ORIGINAL ARTICLE

Randomized Trial of Very Early Medication Abortion

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ABSTRACT

BACKGROUND

Medication abortion, with a combination of mifepristone and misoprostol, is highly effective and safe. However, there is insufficient evidence on efficacy and safety at very early gestations before a pregnancy can be visualized with ultrasonography.

METHODS

We conducted a multicenter, noninferiority, randomized, controlled trial involving women requesting medication abortion at up to 42 days of gestation with an unconfirmed intrauterine pregnancy on ultrasound examination (visualized as an empty cavity or a sac-like structure without a yolk sac or embryonic pole). Participants were randomly assigned to either immediate start of abortion (early-start group) or standard-care treatment delayed until intrauterine pregnancy was confirmed (standard group). The primary outcome was complete abortion. The noninferiority margin was set at 3.0 percentage points for the absolute between-group difference.

RESULTS

In total, 1504 women were included at 26 sites in nine countries and were randomly assigned to the early-start group (754 participants) or the standard group (750 participants). In an intention-to-treat analysis, a complete abortion occurred in 676 of 710 participants (95.2%) in the early-start group and in 656 of 688 (95.3%) in the standard group; the absolute between-group difference was −0.1 percentage points (95% confidence interval, −2.4 to 2.1). Ectopic pregnancies occurred in 10 of 741 participants (1.3%) in the early-start group and in 6 of 724 (0.8%) in the standard group, with one rupture before diagnosis (early-start group). Serious adverse events occurred in 12 of 737 participants (1.6%) in the early-start group and in 5 of 718 (0.7%) in the standard group (P=0.10); the majority were uncomplicated hospitalizations for treatment of ectopic pregnancy or incomplete abortion.

CONCLUSIONS

Medication abortion before confirmed intrauterine pregnancy was noninferior to standard, delayed treatment with respect to complete abortion. (Funded by the Swedish Research Council and others; VEMA EudraCT number, 2018-003675-35; ClinicalTrials.gov number, NCT03989869.)

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CME

Medication abortion with a combination of mifepristone and misoprostol is a highly effective and safe method of first-trimester induced abortion.[1,2] As compared with procedural abortion, medication abortion has the advantage that the provision, treatment, and outcome assessment can be managed by the patient.[1] Although medication abortion is recommended by both national and international organizations, there is limited evidence regarding its efficacy when provided at very early gestations before a pregnancy can be visualized on ultrasound examination. Therefore, many clinical guidelines refrain from specific recommendations on clinical management for induced abortion before confirmed intrauterine pregnancy.[1,3-5]

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Where medication abortion is available and barriers such as mandatory waiting times and provider referrals are removed, an increasing proportion of women present to abortion services even before an intrauterine pregnancy can be visualized with ultrasonography.[6-8] In services that routinely use ultrasonography before abortion, this scenario can lead to the labeling of a pregnancy as having an unknown location (positive pregnancy test but no ultrasonographic evidence of intrauterine pregnancy) or as being a probable intrauterine pregnancy (a sac-like intrauterine structure without a yolk sac or embryonic pole).[9] Providers may then delay treatment or recommend a diagnostic uterine aspiration owing to concerns that the pregnancy may be ectopic.[10,11] However, observational studies have shown that with assessment of human chorionic gonadotropin (hCG) levels before and after abortion, the time to diagnosis of pregnancy location does not increase (as compared with delaying abortion treatment until pregnancy location is confirmed).[5,12,13]

Evaluating provision of very early abortion is particularly important given recent legal changes in some U.S. states that limit access to abortion at gestations of more than 6 weeks.[14] A small number of observational studies of medication abortion performed before ultrasonographic confirmation of an intrauterine pregnancy suggest treatment efficacy ranging from 85 to 100%.[5,12,13,15-18] However, these studies differed in inclusion criteria for maximum gestational length, ultrasound criteria for unconfirmed intrauterine pregnancy, and definitions of failed abortion.[19] We conducted a multicenter, multinational, noninferiority, randomized, controlled trial to evaluate the efficacy and safety of early as compared with delayed start for women seeking medication abortion before confirmed intrauterine pregnancy.

Method

Trial Design

The VEMA (Very Early Medication Abortion) trial took place at 26 sites in nine countries (1 site in Austria, 1 in Australia, 2 in Denmark, 1 in Finland, 7 in Nepal, 1 in New Zealand, 1 in Norway, 2 in Scotland, and 10 in Sweden) from March 2019 through April 2023. The original protocol included 11 sites, but owing to slow recruitment, we added trial sites. The trial protocol (available with the full text of this article at NEJM.org) was approved by the Swedish Ethical Review Authority and local ethics committee at each trial site or in each country. (Trial sites are listed in the Supplementary Appendix, available at NEJM.org.) Participants were included after providing written informed consent. An external monitor and data and safety monitoring board were appointed. The data and safety monitoring plan is included in the Supplementary Appendix. Blinding with respect to trial-group assignments was not deemed to be feasible.

The trial funders did not have any involvement in or influence on the trial protocol or trial conduct. The first author wrote the first draft of the manuscript. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Trial Participants

Women seeking medication abortion with a maximum estimated gestational length of 42 days and an unconfirmed intrauterine pregnancy on vaginal ultrasound examination were screened for inclusion. We used the definition of an unconfirmed intrauterine pregnancy as either pregnancy of unknown location or probable intrauterine pregnancy.[9] For women with irregular menstrual cycles or an unknown date of the last menstrual period, enrollment was at the discretion of the local investigator. Women were eligible if they were 18 years of age or older, spoke English or a local language, and consented to participate after receiving written and oral information about the trial. Exclusion criteria were symptoms or signs of pathologic pregnancy (e.g.,

bleeding or unilateral abdominal pain), risk factors for ectopic pregnancy (previous ectopic pregnancy or the presence of an intrauterine device), or any contraindications to medication abortion (see the Supplementary Appendix). Baseline data on age, body-mass index, and previous and current pregnancy, as well as baseline ultrasound findings and hCG level, were collected for all the participants; data were not collected on race, ethnic group, and gender.

TRIAL PROCEDURES

Participants were randomly assigned, by means of block randomization with varying block size and stratification according to center, in a 1:1 ratio to receive either early treatment (early-start group) or delayed treatment (standard group). Participants in the early-start group initiated medication abortion on the day of or the day after trial inclusion. We delayed treatment for participants in the standard group until a repeat ultrasound examination on trial day 7 (with a window of ±2 days) visualized an intrauterine pregnancy. If an intrauterine pregnancy was still not confirmed, participants in the standard group had a third ultrasound evaluation at trial day 14 (with a window of ±2 days). If an intrauterine pregnancy could still not be confirmed, the participant was considered to have a pathologic pregnancy. Participants with a pathologic pregnancy that was diagnosed at any time during the trial were treated according to local clinical practice but followed for assessment of outcome and adverse events.

All the participants received the World Health Organization–recommended protocol for medication abortion: mifepristone at a dose of 200 mg orally, followed 24 to 48 hours later by misoprostol at a dose of 800 μg administered vaginally, sublingually, or buccally according to local standard practice.[1] An additional dose of misoprostol (400 μg) was administered if bleeding had not started within 3 hours (except in Australia).[4] Oral analgesia was offered according to local clinical routine with a combination of nonsteroidal antiinflammatory drugs and paracetamol with repeat doses or oral opioids (or both) if needed. The level of serum or plasma hCG was assessed at all preabortion visits for both groups (with the exception of Nepalese sites, where it was assessed only before intrauterine pregnancy had been confirmed). If the baseline hCG level was more than 5000 IU per liter, the participant was evaluated by a gynecologist for possible ectopic pregnancy before continuing in the trial.

Assessment of treatment outcome in the early-start group was by means of hCG measurements at mifepristone intake and on day 7. The treatment was deemed to be successful if a decrease of at least 80% was seen.[20] Additional clinical assessments were performed if there were signs or symptoms of complications or ongoing pregnancy. Assessment of treatment in the standard group was according to local clinical routine, including either blood or urine hCG levels (at home or in the clinic) or ultrasound examination.

All the participants were followed up at 4 weeks after abortion, by telephone or in person. If participants could not be reached for follow-up, medical records were retrieved and assessed.

OUTCOME MEASURES AND ADVERSE EVENTS

The primary outcome was complete abortion, with no ongoing intrauterine pregnancy and no need for surgical intervention for incomplete abortion within 30 days after treatment.[21] Adverse events were defined as complications related to the abortion treatment or trial conduct (e.g., pelvic infection, uterine perforation or other complications of surgery, side effects of mifepristone or misoprostol, and prolonged or heavy bleeding). Serious adverse events were defined as all conditions resulting in hospitalization (for ≥24 hours) or hemorrhage resulting in blood transfusion. Detailed data on all ectopic pregnancies were collected, including status at diagnosis (ruptured or unruptured) and type of treatment.

Secondary outcomes included incomplete abortion, additional medical treatment for incomplete abortion, infections treated with antibiotics, unscheduled telephone contacts, unscheduled visits, and acceptability measures including days with bleeding and maximum pain (assessed by means of a numerical rating scale, with scores ranging from 0 to 10 and a score of >7 classified as severe pain) as well as satisfaction with assigned treatment (assessed by means of the Likert scale, with scores ranging from 0 to 6 and a score of ≥5 classified as satisfied) and preferred and recommended treatment (early or standard treatment) (see the Supplementary Appendix). For data management, we used Research Electronic Data Capture (REDCap) software.[22]

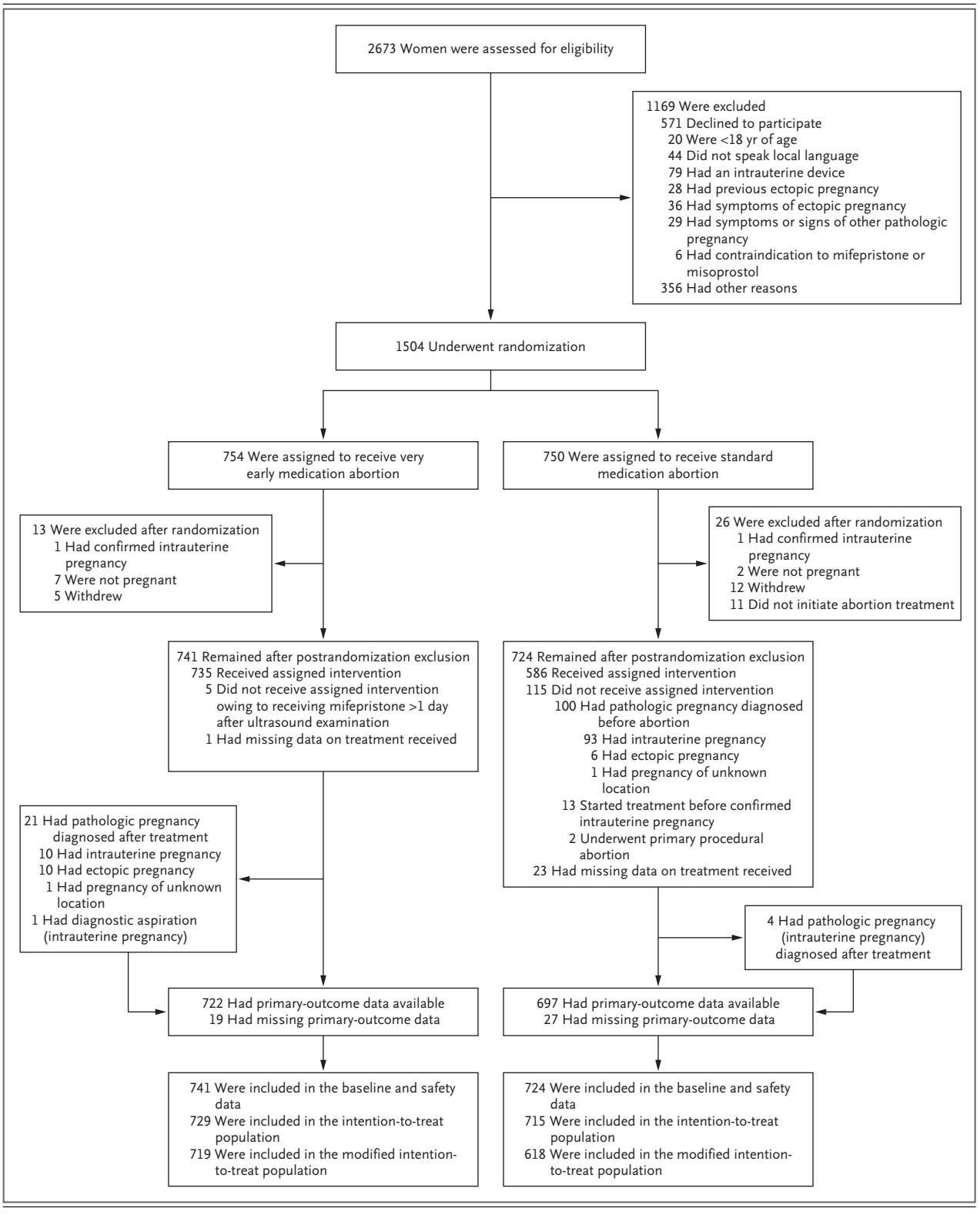

Figure 1 (facing page). Enrollment, Randomization, Received Treatment, and Follow-up.

Among the women assessed for eligibility, exclusion data were missing from one site in Stockholm, and linear approximation was used for exclusion data from Helsinki before February 17, 2022. The intention-to-treat population included participants who started medication abortion, excluding those with ectopic pregnancy, primary procedural abortion, diagnostic aspiration, or a final diagnosis of pregnancy of unknown location. The modified intention-to-treat population included participants who started medication abortion, excluding those with a pathologic pregnancy, primary procedural abortion, or a final diagnosis of pregnancy of unknown location.

STATISTICAL ANALYSIS

We calculated that 1360 participants were needed to show noninferiority of early as compared with standard treatment with a power of 90%. The calculation was based on an estimated efficacy of 97% in both groups, on the basis of previous studies of very early medication abortion, and calculated by the construction of a two-sided 95% confidence interval for the difference in efficacy between the two groups.[5] The noninferiority margin was set at 3.0 percentage points, because this was deemed to be clinically relevant. Power calculation was done with the use of R software, version 3.3. To compensate for a 10% loss to follow-up (including participants with pathologic pregnancies diagnosed), we planned to include a total of 1500 participants.

The confidence interval for the primary-outcome analysis was constructed with the use of the proportion test for calculating the absolute between-group difference. According to our initial statistical analysis plan, a modified intention-to-treat analysis would include participants who started medication abortion and had a known outcome, excluding participants with pathologic pregnancies. We had anticipated a combined incidence of loss to follow-up and pathologic pregnancies of 10%. This calculation was exceeded in our standard group with 104 pathologic pregnancies (14.4%), as compared with 21 (2.8%) in the early-start group. To avoid selection bias, we opted to use a strict intention-to-treat approach that included participants with intrauterine pathologic pregnancies. Pathologic intrauterine pregnancies included early pregnancy loss and molar pregnancy, which can be treated with mifepristone or misoprostol (or both) or uterine aspiration in a fashion similar to induced abortion.[23,24] A modified intention-to-treat analysis and a per-protocol analysis were also performed as additional analyses of the primary outcome. Sensitivity analyses also included multivariate logistic regression with adjustment for country and ultrasound findings in the intention-to-treat population. According to our statistical analysis plan, adjustments were planned at the site level, but owing to the large number of sites (some of which had no failed abortions), we adjusted instead at the country level. Adjusted between-group differences were calculated as marginal means from a logistic-regression model.

The only prespecified subgroup analysis for the primary outcome was according to baseline ultrasound finding (pregnancy of unknown location or probable intrauterine pregnancy). Post hoc exploratory analyses included subgroups defined on the basis of baseline hCG level (≤1000, 1001 to 5000, or >5000 IU per liter) and gestational length in weeks according to the last menstrual period. All between-group differences for subgroup analyses were calculated as marginal means from a logistic-regression model that included interaction terms for the analyzed subgroup.

Secondary outcomes were analyzed in the modified intention-to-treat population. Risk ratios were calculated for binary outcomes. Confidence intervals around risk ratios for these outcomes were not adjusted for multiplicity and should not be used for hypothesis testing. For the main analysis of primary and secondary outcomes, the complete case analysis was used. As a sensitivity analysis, we imputed missing data using multiple imputation with chained equations.[25] All analyses were performed with the use of Stata software, version 17 (StataCorp).

RESULTS

PARTICIPANTS

In total, 2673 women were assessed for eligibility, of whom 1169 were excluded and 1504 were included in the trial (Fig. 1). We randomly assigned 754 participants to the early-start group

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Early Start (N=741)	Standard (N=724)
Age — yr	29.6±6.4	29.7±6.5
Body-mass index†	24.9±4.8	24.9±4.9
No. of pregnancies, including current pregnancy — no. (%)		
1	167 (22.5)	179 (24.7)
2	132 (17.8)	116 (16.0)
≥3	442 (59.6)	429 (59.3)
Nulliparous — no. (%)	254 (34.3)	247 (34.1)
Previous miscarriage — no. (%)	141 (19.0)	145 (20.0)
Previous ectopic pregnancy — no. (%)‡	2 (0.3)	3 (0.4)
Previous abortion — no. (%)	328 (44.3)	324 (44.8)
Last menstrual period — no. (%)		
Certain	650 (87.7)	634 (87.6)
Uncertain	91 (12.3)	90 (12.4)
Median length of gestation (IQR) — days§	37 (33–40)	36 (33–40)
Ultrasound finding — no./total no. (%)		
Pregnancy of unknown location	241/741 (32.5)	261/723 (36.1)
Probable intrauterine pregnancy	500/741 (67.5)	462/723 (63.9)
Median serum hCG level (IQR)¶	2220 (747–5200)	1850 (707–5900)
Pathologic pregnancy — no. (%)‖	21 (2.8)	104 (14.4)
Early pregnancy loss	9 (1.2)	96 (13.3)
Molar pregnancy	1 (0.1)	1 (0.1)
Pregnancy of unknown location	1 (0.1)	1 (0.1)
Ectopic pregnancy	10 (1.3)	6 (0.8)

* Plus–minus values are means ±SD. All the participants had requested medication abortion up to 42 days of gestation, with an unconfirmed intrauterine pregnancy on ultrasound examination. Participants in the early-start group were assigned to immediate start of abortion, and those in the standard group were assigned to standard-care treatment delayed until intrauterine pregnancy was confirmed. Shown are data from all randomly assigned participants without inclusion failure. The term hCG denotes human chorionic gonadotropin, and IQR interquartile range.

† The body-mass index is the weight in kilogram divided by the square of the height in meters. Data were missing for 5 participants in the early-start group and 14 participants in the standard group.

‡ These participants were enrolled by mistake. They are included in the intention-to-treat and modified intention-to-treat analyses but not in the per-protocol analysis.

§ Shown is the number of days since the last menstrual period, if known. One participant in the early-start group and five participants in the standard group had values for the last menstrual period that were outside a reasonable range (0 to 100 days).

¶ Data were missing for 3 participants in the early-start group and 11 participants in the standard group.

‖ Shown are data for pathologic pregnancies that were diagnosed after trial inclusion.

and 750 to the standard group. After randomization, 13 participants in the early-start group and 26 in the standard group were excluded owing to not meeting inclusion criteria. A total of 7 participants were erroneously enrolled in the trial (5 had a previous ectopic pregnancy and 2 had an intrauterine device in situ during this pregnancy). These participants received trial interventions and are included in the analysis. More participants in the early-start group than in the standard group received their assigned treatment (735 vs. 586), mainly owing to the diagnosis of 100 pathologic pregnancies in the standard group before abortion (93 intrauterine pregnancies [including 92

Table 2. Complete Abortion (Primary Outcome).*

Population and Outcome	Early Start (N = 729)	Standard (N = 715)	Primary Analysis†		Multiple-Imputation Analysis	
	no./total no. (%)		Difference (95% CI) *percentage points*	Risk Ratio (95% CI)	Difference (95% CI) *percentage points*	Risk Ratio (95% CI)
Intention-to-treat population‡						
Complete abortion§	676/710 (95.2)	656/688 (95.3)	−0.1 (−2.4 to 2.1)	1.00 (0.98 to 1.02) ¶	−0.2 (−2.4 to 2.0)	1.00 (0.98 to 1.02)
Ongoing pregnancy	21/710 (3.0)	1/688 (0.1)	2.8 (1.5 to 4.1)	20.35 (2.74 to 150.87) ‖		
Surgical intervention for incomplete abortion**	13/710 (1.8)	31/688 (4.5)	−2.7 (−4.5 to −0.8)	0.41 (0.21 to 0.77) ‖		
Per-protocol population						
Complete abortion§	664/693 (95.8)	546/574 (95.1)	0.7 (−1.6 to 3.0)	1.01 (0.98 to 1.03)		

* Shown are unadjusted between-group differences and risk ratios in the intention-to treat population (participants who started medication abortion, excluding those with ectopic pregnancy, primary procedural abortion, diagnostic aspiration, or a final diagnosis of pregnancy of unknown location) and the per-protocol population (participants who met all inclusion criteria and no exclusion criteria; adhered to the protocol, including the timing of assigned treatment [early start or standard]; and had a known outcome). Data on unadjusted and adjusted between-group differences in the modified intention-to-treat population are provided in Table S4 in the Supplementary Appendix.

† Shown are complete case analyses without data imputation.

‡ Outcome data were missing for 19 participants in the early-start group and 27 participants in the standard group.

§ Complete abortion was defined as both no ongoing pregnancy and no need for surgical intervention for incomplete abortion (including surgical intervention for spontaneous abortion and missed abortion) within 30 days after abortion.

¶ P = 0.90 for superiority.

‖ Analyses were not adjusted for multiplicity and should not be used for hypothesis testing.

** Includes surgical intervention for spontaneous abortion and missed abortion, but not for ongoing pregnancy.

Table 3. Secondary Outcomes in the Modified Intention-to-Treat Population.*

Outcome	Early Start (N=719)	Standard (N=618)	Risk Ratio or Median Difference (95% CI)†	
			Primary Analysis	Multiple-Imputation Analyses
Additional abortion treatment — no./total no. (%)‡	49/700 (7.0)	52/591 (8.8)	0.80 (0.55 to 1.16)	0.82 (0.56 to 1.19)
Surgical	17/700 (2.4)	28/591 (4.7)	0.51 (0.28 to 0.93)	
Misoprostol	24/700 (3.4)	29/591 (4.9)	0.70 (0.41 to 1.19)	
Mifepristone and misoprostol	15/700 (2.1)	3/591 (0.5)	4.22 (1.23 to 14.51)	
Median no. of bleeding days (IQR)§	5 (3 to 7)	6 (4 to 8)	−1 (−1.6 to −0.4)	−1 (−1.6 to −0.4)
Severe pain — no./total no. (%)¶	125/622 (20.1)	131/528 (24.8)	0.81 (0.65 to 1.01)	0.80 (0.64 to 1.01)
Infection treated with antibiotics — no./total no. (%)	11/646 (1.7)	25/543 (4.6)	0.37 (0.18 to 0.74)	0.40 (0.20 to 0.80)
≥1 Unscheduled telephone contact — no./total no. (%)	114/648 (17.6)	98/543 (18.0)	0.97 (0.76 to 1.25)	1.02 (0.87 to 1.33)
≥1 Unscheduled visit — no./total no. (%)	85/646 (13.2)	65/543 (12.0)	1.10 (0.81 to 1.49)	1.18 (0.86 to 1.63)
Satisfaction with treatment — no./total no. (%)‖	568/612 (92.8)	446/521 (85.6)	1.08 (1.04 to 1.13)	1.08 (1.04 to 1.13)
Preference — no./total no. (%)				
Standard	11/619 (1.8)	161/528 (30.5)		
Early start	570/619 (92.1)	277/528 (52.5)		
Unsure	38/619 (6.1)	90/528 (17.0)		
Recommendation — no./total no. (%)**				
Standard	9/615 (1.5)	150/520 (28.8)		
Early start	524/615 (85.2)	241/520 (46.3)		
Unsure	82/615 (13.3)	129/520 (24.8)		

* The modified intention-to-treat population included participants who started medication abortion, excluding those with a pathologic pregnancy, primary procedural abortion, or a final diagnosis of pregnancy of unknown location.
† Risk ratios are shown for all outcomes except median number of bleeding days, for which median differences are shown. Risk ratios and median differences were not adjusted for multiplicity and should not be used for hypothesis testing.
‡ Shown are additional treatments for ongoing pregnancy or incomplete abortion. Participants could receive a combination of additional treatments.
§ Data were missing for 103 participants in the early-start group and 96 participants in the standard group.
¶ Maximum pain was assessed by means of a numerical (integer) rating scale, with scores ranging from 0 to 10 and a score of more than 7 classified as severe pain.
‖ Satisfaction with treatment was assessed by means of a Likert scale, with scores ranging from 0 (dissatisfied) to 6 (very satisfied). Shown are participants with a score of 5 or 6.
** Shown is which treatment would be recommended to a friend.

early pregnancy losses and 1 molar pregnancy], 6 ectopic pregnancies, and 1 pregnancy of unknown location). Pathologic pregnancies that were diagnosed after treatment were followed for outcome and safety assessments. Primary-outcome data were not available for 19 participants in the early-start group and 27 in the standard group.

Baseline characteristics were similar in the two groups other than diagnosed pathologic pregnancies (Table 1 and Table S1 in the Supplementary Appendix). The demographic characteristics of the background population seeking induced abortion are shown in Table S2.

OUTCOMES

In an intention-to-treat analysis using complete data, the efficacy of medication abortion with respect to complete abortion was 95.2% (676 of 710 participants) in the early-start group and 95.3% (656 of 688 participants) in the standard group. The between-group difference was −0.1 percentage points (95% confidence interval [CI], −2.4 to 2.1), a finding consistent with noninferiority of early start to standard treatment (prespecified margin, 3.0 percentage points). Results were materially unchanged in analyses of the per-protocol population, the modified intention-

to-treat population, and the intention-to-treat population with missing data imputed and in analyses adjusted for country and baseline ultrasound finding (Table 2 and Table S4).

Failed abortion included either ongoing pregnancy or surgical intervention for incomplete abortion; the reasons for failure differed between the two groups. The number of ongoing pregnancies was 21 (3.0%) in the early-start group and 1 (0.1%) in the standard group (risk ratio, 20.35; 95% CI, 2.74 to 150.87); surgical interventions for incomplete abortion were performed in 13 of 710 participants (1.8%) in the early-start group and in 31 of 688 (4.5%) in the standard group (risk ratio, 0.41; CI, 0.21 to 0.77) (Table 2).

Results of subgroup analyses, including subgroups stratified according to baseline ultrasound finding (pregnancy of unknown location or probable intrauterine pregnancy), hCG levels, and gestational length, are shown in Figure S1. These analyses were not adjusted for multiplicity, but they suggest a possible advantage of standard (over early) treatment for pregnancies of unknown location or with an hCG level of less than 1000 IU per liter, as compared with a possible advantage of early treatment for probable intrauterine pregnancy and when the hCG level was more than 5000 IU per liter.

Results of secondary-outcome analyses are shown in Table 3. In both groups, responses to questions about preference for future treatment and which treatment one would recommend to a friend favored early treatment.

There were 10 ectopic pregnancies (1.3%) in the early-start group and 6 (0.8%) in the standard group (Table 1), with one rupture occurring before diagnosis (early-start group). Clinical details are shown in Table S5. Serious adverse events were reported in 12 of 737 participants (1.6%) in the early-start group and in 5 of 718 (0.7%) in the standard group (P=0.10); most were uncomplicated hospitalizations (for ≥24 hours) for treatment of ectopic pregnancy or incomplete abortion (Table 4 and Table S6).

Table 4. Safety Outcomes.*

Event	Early Start (N=741)	Standard (N=724)	P Value
Adverse events†			
Any event — no./total no. (%)	15/737 (2.0)	35/718 (4.9)	0.003
Type of event — no. of participants			
Bleeding	0	10	
Pain	2	1	
Allergy	2	1	
Infection	11	23	
Other	1	5	
Serious adverse events‡			
Any event — no./total no. (%)	12/737 (1.6)	5/718 (0.7)	0.10
Type of event — no. of participants			
Blood transfusion	1	1	
Bleeding, no blood transfusion	3	0	
Infection (inpatient)	1	2	
Laparoscopy	6	2	
Laparotomy	0	1	
Uterine aspiration (inpatient)	3	0	
Medical treatment (inpatient)	0	1	

* Shown are data for all randomly assigned participants without inclusion failure. Data were missing for four participants in the early-start group and six participants in standard group.
† Serious adverse events are not included and are presented separately.
‡ Details regarding serious adverse events are provided in Table S6 in the Supplementary Appendix.

DISCUSSION

In this large, multicenter, randomized, controlled trial involving women with a maximum estimated gestational length of 42 days, we found that early start of medication abortion before confirmed intrauterine pregnancy was noninferior to delayed treatment after confirmed intrauterine pregnancy with respect to completing abortion. Reasons for failed abortion differed between the two groups, with a higher incidence of surgical intervention for incomplete abortion after standard treatment and a higher incidence of ongoing pregnancy after early start.

Our results are consistent with findings from the largest observational study on very early medication abortion[5], which included 2643 patients and showed a similarly high incidence of complete abortion for treatment with and without confirmed intrauterine pregnancy. Yet more recent observational studies on medication abortion that were limited to pregnancy of unknown location showed a lower efficacy of early treatment than delayed treatment.[12,13] Our trial was not powered to detect noninferiority within this subgroup. However, subgroup analyses involving our large population with pregnancy of unknown location suggested the possibility of an advantage of

delayed treatment in this subgroup (unlike in the subgroup with probable intrauterine pregnancy).

Findings for some secondary outcomes, such as postabortion infections, days with bleeding, satisfaction with assigned treatment, and preferred treatment, appeared to favor early start over standard treatment. However, the absence of adjustment for the multiplicity of testing precludes firm conclusions about these outcomes.

In this trial, as well as in previous observational studies, early diagnosis of an ectopic pregnancy was possible regardless of whether abortion treatment was started early or delayed.[5,12,13,18] Making this diagnosis requires adherence to follow-up with hCG assessment, ultrasonography, or both.

Limitations of our trial should be recognized. Women with pregnancy of unknown location and those with probable intrauterine pregnancy were included, and the trial was not designed to evaluate these groups separately. In addition, participants who received a diagnosis of a pathologic pregnancy were not followed for secondary outcomes such as bleeding, pain, and acceptability of assigned treatment. Because we had underestimated the prevalence and imbalance of diagnosed pathologic pregnancies between the groups, we have unbalanced groups for these analyses. Moreover, treatment outcome was assessed with the hCG level in the early-start group and according to local clinical practice in the standard group. In Nepal, the routine use of ultrasonography for participants in the standard group might have led to "unnecessary" uterine aspirations for this group. To control for this possibility and for other potential differences in clinical practice, we adjusted for country in our sensitivity analysis of the primary outcome and found consistent results.

Whereas participants in our trial were included on the basis of ultrasound findings, there has been a shift toward selective use of ultrasonography only for those at high risk for pathologic pregnancy or with uncertain gestational length.[1,4] Nevertheless, we consider our results to be relevant to women with early pregnancy regardless of whether an ultrasound examination was performed. In our trial, we determined success in the early-start group on the basis of the decrease in blood hCG levels over a period of 7 days. It would be of value to evaluate whether this could be determined with urine hCG levels or could be determined sooner, especially for settings where abortion is restricted after 6 weeks of gestation.[12,13,26] In addition, we did not include procedural abortion, which has shown potential to offer rapid diagnosis of pregnancy location and to be highly effective.[13] Finally, we did not collect data on race or ethnic group in our trial population and hence cannot address the generalizability of our findings according to these characteristics (Table S3).

The results of this large multicenter trial indicate the noninferiority of the early start of medication abortion before confirmed intrauterine pregnancy, as compared with the standard approach of delaying abortion until an intrauterine pregnancy is confirmed.

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APPENDIX

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