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Feasibility of a hospital outpatient day procedure for medication abortion at 13–18 weeks gestation: Findings from Nepal☆,☆☆

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ABSTRACT

Objectives: To evaluate the safety, acceptability and feasibility of a one-day outpatient medication abortion service at gestations 13–18 weeks.

Study design: Open-label prospective study in which participants received mifepristone 200 mg orally to swallow at home or at the clinic followed 24 h later by misoprostol 400 mcg buccally. They presented to the outpatient clinic 24–48 h after mifepristone for misoprostol 400 mcg buccally every three hours (no maximum dose). The primary outcome was successful abortion without transfer to overnight inpatient care. Secondary outcomes included time to abortion from initial misoprostol dose, safety, additional interventions and side effects.

Results: We enrolled 230 women from December 2017 to November 2018. Approximately nine of ten (n = 206, 89.6%) achieved a successful abortion without transfer to overnight care. Twenty-four were transferred to overnight inpatient care; of these 18 were to manage a complication, five for incomplete abortion and two by choice. Among these 24, three women experienced an SAE. The median time to successful abortion from time of the first misoprostol dose was 7.2 h (range: 0.75–92.3), with an average of three misoprostol doses. Most participants expelled the fetus and the placenta at or around the same time; median time between fetal and placental expulsion was 15 minutes (range: 0–4.5 h). Fifteen participants (6.6%) received more than five misoprostol doses and were transferred to inpatient care. Administration of more than five doses of misoprostol was associated with nulliparity. Provision of antibiotics (27.9%, n = 64), manual removal of placenta (15.3%, n = 35), uterotonics (4.4%, n = 10) and surgical interventions (4.4%, n = 10) were also reported. About one in four participants experienced nausea, vomiting and chills; fever was infrequent (2.5%, n = 5).

Conclusions: For gestations 13–18 weeks, an outpatient day process for medication abortion is safe, effective and feasible.

Implications: Medication abortion in 13 – 18 weeks need not be limited to inpatient care; nine of ten cases can be managed as an outpatient day service.

1. Introduction

While second trimester abortions account for a small proportion of total abortions annually, they are responsible for the majority of abortion-related deaths and injuries [1]. In many parts of the world, access to safe second trimester abortion services is limited or unavailable. Service models for second trimester medical induction are largely based on earlier guidelines that focus on surgical terminations later in pregnancy and often mandate more sophisticated facilities and highly skilled providers. Consequently, the pro-

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vision of second trimester abortion has remained largely under the scope of practice for obstetrician-gynecologists and, in many settings, is offered only at higher-level facilities. These factors have resulted in limiting the availability and reach of medication abortion beyond 12 weeks despite growing evidence demonstrating that it is safe, effective and acceptable in the second trimester [2–8] and possibly feasible as an outpatient service [9].

A pooled analysis of data from 868 women concluded that offering medication abortion between 13 and 18 weeks as an outpatient day procedure is feasible [9]. The World Health Organization's guidance on health worker roles in abortion and post abortion care states that midwives, nurses, and advanced practice clinicians can provide second trimester medication abortion while acknowledging a need for more robust reporting of outcomes when care is provided by non-physician providers [10].

We designed this study to evaluate the safety, effectiveness and feasibility of a medication abortion outpatient day procedure for gestations of 13–18 weeks. We conducted this study in Nepal, where national guidelines stipulate that only licensed certified doctors (trained ob-gyns with certification to provide second trimester abortion) can perform second trimester abortions [11,12]. Accordingly, we also evaluated the roles of specialist doctors (licensed, certified ob-gyns), non-specialist doctors and nurses in providing this service.

2. Material and methods

This open-label prospective study was conducted at three tertiary hospitals in Kathmandu valley, Nepal (Kathmandu Medical College, Kathmandu Model Hospital, KIST Medical College). The protocol was approved by the Nepal Health Research Council (NHRC) and all hospital ethical review committees. Informed consent was obtained in writing from all study participants. All of the hospitals have inpatient care but participant care was managed in their routine outpatient ob-gyn ward. This was typically a separate room, set of rooms or section of the hospital itself. All of the hospitals were equipped to manage hemorrhage and/or any other urgent care issues if they occurred.

Women presenting at a study site for voluntary termination of an intrauterine pregnancy with a single live fetus of 13–18 weeks gestation determined by ultrasound were screened for participation. Use of ultrasound to determine gestational age is standard at all Nepalese hospitals licensed to offer second trimester abortion. Inclusion criteria included being reachable by phone for the two-week follow up and willingness to follow study procedures. Those with allergies or contraindications to mifepristone or misoprostol, contraindications to vaginal delivery, more than one cesarean delivery, or who lived more than two hours away from the hospital were excluded from the study.

Study procedures included three contacts: an initial visit for consent and enrollment, a second visit for misoprostol induction and, two weeks later, a follow-up phone call. After providing informed consent, a clinician gave participants one tablet of mifepristone 200 mg orally and an envelope containing two misoprostol pills (200 mcg each), along with instructions on how to take the medications. They took the mifepristone immediately at the hospital or at home. They swallowed misoprostol buccally (holding one 200 mcg tablet in each cheek for 30 min before swallowing remaining fragments) at home approximately 24–48 hours after mifepristone, early in the morning before their scheduled clinic appointment.

At the hospital the following morning, a study staff member gave the participant misoprostol buccal doses (2×200 mcg) every three hours (no maximum dose) until expulsion of the fetus and placenta. A study staff member recorded timing of misoprostol administration and monitored and documented blood pressure, temperature, pain, and bleeding every three hours per protocol. Non-steroidal anti-inflammatory drugs (NSAIDs) or stronger pain medicines (narcotic analgesics) were given by a clinician for pain management. Study staff members documented use of all pain medications and measured pain using a standard zero to ten point visual analog scale that had been used in previous multi-center trials, including sites in Nepal [13]. Providers could give women antibiotics prophylactically to prevent against potential infection as per standard of care. Removal of the placenta either manually or with sponge forceps or use of uterine massage were not considered additional interventions.

Additional misoprostol 200 mcg buccally was administered to facilitate complete expulsion if the placenta did not expel within 30 min of the fetus. If this did not occur within three hours, standard interventions were done to achieve successful abortion. Timing of the initial at-home dose of misoprostol and additional hospital-based doses was not specified per protocol. There was not a pre-set time in the evening for transfer to inpatient care; providers could choose to keep participants in outpatient care as long as feasible (e.g. available staff).

After successful abortion, all participants stayed at the hospital for approximately two hours to recover, after which they were discharged, if stable. Anyone with incomplete abortion, complications requiring additional care or not ready to return home the same day was transferred to inpatient care. Inpatient care was received at the same facility; participants were transferred to the inpatient ward at each participating facility. Two weeks later, participants were interviewed by phone to confirm their health status.

The primary outcome was the proportion of women achieving successful medication abortion who returned home on the same day as misoprostol initiation. Secondary outcomes included the induction-to-abortion interval (defined as time elapsed between administration of the first misoprostol dose until expulsion of both fetus and placenta); the initiation-to-abortion interval (defined as time elapsed between administration of the mifepristone until expulsion of both fetus and placenta); total dose of misoprostol; safety including any complications; pain; side effects; satisfaction. Data on pain and side effects were collected upon hospital arrival for misoprostol dosing. Additional pain scores were collected at the time of each subsequent misoprostol dose and at study end. Serious adverse events were defined as any event causing prolonged hospitalization, permanent or serious disability, and threat to life or death. Satisfaction was measured at study end. The study also documented which tasks performed by each cadre of provider (specialist doctor, non-specialist doctor, staff nurse).

A sample size of 200 was selected to demonstrate with 95% confidence a same day success rate of 73% within ± 6.1% [9]. Recognizing the possibility that some participants might not be reachable for the 2-week follow up interview, the sample size was increased by 30 (15%) to 230 to collect additional data on secondary outcomes.

All data were entered and analyzed using SPSS 19 and SPSS 21 from IBM SPSS Statistics, USA. Analysis was done in both SPSS 19 and Stata SE version 12.1 from StataCorp LLC, USA. Project staff at CREHPA and Gynuity Health projects verified and cleaned the data. Data on continuous variables are summarized as medians and ranges or means and standard deviation. Categorical data are reported using frequency distributions. A data safety and monitoring board (DSMB) provided oversight and reviewed outcome and safety data midway through enrollment.

Clinical Trial Registration: www.clinicaltrials.gov, NCT0 3346629.

Table 1
Characteristics of women undergoing outpatient second trimester abortion at three hospitals in Nepal.

Outcomes	All participants (*N* = 230)
Age (years)	27
(range)	(17–45)
Parity	
0	64 (27.8)
1–2	149 (64.8)
3	17 (7.4)
Gravidity	2 (1–8)
Gestational age by weeks/days (range of days)	14.9/104.5 (91–126)
One or more previous medical abortions	335 (15.3)
One or more previous surgical abortions	16 (6.9)

Data are expressed as percentage, median (range) or *n* (%).
* One participant scheduled to take mifepristone at clinic, but then took it at home and expelled at 3am prior to misoprostol administration.

3. Results

Two hundred and thirty women were enrolled from December 24, 2017 through November 21, 2018. Table 1 presents the participant characteristics. Four of five ($n = 180$, 78.3%) participants chose to swallow mifepristone at home. The other 50 participants (21.7) took mifepristone at the clinic.

The study flow diagram appears as Fig. 1. As shown on Table 2, nearly nine of ten, 206 (89.6%) participants achieved a successful abortion without transfer to inpatient care. Twenty-four were transferred to overnight inpatient care. The median time from the first misoprostol dose until successful abortion was 7.2 h (range: 0.75–92.3). Median time of hospitalization for those not transferred to overnight inpatient care was seven hours (range: 2–15). The median time between arrival and transfer (among 24 women transferred) was 12.5 hours (range = 6–15 h). Most participants expelled the fetus and the placenta at or around the same time; median time between fetal and placental expulsion was 15 min (range: 0–4.5 hours). One woman expelled prior to arrival at the hospital after taking mifepristone only.

A median of three doses of misoprostol 400 mcg buccally were used to achieve successful abortion. Fig. 2 shows the number of misoprostol doses until placental expulsion for all participants. Fifteen participants (6.6%) received more than five misoprostol doses. All of these participants were transferred to inpatient care; none experienced an adverse event, and the highest reported pain scores (e.g. 9–10/10) did not differ from those reported among women who received fewer doses of misoprostol ($p > 0.99$). Pain was self-reported as acceptable or very acceptable by 6/15 (40%) of those receiving more than five doses compared to 164/212 (77%) of those receiving five doses or less ($p = 0.003$). There were no differences in background characteristics or rate of adverse events between those receiving up to five doses of misoprostol and those receiving more than five doses, other than parity. Participants receiving more than five doses were more likely to be nulliparious (parity 0 = 12.5%, 8/64; parity >1 = 4.2%, 7/165; one-sided Fisher's exact test = 0.029).

Table 3 reports on provision of other services. Manual removal of placenta was done in 35 cases; of which 34 were done at one hospital ($p < 0.001$). Side effects and pain were recorded at time of arrival to the hospital for misoprostol dosing and at the end of the abortion process (Table 4). Sixty percent of women ($n = 138$) requested pain medication. Of these, 104 (75%) reported that these medications helped manage their pain.

Three participants experienced serious adverse events. One participant age 30 (17.2 weeks gestation) received three doses of misoprostol, expelled both the fetus and placenta and went on to

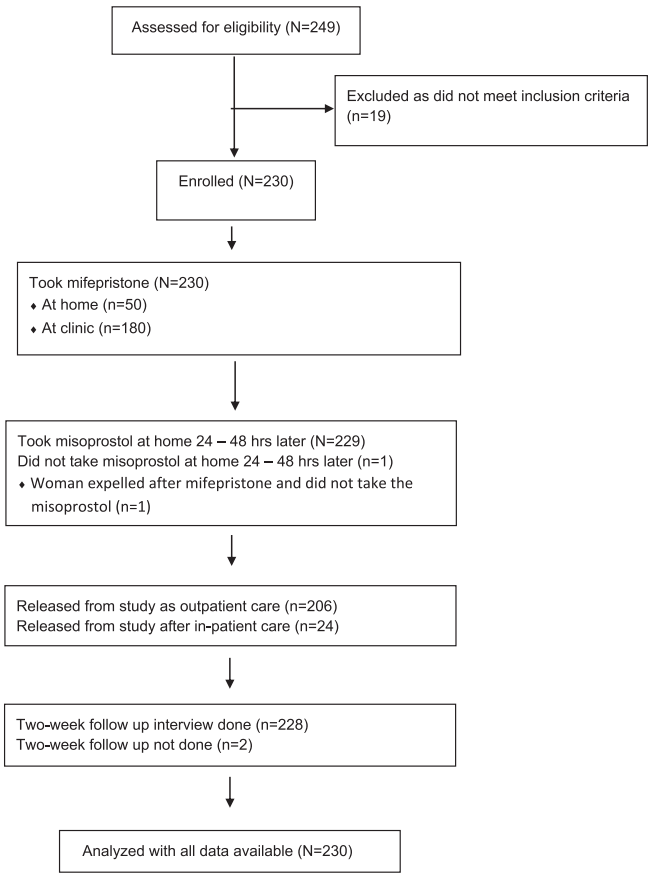

Fig. 1. Study flow diagram among women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal.

experience heavy bleeding that required additional management, including administration of misoprostol, methylergonovine and carboprost. She was taken to the operation ward for exploration of the uterine cavity and received a blood transfusion. A second participant age 30 (16.5 weeks gestation) experienced retained placenta and heavy bleeding after four doses of misoprostol. She received an additional dose of misoprostol for placental expulsion and standard interventions, including aspiration, additional misoprostol, tranexamic acid, IV fluids and antibiotics. A third participant, age 31 (15.2 weeks gestation), received three doses of misoprostol and experienced retained placenta and heavy bleeding for which she received interventions (including insertion of a balloon tamponade, oxytocin, misoprostol, tranexamic acid and IV fluids) to control bleeding. She also received a blood transfusion. All three participants were discharged in good health one to two days after initiation of misoprostol dosing.

For the most part, specialized doctors (licensed, certified obgyns) performed physical examinations, ascertained gestational age, and performed interventions when needed (Table 5). Nurses shared the responsibility of counseling on timing of medications, the abortion process, potential side effects, as well as monitoring participants and performing uterine massage with specialist doctors. Non-specialist doctors assisted with ongoing monitoring and performed and/or assisted with clinical interventions.

Two participants could not be reached by telephone at the two week follow-up. The clinical outcome of their abortions had been confirmed at the hospital prior to discharge. Five women made unscheduled visits or telephone calls for questions pertaining to retained products of conception, none of which required an addi-

Table 2
Outcomes of the abortion and time to expulsion among women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal.

	All (N = 230)
Successful abortion without transfer for overnight care	206 (89.6)
Gestational age 13w0d–13w6d	58/61 (95.1)
Gestational age 14w0d–14w6d	52/54 (96.3)
Gestational age 15w0d–15w6d	23/26 (88.5)
Gestational age 16w0d–16w6d	23/28 (82.1)
Gestational age 17w0d–17w6d	23/29 (79.3)
Gestational age 18w0d	27/32 (84.4)
Transferred to overnight care	24 (10.4)
Reason for transfer*	
Abortion process incomplete	5 (2.2)
To manage a complication	18 (7.8)
By choice/preference	2 (0.9)
Median time, in hours, to successful abortion (fetal and placental expulsion) from initial misoprostol dose^	(n = 228) 7.2 (0.75–92.3)
Median time, in hours, to fetal expulsion from initial misoprostol dose	(n = 228) 7.0 (0.75–92.3)
Median number of misoprostol doses to successful abortion, *i.e.* fetal and placental expulsion (range)	(n = 229) 3 (0–23)
Median number of misoprostol doses to fetal expulsion (range)	(n = 229) 3 (0–23)
Number of women receiving an additional dose of misoprostol for placental expulsion	(n = 229) 23 (10.0)
Received >5 misoprostol doses	(n = 229) 15 (6.6)
Serious adverse events	3/230 (1.3)

Data are expressed as n (%) or median (range).
* One woman transferred for two reasons (abortion process incomplete and to manage a complication.)
^ Data missing for two cases.

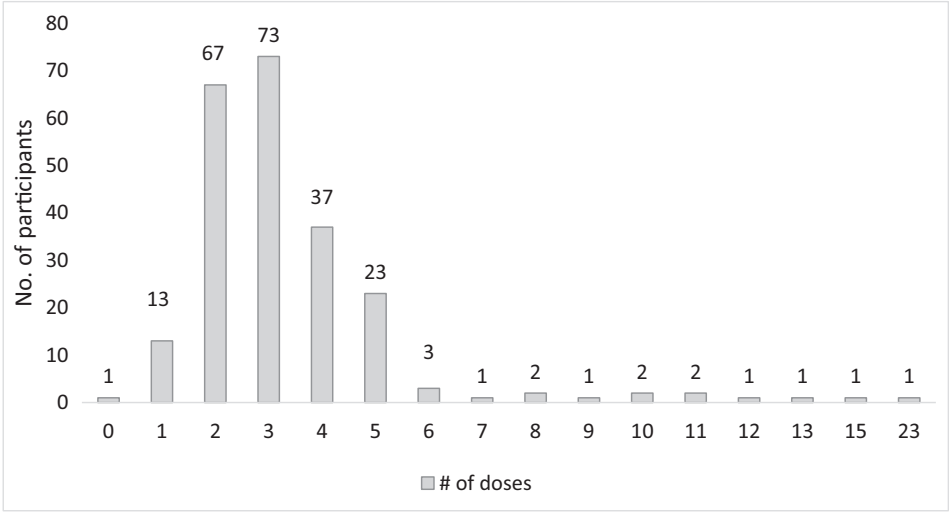

Fig. 2. Misoprostol doses until placental expulsion^ among women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal. ^One person each received 12, 13, 15 and 23 doses.

tional intervention. Another woman administered misoprostol at home as instructed, presented at the day clinic, received four doses of misoprostol, was transferred to inpatient later that evening and received an additional six misoprostol doses (12 in total). She complained of pain in her mouth and was tired of the process so providers allowed her to go home to return the next day for continued dosing. When contacted for her return visit, she reported that she had gone elsewhere for a surgical completion. One person was hospitalized after discharge due to infection resulting from incomplete abortion and was given a surgical aspiration at the study site.

4. Discussion

In this study, nine of ten participants were able to finish the abortion process on the day of misoprostol. Ten percent of participants were transferred for overnight care. Expulsion occurred around seven hours after the initial dose of misoprostol, as seen in studies of inpatient second trimester MA services [2–8]. Pain scores mirrored those in previous clinical studies using similar regimens [2–8]. Although pain scores among women receiving more than five doses of misoprostol were higher than those among women having a successful abortion with five or fewer doses,

Table 3
Other services provided to women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal.

	All participants (n = 229*)	Among those who were transferred for inpatient care (n = 23*)	Among those receiving all care outpatient (n = 206)	p Values
Uterine massage	100 (43.7)	11 (47.8)	89 (43.2)	p = 0.67
Antibiotics	64 (27.9)	16 (69.6)	48 (23.3)	p < 0.0001
Manual removal of placenta	35 (15.3)	6 (26.1)	29 (14.1)	p = 0.13
Uterotonics	10 (4.4)	6 (26.1)	4 (1.9)	p < 0.0001
Surgical intervention	10 (4.4)	5 (21.7)	5 (2.4)	p < 0.001
Blood transfusion	2 (0.9)	2 (8.7)	0 (0.0)	p = 0.01

* Missing data for one woman in this category because she exited the study prior to successful abortion.

Table 4
Reports of pain, side effects, acceptability, and satisfaction among women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal.

	All participants, as reported on arrival at clinic on morning of misoprostol dosing (n = 229)*	All participants during course of abortion process (N = 230)
Highest pain score on 0–10 scale: median (range)	2 (0–8)	7 (0–10)
Pain	–	
Acceptable or very acceptable		170/228 (74.6)
Neutral		57/228 (25.0)
Unacceptable		1/228 (0.4)
Diarrhea	27/229 (11.8)	100/229 (43.5)
Nausea	71/229 (31.0)	56.3 (129/229)
Vomiting	60/229 (26.2)	108/229 (47.2)
Fever	5/229 (2.5)	8.7 (20/229)
Chills	59/229 (25.7)	159/229 (69. 4)
Length of time at the hospital for the abortion process to be a success		
Just right		180 (78.3)
Too short		9 (3.9)
Too long		40 (17.4)
Satisfaction with abortion process		
Satisfactory or very satisfactory		224/230 (97.4)
Neutral		4/230 (1.7)
Unsatisfactory or very unsatisfactory		2/230 (0.9)

Data are expressed as median (range) or n (%).
* Missing data for one woman in this category because she aborted after mifepristone and was exited from the study prior to collection of these data.

Table 5
Provider roles in health care provision and supervision among women undergoing outpatient second-trimester medical abortion at three hospitals in Nepal.

	Staff nurse	Non specialist doctor	Specialist doctor
Providers' roles at initial visit			
Performed physical exam	0 (0.0)	0 (0.0)	230 (100)
Ascertained gestational age	0 (0.0)	0 (0.0)	230 (100)
Counseled about timing of medication, abortion process, potential side effects	132 (57.4)	0 (0.0)	98 (42.6)
Providers' roles during induction process			
Monitoring during induction process*	79/216 (36.6)	36/216 (16.7)	131/216 (60.6)
Performed interventions			
Uterine massage**	60/100 (60.0)	36/100 (36.0)	1/100 (1.0)
Manual removal of placenta	14/35 (40. 0)	20/35 (57.1)	1/35 (2.9)
Surgical intervention***	0/9 (0.0)	1/9 (11.1)	9/9 (88.9)
Blood transfusion	2/2 (100)	0/2 (0.0)	0/2 (0.0)
Provided uterotonics	10/10 (100)	0/10 (0.0)	0/10 (0.0)
Provided antibiotics	57/64 (89.1)	8/64 (12.5)	0/64 (0.0)
Assisted with interventions			
Uterine massage	1/100 (1.0)	4/100 (4.0)	58/100 (58.0)
Manual removal of placenta	1/35 (2.9)	6/35 (17.1)	28/35 (80.0)
Surgical intervention***	4/9 (44.4)	3/9 (33.3)	1/9 (11.1)
Blood transfusion	0/2 (0)	1/2 (50.0)	2/2 (100)
Provided uterotonics	0/10 (0.0)	2/10 (20.0)	8/10 (80.0)
Provided antibiotics	5/64 (7.8)	5/64 (7.8)	53/64 (82. 8)

* Monitoring includes providing misoprostol and pain medication and routine checks of blood pressure and body temperature. Number excludes 14 participants who expelled the placenta prior to first in-clinic dose of misoprostol.
** Three participants reported that they performed uterine massage on their own.
*** One woman had a surgical intervention after discharge so this data is not available.

overall pain was considered acceptable by three-quarters of all participants. The pooled analysis that formed the hypothesis for this study [9] had similar safety, efficacy and side effects findings, suggesting that clinical quality of care was not compromised by outpatient treatment.

In this study, participants could take mifepristone at home. Availability of this option increases the flexibility of the abortion process and can improve acceptability and reduce use of resources at clinics. Enabling participants to administer the first dose of misoprostol at home, on their own, also fosters efforts to achieve abortion induction at a health care facility more quickly. Home administration of mifepristone and the first dose of misoprostol were implemented seamlessly and without affecting safety or effectiveness. Per protocol, timing of the doses was not stringent; but it is worth noting that our findings are not clinically different from other studies using similar dosing regimens with more precise timing intervals [2–9]. On average, one in four women reported having experienced side effects when they presented at the hospital the morning of their medical induction, with a median pain score of two. Enabling women to manage these steps themselves fosters efforts to transition later abortion care to a standard outpatient service. In 2018, the World Health Organization issued updated clinical guidance in recommending the same dosing regimen as used in this study [14]. Further editions of the guidance should consider recommending outpatient administration of both mifepristone and the initial dose of misoprostol.

While we did not document specific costs in this study, these findings suggest potential economic benefits for families and all service delivery systems if protocols enable women to avoid hospital admission thereby eliminating inpatient fees and other associated costs, as well as reducing household costs from missed work and/or childcare needs. In this study, all sites were tertiary level hospitals and thus had capacity to manage any urgent care issues. As with previous studies [5–9], emergencies were infrequent; indicating that the method could be safely and effectively offered at other levels of the health care system. At a systems level, an outpatient, day service would enable clinics currently unable to offer second trimester abortion to consider introduction of a day service, with referral networks in the event overnight, inpatient care is needed. As referral services are standard for other medical procedures that cannot be treated outside of tertiary level facilities, those same existing networks can be expanded to ensure timely and appropriate transfer of persons needing additional care and/or overnight care to manage their abortion.

This study also fills an important evidence gap with respect to task sharing. While the World Health Organization, numerous countries, and individual health systems have now recommended task sharing for early abortion, data on task sharing in the second trimester are limited, hindering efforts to expand the pool of providers. In this study, task sharing was not a requirement, but each site was asked to record the tasks performed by nurses, non-specialist and specialist providers. In keeping with trends in early abortion care, nurses played a crucial role in counseling, administration of misoprostol doses and monitoring. In this setting, we found that a team approach; including ob-gyn specialists, non-specialists and nurses was effective in managing second trimester abortion.

One strength of this study is that it was conducted in Nepal, a country with excellent research capacity and trained second trimester abortion providers willing to conduct innovative service delivery research. A weakness, however, is that Nepal was the only site, and the study was conducted at one level of the health care system: tertiary level private health facilities. Another limitation is that we had self-reported data for timing of the self-administered drugs, which somewhat limited our ability to calculate the total duration of the abortion process. Therefore, exact duration to the minute is unknown. Future research should engage providers at other levels of the health care system including in government-run health facilities. Delivery of health care services often differs from one setting to the next, so the logistics of offering outpatient care will need to be adapted to each landscape. Although randomized trials are often required for guidelines changes; given the copious available evidence on the regimen studied, it did not seem efficient or cost-effective to compare outpatient versus inpatient care.

These findings are sufficient to advocate for health systems to introduce, and then monitor, quality delivery of outpatient second trimester medication abortion.

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