santa Catarina, Calle Nuevo León Mz. 38, Lt. 9., Col. Miguel de la Madrid, Del. Iztapalapa, 09698 Mexico City, Mexico
[e] Center for Research and Consultancy on Reproductive Health, 16D Luy Ban Bich, Tan Thoi Hoa, Tan Phu, Ho Chi Minh City, Viet Nam
[f] John H. Stroger, Jr. Hospital of Cook County, Department of Obstetrics and Gynecology, 1901 W Polk Street, Chicago, IL 60622, USA
[g] Scientific Research Institute of Obstetrics and Gynecology, Baku 560-th block K. Kazimzadeh str. 118, Azerbaijan
[h] Department of Reproductive Health, Secretariat of Health of Mexico City, Calle Altadena #23, Col. Nápoles, Del. Benito Juárez, 03810 Mexico City, Mexico
[i] David Gagua Clinic, 2/6 Ljubljana Street, Digomi Masivi, Tbilisi, Georgia

ARTICLE INFO

Article history:
Received 10 August 2019
Received in revised form 21 December 2019
Accepted 20 January 2020

Keywords:
Abortion
Mifepristone
Misoprostol
Outpatient
First trimester
Non-inferiority

ABSTRACT

Objectives: This open-label non-inferiority study assessed efficacy of a common outpatient medical abortion regimen among people with pregnancies 64–70 days and 71–77 days of gestation.
Study design: We defined non-inferiority by a 6% margin of method success. People with intrauterine pregnancies 64–77 days' gestational age by abdominal ultrasound seeking medical abortion at one of eight clinics and met eligibility criteria were offered participation. Consenting participants took mifepristone 200 mg followed 24–48 h later by misoprostol 800 mcg buccally, and returned after one week for provider evaluation and abdominal ultrasound to determine abortion status. Participants recorded medication use, pregnancy expulsion, daily bleeding and pain scores until the one-week follow up. Clinic staff interviewed participants prior to study discharge to assess acceptability.
Results: Seven hundred and nineteen participants were enrolled, 393 and 326 in the respective groups. Successful expulsion without surgical intervention was achieved in 92.3% of the earlier gestational age group and 86.7% of the later group (difference in proportions 5.6%, 1-sided 95% CI 9.6). Ongoing pregnancy accounted for 3.6% and 8.7% (p = 0.007) of outcomes, respectively. Participants in the 71–77 day group reported nausea and weakness more frequently. Pain, bleeding and acceptability measures between groups were similar.
Conclusion: Although the success rate at 71–77 days of gestation was within the non-inferiority margin, we cannot rule out that it is statistically worse than in the previous gestational week. Significantly more ongoing pregnancies in the later group raise concerns about using the regimen at 71–77 days.

1. Introduction

Since 2000 when the anti-progestin, mifepristone, was registered in the United States (US) for abortion (in combination with the prostaglandin misoprostol), medical abortion (MA) has been increasingly used as an outpatient alternative to aspiration in the first trimester of pregnancy. As of 2017, the proportion of non-hospital facility-based abortions induced with mifepristone and misoprostol was 39% [1]. In March 2016, the US Food and Drug Administration updated the Mifeprex label, which expanded the gestational age (GA) limit for its use from 49 to 70 days (10 weeks) to better correspond with evidence-based clinical guidelines and

☆ Funding: This work was supported by an Anonymous donor. The funding source had no involvement in study conduct, analysis or write-up.
☆☆ Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
★ IRB approval: IRB approval was granted by The New England Institutional Review Board, Cook County Health and Hospitals System IRB, and local ethical committees in Mexico, Vietnam, Azerbaijan and Republic of Georgia.
* Corresponding author.
E-mail addresses: idzuba@gynuity.org (I.G. Dzuba), echong@gynuity.org (E. Chong), channum@thewomenscenters.com (C. Hannum), jodotter@aol.com (E.S. Lichtenberg), elbalugohdz@gmail.com (E.M. Lugo Hernández), nhungoccrcrh@gmail.com (N.N. Ngoc), apatel2@cookcountyhhs.org (A. Patel), gulnara_rzaeva@rambler.ru (G. Rzayeva), patriciosanhueza@prodigy.net.mx (P. Sanhueza Smith), tsertsvadzegogi@yahoo.com (G. Tsertsvadze), bwinikoff@gynuity.org (B. Winikoff).

https://doi.org/10.1016/j.contraception.2020.01.009
0010-7824/

well-established advances in practice [2,3]. Approximately 80% of all abortions occur within the first 10 weeks of pregnancy, [4] therefore the vast majority of people seeking early pregnancy termination are eligible to have a medical abortion.

Although medical abortion success rates decline gradually with increasing GA, it is still highly effective through the 10th week of pregnancy [2,5]. A systematic review reported average rates of 96.7% in the 8th week, 95.2% in the 9th week, and 93.1% in the 10th week [3]. Conversely, ongoing pregnancy after MA, while still infrequent, becomes more likely in the 9th and 10th weeks than in earlier gestational weeks (3–3.8% [5–8] vs 0.5–1.0% [9–11]). Late first trimester inpatient MA studies demonstrate high efficacy (92–97%), but are not directly translatable to outpatient services in many places as most regimens studied used repeated misoprostol doses and did not include administration by the buccal route [12–15]. Despite limited and low-quality evidence, the World Health Organization recommends mifepristone-misoprostol MA to 12 weeks with the possibility of repeated misoprostol doses, [16] and some countries, such as Uruguay, include the option in technical guidelines.

As first trimester outpatient MA in many facilities is capped at 10 weeks and 2nd trimester protocols start at 13 weeks, we sought to provide much-needed data to bridge the evidence gap for an outpatient MA regimen in the later first trimester [17]. Broadening the GA range an additional week to 77 days would be beneficial for people who prefer a non-surgical option and could increase access to safe abortion care [18,19]. We studied a first trimester outpatient regimen of mifepristone and one misoprostol dose, considering the potential for increased side effects with more misoprostol doses, the ease with which health systems could adapt this innovation, and demonstrated high success in the 10th week of gestation.

2. Materials and methods

2.1. Study design

We conducted an open-label, prospective non-inferiority study to assess the efficacy of mifepristone and buccal misoprostol for outpatient MA in participants with pregnancies 64–70 days and 71–77 days of gestation. The study was conducted at eight facilities in the US, Vietnam, Mexico, Republic of Georgia, and Azerbaijan from December 2014 to April 2016. New England IRB and Cook County Health and Hospitals System IRB approved the protocol for US sites, and local ethical committees approved it for non-US sites. The study was registered on clinicaltrials.gov (NCT02314754).

2.2. Procedures

Clinic staff trained in the research protocol invited people with intrauterine pregnancies 64–77 days of gestation by abdominal ultrasound and seeking abortions at study sites to participate in the study. Additional inclusion criteria included willingness and ability to provide informed consent, confirmed eligibility for MA, agreement to comply with study procedures, and (in the US and Azerbaijan) age 18 years or older. All participants received counseling per each clinic's standards, were told the probable size of the expulsion and what they might see, and were offered the option to view images (standardized across sites) to manage expectations.

Clinic staff obtained study consent and gave participants mifepristone 200 mg and misoprostol 800mcg, instructing them to place the misoprostol buccally (in the cheeks) 24–48 h after mifepristone. Per standard clinic protocols, participants either received directly or were given a prescription for analgesia (narcotic and/or NSAID or paracetamol) and anti-emetic medications. Study clinics also followed their usual protocols and did not provide prophylactic antibiotics, in line with practice guidelines [20]. Clinic staff instructed participants to maintain a standardized diary until follow up to record the moment of expulsion, daily pain scores and bleeding levels.

Participants returned to the clinic approximately one week after taking mifepristone to assess abortion status via provider evaluation and abdominal ultrasound. If the pregnancy continued, aspiration was recommended. If the abortion was incomplete (persistent non-viable pregnancy, such as sac or products of conception, but no gestational growth or fetal cardiac activity, or substantial uterine debris) participants could choose expectant management or more misoprostol and another one-week follow up, or aspiration. Prior to study discharge, clinic staff administered a standardized structured interview to participants to assess satisfaction, acceptability (including regarding the expulsion), pain, bleeding, side effects and visits to other facilities for reasons related to the abortion. If participants were unable or unwilling to attend in-clinic follow up, clinic staff collected information to the extent possible by telephone.

2.3. Outcomes and analysis

The study's primary objective was to assess whether success with an outpatient mifepristone-misoprostol regimen in participants with pregnancies 71–77 days of gestation was not worse than success with the same regimen in participants with pregnancies 64–70 days of gestation. We chose a non-inferiority design, as method effectiveness diminishes slightly with increasing GA through 70 days, and we expected that trend to continue in the subsequent gestational week. We defined abortion success as complete abortion without surgical intervention. We selected a 6% non-inferiority margin, hypothesizing a lower efficacy limit that might be acceptable to abortion-seekers and considering a reasonable timeframe for sample enrollment.

Assuming an efficacy rate of 93% in the 64–70 days group [21], we required 310 participants per group to determine non-inferiority in the 71–77 days group with a one-sided margin of 6% ($\alpha = 0.05$, $1\text{-}\beta = 0.90$) [22,23]. Based on lower client volume in the 71–77 days group, we assumed an enrollment ratio of 1:0.75. To attain a harmonic mean of 310 participants and account for an estimated 10% loss to follow up, we sought to enroll 384 participants with pregnancies 64–70 days and 307 participants with pregnancies 71–77 days [24].

Secondary outcomes included side effects, days of heavy bleeding, time to expulsion, and participant satisfaction and acceptability. To better understand participants' experiences with home expulsion, we evaluated their reactions to the expulsion and how prepared they felt. To determine the potential burden on clinics of adding an additional week we documented clinic calls and unscheduled visits.

Data were analyzed using SPSS 20 (IBM, Armonk, NY). Non-inferiority of the MA regimen in the 71–77 days group was determined if the upper limit of the 1-sided 95% CI for the difference in success rates between the two study groups did not exceed a relative margin of 6%, equivalent to a one-sided test with an alpha of 0.05. For all other analyses, we used a two-sided alpha of 0.05. We used Fisher's exact test (or Pearson's χ^2 as appropriate) to evaluate group differences for outcomes based on categorical variables. Continuous variables were analyzed using Independent *t*-tests, or if not normally distributed, non-parametric tests (Mann-Whitney *U*). Relative risk and 95% confidence intervals were calculated as appropriate. An independent data and safety monitoring board reviewed interim safety and efficacy outcomes once 50% of the data were available.

3. Results

Of the 719 participants enrolled in the study, 393 had pregnancies 64–70 days of gestation and 326 had pregnancies 71–77 days. We excluded five participants in the 64–70 days group and four in the 71–77 days group due to improper enrollment or because they changed their mind about the abortion before taking mifepristone. Baseline participant characteristics by study group were similar, except for mean GA, which we expected based on the study design (Table 1). One participant opted to continue the pregnancy before completing the study regimen. We analyzed 362 people in the 64–70 days group and 286 in the 71–77 days group for efficacy, including 12 participants who took incorrect misoprostol doses, administered it by the wrong route, or took it outside the 24–48 h time interval (Fig. 1). Participants lost to follow-up were excluded from the primary analysis (64–70 days: 6.7% vs 71–77 days: 10.9%; $p = 0.06$).

In the 71–77 days group, 86.7% of participants had successful MA's compared with 92.3% of participants in the 64–70 days group (difference in proportions 5.6%, 1-sided 95% CI 9.6) (Table 2, Fig. 2). The lower success rate in the later GA group was attributable to a higher frequency of ongoing pregnancies compared to the earlier GA group. Otherwise, all other reasons for intervention between GA groups were similar (Table 2). Of the 40 participants in the 64–70 days group who had expelled the gestational sac by initial follow up, but were further managed with additional misoprostol or expectant management and returned for extended follow up, 87.5% had successful MA's without aspiration. Of the 40 participants in the 71–77 days group with the same conditions, 85.0% had successful MA's without aspiration.

Participants in each of the 64–70 and 71–77 days groups took misoprostol at a median interval of 24 h (IQR 24, 26 vs. 24, 29, respectively; p = 0.02) after mifepristone. Participants in the 64–70 days group reported seeing the products of conception more frequently than those in the 71–77 days group (68.5% vs 55.6%, $p < 0.001$). Three-quarters of participants in each GA group felt prepared for what they saw, but those who opted to view images of MA expulsions and likely fetal size and development at this GA range (32.7% at 64–70 days vs 38.2% at 71–77 days, $p = 0.13$) reported feeling more prepared than those who opted not to view the images (91.8% vs. 65.7%, $p < 0.001$).

Table 1
Characteristics of participants with pregnancies of 64–70 days and 71–77 days of gestation.

	64–70 days (n = 388)	71–77 days (n = 322)	p-value
Age (years)	26.7 ± 6.2	26.5 ± 6.2	0.79
Years of school completed	12.2 ± 2.8	12.5 ± 2.7	0.07
Gravidity			
1	99 (25.5)	77 (23.9)	0.42
2	91 (23.5)	84 (26.1)	
3	74 (19.1)	66 (20.5)	
4	56 (14.4)	35 (10.9)	
5	35 (9.0)	23 (7.1)	
≥6	33 (8.5)	37 (11.5)	
Parity			
0	137 (35.3)	113 (35.1)	0.96
1	115 (29.6)	94 (29.2)	
2	93 (24.0)	75 (23.3)	
≥3	43 (11.1)	40 (12.4)	
Prior induced abortion	146 (37.6)	129 (40.1)	0.54
Prior induced medical abortion	73 (18.8)	65 (20.3)*	0.64
Gestational age (days)	66.7 ± 2.0	73.1 ± 1.9	≤0.001

n: number of participants; SD: standard deviation.
All data are presented as n (%) or mean ± SD.
*Denominator does not include 2 participants with unknown number of previous medical abortions (N = 320).

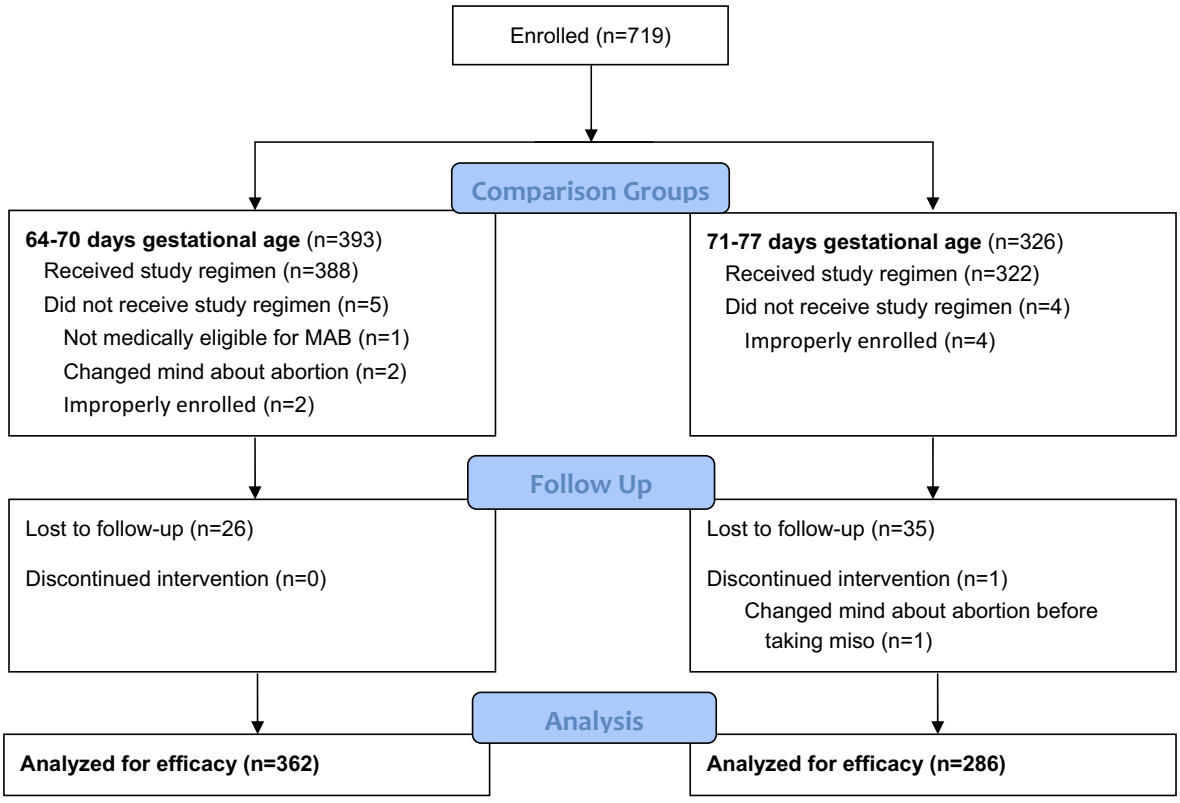
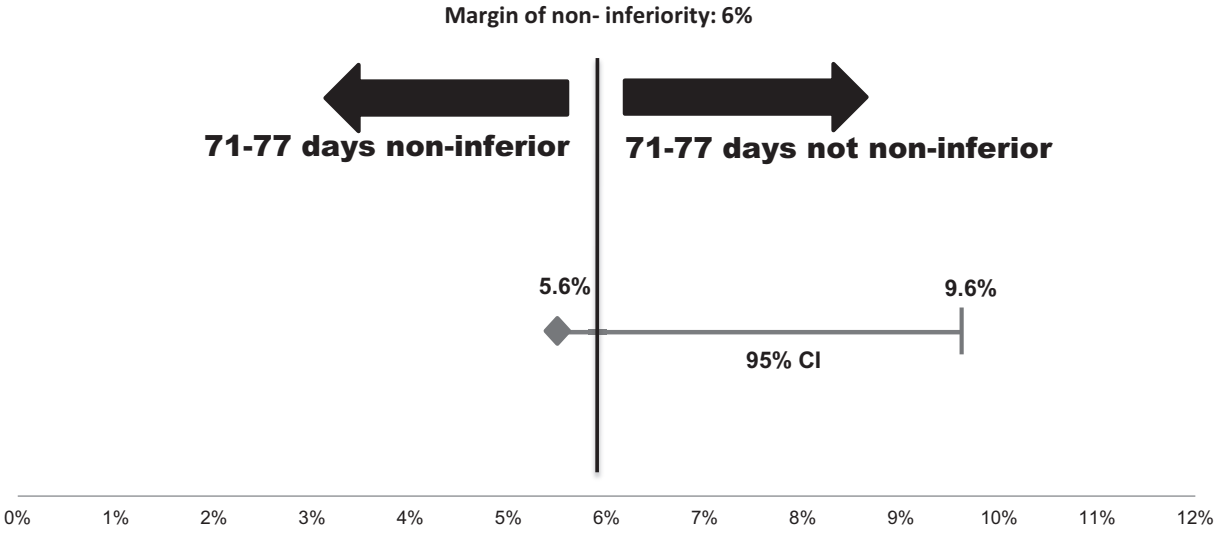


Fig. 1. Study flow of participants with pregnancies of 64-70 days and 71-77 days of gestation.

Table 2
Follow up, abortion outcome, reasons for intervention and time-to-expulsion among participants with pregnancies of 64–70 days and 71–77 days of gestation.

	64–70 days n = 362	71–77 days n = 286	Difference in proportions	1-sided 95% CI	
Success	334 (92.3)	248 (86.7)	5.6	9.6	
Reason for intervention			RR	95% CI	p-value
Ongoing pregnancy	13 (3.6)	25 (8.7)	2.43	1.22–4.95	<0.007
Persistent non-viable pregnancy/sac	5 (1.4)	5 (1.7)	1.27	0.32–4.99	0.76
Substantial debris in uterus	3 (0.8)	3 (1.0)	1.27	0.21–7.79	1.0
Excessive/prolonged bleeding	6 (1.7)	5 (1.7)	1.06	0.28–3.86	1.0
Unknown*	1 (0.3)	0 (0)	n/a	n/a	1.0
Expulsions prior to misoprostol dosing†	15 (6.0)	7 (4.2)	0.69	0.26–1.77	0.51
Median time to expulsion (hours)§	4.0 (3, 6)	4.0 (3, 7)	n/a	n/a	0.44
Expulsion within 24 h§	220 (93.6)	146 (90.7)	0.97	0.91–1.03	0.33
Median days to follow up	7 (7, 14)	7 (7, 7)	n/a	n/a	<0.001

n: number of participants; CI: confidence interval; IQR: interquartile range.
All data are presented as n (%) or median (IQR).
* Intervention done at local hospital ambulatory clinic in exchange for doctor's note to excuse absence from work; participant could not relay clinical reason for intervention.
† Excludes 112 participants in 64–70 d group and 118 in 71–77 d group who did not record a misoprostol administration time or had a surgical intervention for ongoing pregnancy or persistent non-viable sac.
§ Excludes 127 participants in 64–70 d group and 125 in 71–77 d group who did not record a misoprostol administration time, had a surgical intervention for ongoing pregnancy or persistent non-viable sac, or expelled before misoprostol was taken.



Non-inferiority of medical abortion success at 71-77 days gestation relative to 64-70 days gestation age. The diamond represents the point estimate of the difference in the success rates between the two gestational age groups and the horizontal bar represents the one-sided 95% CI for testing non-inferiority. Non-inferiority is not accepted since the 95% CI fell above the pre-defined non-inferiority margin of 6%.

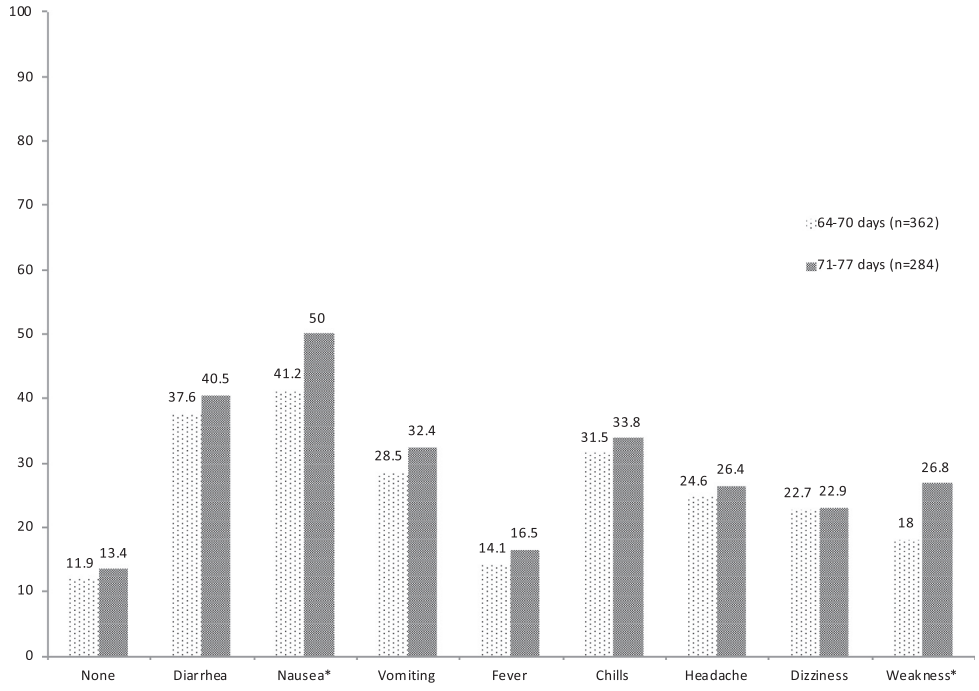
Fig. 2. Difference in proportions of women with successful medical abortion at 71–77 and 64–70 days of gestational age.

The side effect profiles between the study groups were similar, except nausea and weakness were higher in the 71–77 days group (Fig. 3). Nearly 90% of the 17% who took anti-emetics said they helped their nausea symptoms (64–70 days: 88.6% vs. 71–77 days: 87.9%, p = 1.0). There were no differences between study groups with regard to pain and bleeding experiences (Table 3). Irrespective of whether participants took ibuprofen, narcotics or paracetamol (n = 648), 86% of those who took analgesics said they helped ease pain. Although rare, participants went to the emergency room, primarily for bleeding or pain, and these were participants enrolled at sites that did not have an afterhours hotline (Table 4). No blood transfusions were reported among study participants.

Overall satisfaction with the abortion process was high, with 89.5% of the earlier GA group and 85.2% of the later GA group reporting that they were satisfied (p = 0.10). The vast majority of participants in each group would prefer MA over surgical methods for a future abortion (64–70 days: 88.7% vs 71–77 days: 83.4%, p = 0.07).

4. Discussion

Even though the proportional difference in success between the two GA groups after using the outpatient regimen with mifepristone 200 mg and misoprostol 800 mcg was less than the 6% non-inferiority margin, the one-sided confidence interval extended to 9.6%. Consequently, we cannot rule out that success with this common regimen at 71–77 days is worse than in the previous gestational week. Regardless, outpatient MA with the study regimen is largely efficacious through 77 days, with the success rate at 64–70 days comparable to previous reports [2,5].



* p<0.05
All data are presented as percentages.

Fig. 3. Self-reported side effects with outpatient medical abortion among participants with pregnancies of 64–70 days and 71–77 days of gestation.

This regimen could be a reasonable option for MA users at 71–77 days, given high success and acceptability, but the significant increase in continuing pregnancies presents valid concerns for MA seekers and providers. While an important consideration for all abortion seekers, less frequent ongoing pregnancies may be especially important for those on the cusp of the second trimester,

Table 3
Self-reported pain and bleeding experiences and pain medication use among participants with pregnancies of 64–70 days and 71–77 days of gestation.

	64–70 days (n = 362)	71–77 days (n = 286)	p-value
Mean highest pain score (0–10)	7.66 ± 2.36 (0–10)	7.82 ± 2.41 (0–10)*	0.38
Highest pain score of 7 or more	260 (71.8)	215 (75.7)	0.28
Analgesic use**			
Any kind of analgesia	227 (62.5)	211 (74.0)	<0.01
Acetaminophen	41 (11.3)	28 (9.9)	0.61
NSAIDs	165 (45.5)	152 (53.3)	0.48
Narcotics	50 (13.8)	56 (19.6)	0.54
Experience of pain during the abortion†			
Less than expected	80 (22.2)	62 (21.8)	0.97
As expected	111 (30.8)	86 (30.3)	
More than expected	169 (46.9)	136 (47.9)	
Acceptability of pain†			
Acceptable	252 (69.8)	180 (63.4)	0.23
Neutral	56 (15.5)	54 (19.0)	
Unacceptable	53 (14.7)	50 (17.6)	
Mean total heavy bleeding days	1.79 ± 1.53 (0–10)	1.79 ± 1.34 (0–10)§	1.0
Experience of bleeding during the abortion			
Less than expected	66 (18.2)	55 (19.4)	0.70
As expected	149 (41.2)	109 (38.4)	
More than expected	142 (39.2)	113 (39.8)	
Don't know	5 (1.4)	7 (2.4)	
Acceptability of bleeding			
Acceptable	292 (80.6)	210 (73.9)	0.32
Neutral	43 (11.9)	44 (15.5)	
Unacceptable	22 (6.0)	24 (8.4)	
Don't know	5 (1.4)	6 (2.1)	

n: number of participants; SD: standard deviation; NSAIDs: non-steroidal anti-inflammatory drugs.
All data are presented as n (%) or mean ± SD (range).
* Excludes two participants with missing data (n = 284).
** Participants could have taken more than one kind of analgesia.
† Excludes participants with missing data.
§ Excludes one participant with missing data (n = 285).

Table 4
Frequency of emergency room visits, clinic calls and unscheduled clinic visits among participants with pregnancies of 64–70 days and 71–77 days of gestation.

	64–70 days (n = 388)	71–77 days (n = 322)	p-value
Participants with ER visits	10 (2.6)	3 (0.9)	0.16
Participants who made clinic calls	17 (4.4)	23 (7.1)	0.14
Median calls	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.11
Participants who made unscheduled visits	5 (1.3)	8 (2.5)	0.27
Median unscheduled visits	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.24

n: number of participants; ER: emergency room; IQR: interquartile range.
All data are presented as n (%) or median (IQR).

which would imply a more expensive and less readily accessible procedure. Since this study was completed, newer evidence demonstrates that more than one misoprostol 800 mcg dose after mifepristone for later-first-trimester outpatient MA holds promise for improved outcomes [25,26]. Fewer ongoing pregnancies may offset the potential discomfort of prolonged side effects caused by additional misoprostol. Evidence suggests that outcomes are improved when the time interval between mifepristone and buccal misoprostol is 24–48 h rather than 24 h [3]. Our findings did not allow us to shed further light on this issue.

The increase in ongoing pregnancies between the 64–70 and 71–77 days groups seems large compared to the more gradual weekly increases with the same regimen earlier in the trimester [3]. The regimen could be significantly less effective at this point in pregnancy because of the intersection of several factors: the luteal-placental shift when the pregnancy becomes independent of progesterone produced by the corpus luteum, [27,28] the increasing size and volume of the uterus, and the larger fetus. In the first instance, the amount of progesterone to be blocked by the same dose of mifepristone increases substantially, so in these cases mifepristone functions to facilitate cervical softening and dilation, but in the second, the force generated by the action of misoprostol is much greater. A larger fetus requires the uterus to generate more force and the cervix to be softer and/or more dilated to allow expulsion. It is therefore likely that adding more misoprostol to the regimen would improve success rates.

A possible concern for MA at 71–77 days is the potential for more bleeding and pain, as well as people's ability to manage larger and more recognizable expulsions. Our results show, however, that bleeding, pain, and acceptability of pain did not differ by GA group, and with accurate information, appropriate preparation, and explanation of warning signs, participants were fully capable of managing later first-trimester expulsions and required minimal additional clinical support.

We selected a 6% non-inferiority margin considering that there are many people who might accept 87% efficacy as sufficient rationale for using the study regimen. Individual providers and abortion seekers will have their own efficacy thresholds with which they are comfortable, and thresholds may vary by whether people live in legally restricted settings or in rural areas, are distant from trained providers, or if they are averse to aspiration.

A study limitation is that abortion counseling was not standardized and was conducted according to each site's usual practices, which may have varied. Similarly, provider experience and comfort with MA may vary across and within sites, which might result in different approaches to patient management. We could not measure total bleeding duration because we did not follow participants until bleeding cessation. Lastly, because clinic staff conducted the exit interviews face-to-face, participants may have been less likely to express dissatisfaction.

Our data underscore the question of whether additional misoprostol doses after 70 days may improve success by reducing ongoing pregnancies [29]. A highly effective outpatient MA regimen at 71–77 days would broaden the scope of where MA can be provided and by whom, and support telemedicine abortion services, where patients may not present to a clinic at all, but rather interact remotely with a clinician and purchase abortion pills at a pharmacy or receive them by mail. People with pregnancies in the later first trimester who self-manage their abortions could rely on a safer and more effective MA method and seek care for complications less often, reducing exposure to risk of arrest and criminal prosecution. More rigorous prospective research should be done to reduce ongoing pregnancies in the later first trimester and evaluate outpatient MA through 84 days.

Acknowledgements

We are grateful to Dina Abbas, Manuel Bousiéguez, Karmen Louie and Dr. Tamuna Tsereteli for expert site coordination; Jennifer Britton, Philicia Castillo and Samantha Lang for data management and other project support; staff at the participating clinics for diligently conducting study procedures and providing excellent care; the study participants for giving their time and helping to advance knowledge about medical abortion in the first trimester; Dr. Paul Blumenthal and Dr. Steve Nakajima for discussions about the luteal-placental shift and progesterone production in early pregnancy; and Dr. Caitlin Gerdts, Dr. Laura Castleman and Kinga Jelinska for their invaluable guidance as members of the study's Data and Safety Monitoring Board.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2020.01.009.

References

[1] Jones RK, Witwer E, Jerman J. Abortion incidence and service availability in the United States, 2017. New York: Guttmacher Institute; 2019. https://www.guttmacher.org/report/abortion-incidence-service-availability-us-2017. Accessed September 18, 2019.
[2] Abbas D, Chong E, Raymond EG. Outpatient medical abortion is safe and effective through 70 days gestation. Contraception 2015;92:197–9.
[3] Chen MJ, Creinin MD. Mifepristone with buccal misoprostol for medical abortion: a systematic review. Obstet Gynecol 2015;126:12–21.
[4] Jones RK, Boonstra HD. The public health implications of the FDA update to the medication abortion label. https://www.guttmacher.org/article/2016/06/public-health-implications-fda-update-medication-abortion-label June 30, 2016. Accessed June 6, 2019.
[5] Hsia JK, Lohr PA, Taylor J, Creinin MD. Medical abortion with mifepristone and vaginal misoprostol between 64 and 70 days' gestation. Contraception 2019;100:178–81.
[6] Schaff EA, Fielding SL, Westhoff C. Randomized trial of oral versus vaginal misoprostol 2 days after mifepristone 200 mg for abortion up to 63 days of pregnancy. Contraception 2002;66:247–50.
[7] Sanhueza Smith P, Peña M, Dzuba IG, et al. Safety, efficacy and acceptability of outpatient mifepristone-misoprostol medical abortion through 70 days since last menstrual period in public sector facilities in Mexico City. Reprod Health Matters 2015;22:75–82.
[8] Boersma AA, Meyboom-de Jong B, Kleiverda G. Mifepristone followed by home administration of buccal misoprostol for medical abortion up to 70 days of

amenorrhoea in a general practice in Curaçao. Eur J Contracept Reprod Health Care 2011;16:61–6.
[9] Gatter M, Cleland K, Nucatola DL. Efficacy and safety of medical abortion using mifepristone and buccal misoprostol through 63 days. Contraception 2015;91:269–73.
[10] Cleland K, Crenin MD, Nucatola D, Nshom M, Trussel J. Significant adverse events and outcomes after medical abortion. Obstet Gynecol 2013;121:166–71.
[11] Winikoff B, Dzuba IG, Creinin MD, et al. Two distinct oral routes of misoprostol in mifepristone medical abortion. Obstet Gynecol 2008;112:1303–10.
[12] Ashok PW, Kidd A, Flett GM, Fitzmaurice A, Graham W, Templeton A. A randomized comparison of medical abortion and surgical vacuum aspiration at 10–13 weeks gestation. Human Reprod 2002;17:92–8.
[13] Gouk EV, Lincoln K, Khair A, Haslock J, Knight J, Cruickshank DJ. Medical termination of pregnancy at 63 to 83 days gestation. Br J Obstet Gynaecol 1999;106:535–9.
[14] Hamoda H, Ashok PW, Flett GM, Templeton A. Medical abortion at 64 to 91 days of gestation: a review of 483 consecutive cases. Am J Obstetrics Gynecol 2003;188:1315–9.
[15] Hamoda H, Ashok PW, Flett GM, Templeton A. Medical abortion at 9–13 weeks' gestation: a review of 1076 consecutive cases. Contraception 2005;71:327–32.
[16] Medical management of abortion. Geneva: World Health Organization; 2018.
[17] Kapp N, Eckersberger E, Lavelanet A, Rodriguez MI. Medical abortion in the late first trimester: a systematic review. Contraception 2019;99:77–86.
[18] An overview of abortion laws. www.guttmacher.org/state-policy/explore/overview-abortion-laws. Guttmacher Institute; Accessed September 20, 2017.
[19] Roberts SCM, Gould H, Kimport K, Weitz TA, Foster Greene D. Out-of-pocket costs and insurance coverage for abortion in the United States. Women's Health Issues 2014;24:e211–8.
[20] Medical management of first-trimester abortion: Society of Family Planning clinical guideline. Contraception. 2014;89:148-61.
[21] Winikoff B, Dzuba IG, Chong E, et al. Extending outpatient medical abortion services through 70 days of gestational age. Obstet Gynecol 2012;120:1070–6.
[22] Blackwelder WC. Proving the null hypothesis in clinical trials. Control Clin Trials 1982;3:345–53.
[23] http://www.sealedenvelope.com/power/binary-noninferior/. Accessed August 12, 2013.
[24] Cohen J. Statistical power analysis for the behavioral sciences. New York: Academic press; 1977.
[25] Larsson A, Rönnberg AM. Expanding a woman's options to include home use of misoprostol for medical abortion up until 76 days: an observational study of efficacy and safety. Acta Obstet Gynecol Scand 2019;98:747–52.
[26] Castillo PW, Sanhueza Smith P, Lugo Hernández EM, Castañeda Vivar JJ, Bousiéguez M, Dzuba IG. Does a repeat dose of 800 mcg misoprostol following mifepristone improve outcomes in the later first trimester? A retrospective chart review in Mexico City. Poster. National Abortion Federation's annual meeting; 2017.
[27] Csapo AI, Pulkkinen M. Indispensability of the human corpus luteum in the maintenance of early pregnancy: luteectomy evidence. Obstet Gynecol Surv 1978;33:69–81.
[28] Nakajima ST, Nason FG, Badger GJ, Gibson M. Progesterone production in early pregnancy. Fertil Steril 1991;55:516–21.
[29] Raymond E, Chong E, Winikoff B, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion Service in the United States. Contraception 2019;100:173–7.