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, randomized, non-inferiority trial including women requesting medication abortion up to 42 days of gestation, with a non-confirmed intrauterine pregnancy (IUP) on ultrasound examination (an empty cavity or a sac-like structure without a yolk sac or embryonic pole). Participants were randomized to either immediate start of abortion (early start) or standard care treatment delayed until IUP was confirmed. The primary outcome was complete abortion. The non-inferiority margin was set at 3% for the upper limit of the confidence interval (CI) for the absolute risk difference.

Results In total, 1504 women were included at 26 sites in 9 countries and randomized to early start (n=754) or standard care (n=750). In an intention-to-treat analysis 676/710 (95.2%) of participants randomized to early start and 656/688 (95.4%) of participants randomized to standard treatment had a complete abortion; the risk difference (standard vs early) was 0.1% (95%CI -2.1,2.3). Ectopic pregnancies occurred in 10 (1.4%) in the early start group and 6 (0.8%) in the standard group, with one rupture before diagnosis (early group). Serious adverse events occurred in 12/736 (1.6%) and 5/718 (0.7%) , respectively (p=0.10), the majority uncomplicated hospitalizations for treatment of ectopic pregnancy or incomplete abortion.

Conclusion Medication abortion before confirmed IUP was non-inferior compared to standard, delayed treatment with respect to having a complete abortion.

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Background

Medication abortion with a combination of mifepristone and misoprostol is a highly effective and safe method of first trimester induced abortion.[1,2] Compared to procedural abortion, medication abortion has the advantage that provision, treatment, and outcome assessment can be self-managed.[1] Although medication abortion is recommended by both national and international organizations, there is limited evidence concerning 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 intra-uterine pregnancy(IUP). [1,3-5]

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 IUP can be visualized with ultrasonography. [6,7,8] In services that routinely use ultrasound prior to abortion, this can lead to many women being labelled with a pregnancy of unknown location (positive pregnancy test but no ultrasonographic evidence of IUP) or a probable IUP (a sac-like intrauterine structure without a yolk sac or embryonic pole).[9] Providers may then delay patients' treatment or recommend a diagnostic uterine aspiration owing to concerns that the pregnancy may be ectopic.[10,11] However, observational studies have shown that by following human chorionic gonadotropin (hCG) dynamics pre and post abortion, time to diagnosis of pregnancy location does not increase. .[5,12,13]

Evaluating provision of very early abortion is particularly important given recent legal changes in some US states that limit access to abortion at gestations above 6 weeks.[14] A small number of observational studies of medication abortion performed before ultrasonographic confirmation of an IUP 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 non-confirmed IUP and definitions of failed abortion.[19]

We conducted a multicenter, multinational, non-inferiority randomized controlled trial to evaluate the efficacy and safety of early versus delayed start for patients seeking medication abortion before confirmed IUP.

Method

Trial Design

The study took place in nine countries and 26 sites (Austria (1), Australia (1), Denmark (2), Finland (1), Nepal (7), New Zealand (1), Norway (1), Scotland (2) and Sweden (10)) from March 2019 to April 2023. The original protocol included 11 sites but due to slow recruitment, we added trial sites. The trial protocol was approved by the Swedish Ethical Review Authority and local Ethics Committee at each study site/country (Supplementary Appendix). Patients were included after providing written informed consent. An external monitor and Data Safety Monitoring Board was appointed. (Plan for interim analyses included in Supplementary Appendix) Blinding was not deemed feasible.

Trial participants

Patients seeking medication abortion with a maximum estimated gestational length of 42 days and a non-confirmed IUP on vaginal ultrasound examination were screened for inclusion. We used the definition of a non-confirmed IUP as either 1) Pregnancy of unknown location or 2) Probable IUP.[9] For patients with irregular menstrual cycles or unknown last menstrual period date, enrollment was at the discretion of the local investigator. Women were eligible if they were ≥18 years, spoke English or a local language and consented to participate after receiving written and oral information about the study. Exclusion criteria were symptoms or signs of pathological pregnancy (e.g. bleeding, unilateral abdominal pain), risk factors for ectopic pregnancy (previous ectopic pregnancy or presence of an intrauterine device), or any contraindications to medication abortion. (Supplementary Appendix). Baseline data on age, body mass index, previous and current pregnancy, baseline ultrasound findings and hCG were collected for all participants; data were not collected on race, ethnicity and gender.

Trial procedures

Participants were randomly assigned, using block randomization with varying block size and stratified by center, in a 1:1 ratio to either the intervention (early start) or standard care. Participants with early start initiated medication abortion the day of or the day after study inclusion. We delayed treatment for participants in the standard arm until a repeat ultrasound examination on trial day 7 (+/- 2 days) visualized an IUP. If an IUP was still not confirmed, participants in the standard arm had a third ultrasound evaluation at trial day 14 (+/- 2 days). If an IUP could still not be confirmed, the patient was considered to have a pathological pregnancy. Participants with pathological pregnancy diagnosed at any time during the study

were treated according to local clinical practice but followed for assessment of outcome and adverse events(AEs).

All participants received the World Health Organization-recommended protocol for medication abortion: mifepristone 200 mg orally, followed 24-48 hours later by misoprostol 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 non-steroid anti-inflammatory drugs and paracetamol with repeat doses and/or oral opioids if needed. Serum or plasma hCG was collected at all pre-abortion visits for both groups (with the exception of Nepalese sites, where it was only assessed before IUP was confirmed.). If baseline hCG was ≥ 5000 IU/L the patient 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 hCG measurements at mifepristone intake and on day 7. The treatment was deemed successful if a decline of ≥ 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, (at home or in clinic) or ultrasound examination.

All participants were followed up at four weeks post 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*, efficacy of medication abortion, was defined as: complete abortion with no ongoing IUP and no need for surgical intervention for incomplete abortion within 30 days of treatment.[21] AEs were defined as complications related to the abortion treatment and/or study conduct (such as pelvic infection, uterine perforation or other complications to surgery, side effects of mifepristone/misoprostol and prolonged or heavy bleeding). Serious AEs (SAE) were defined as all conditions necessitating hospitalization (≥24 hours) and/or hemorrhage in need of blood transfusion. Detailed data on all ectopic pregnancies were collected including status at diagnosis (ruptured/unruptured) and type of treatment. Secondary

outcomes included in this publication were rate of incomplete abortion, additional medical treatment for incomplete abortion, infections treated with antibiotics, unscheduled contacts or visits, and acceptability measures including bleeding (days) and maximum pain (Numerical Rating Scale 0-10, >7 classified as severe pain) as well as satisfaction with allocated treatment (Likert scale 0-6, ≥5 classified as very satisfied), preferred and recommended treatment (early or standard treatment). (Supplementary Appendix) For data management we used the Research Electronic Data Capture software.[22]

Statistical analysis

We calculated that 1360 participants were needed to demonstrate non-inferiority of early compared with standard treatment with a power of 90%. The calculation was based on an estimated efficacy of 97% in both groups, shown in previous studies on very early medication abortion, and calculated by constructing a two-sided 95% confidence interval (CI) for the difference in efficacy of the two groups.[5] The non-inferiority margin was set at 3%, as this was deemed clinically relevant. Power calculation was done in R version 3.3 (https://www.r-project.org/). To compensate for a 10% loss to follow-up, (including pathological pregnancies diagnosed) we planned to include a total of 1500 participants.

The CI for the primary outcome analysis was constructed using the proportion test for calculating absolute risk difference. According to our initial Statistical Analytical Plan a modified intention to treat (mITT) analysis would be performed including participants who started medication abortion and had known outcome, excluding participants with pathological pregnancies. We had anticipated a combined rate of loss to follow-up and pathological pregnancies of 10%. This was exceeded in our standard group with 104 (14.4%) pathological pregnancies, versus 21 (2.8%) in the early start group. To avoid selection bias, we opted to use a strict ITT-analysis approach that included participants with intrauterine pathological pregnancies. Pathological IUPs include early pregnancy loss and molar pregnancy, which can be treated with mifepristone and/or misoprostol or uterine aspiration in a similar way as induced abortion.[23,24] The mITT-analysis and per protocol-analysis were also performed as additional analyses for the primary outcome. Sensitivity analyses also included multivariate logistic regression with adjustment for country and ultrasound findings on the ITT population. According to our Statistical Analytical Plan, adjustments were planned at 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 risk differences were calculated as marginal means from a logistic regression model.

The only pre-specified subgroup analysis for the primary outcome was using baseline ultrasound grouping (pregnancy of unknown location vs probable IUP). Post hoc exploratory analyses included subgroups based on baseline hCG-levels (≤1000, 1001-5000, >5000 IU/l), and gestational length in weeks according to last menstrual period. All risk differences for subgroup analyses were calculated as marginal means from a logistic regression model including interaction terms for the analyzed subgroup.

Secondary outcomes were analyzed on the mITT-population. Relative risks were calculated on binary outcomes. Confidence intervals around relative risks for these outcomes were not adjusted for multiplicity and should not be used for hypothesis testing. All analyses were performed in STATA version 17.[25]

Missing data

For the main analysis of primary and secondary outcomes complete case analysis was used. As a sensitivity analysis, we imputed missing data using multiple imputation with chained equations.[26]

Results

Participants

In total, 2673 patients were assessed for eligibility, of whom 1169 were excluded and 1504 participants were included in the trial (Figure 1). We randomly allocated 754 participants to early start and 750 to standard treatment. After randomization, 13 and 26 participants in the early and standard group, respectively, were excluded due to not meeting inclusion criteria. There were 7 participants erroneously enrolled in the study (previous ectopic, n=5, and intra-uterine device in situ this pregnancy, n = 2). These participants received study interventions and are included in the analysis. More participants in the early start group (n=735) received their allocated treatment compared to the standard group (n=586), mainly due to diagnosis of pathological pregnancies in the standard group pre-abortion (n=100; 92 early pregnancy losses, 6 ectopic pregnancies, one molar pregnancy and one pregnancy of unknown location). Pathological pregnancies 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 2 groups other than diagnosed pathological pregnancies (Table 1, Table S1). (Demographics of background population seeking induced abortion are shown in Table S2 and S3).

Outcomes

In an ITT analysis using complete data, the efficacy of medication abortion was 95.2% (676/710) in the early group and 95.4% (656/688) in the standard group. The risk difference was 0.1 (CI -2.3, 2.3), consistent with non-inferiority of early start to standard treatment (prespecified margin 3.0%). Results were materially unchanged in analyses using the per protocol population, the mITT-population and in the ITT-population with missing data imputed (Table 2, 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(2.9%) in the early start group and 1 (0.2%) in the standard group (RR 20.3 (CI 2.74, 151); surgical interventions for incomplete abortion were performed in 13/710 (1.8%) and 31/688 (4.5%), respectively (RR 0.41 CI (0.21, 0.77)) (Table 2).

Results of subgroup analyses, including subgroups stratified by baseline ultrasound findings (pregnancy of unknown location or probable IUP), hCG-levels and gestational length, are shown in Figure S1(Supplemental Appendix). These analyses were not adjusted for multiplicity, but they suggest a possible advantage to standard (over early) treatment for pregnancies of unknown location or with hCG level <1000, versus the reverse (possible advantage to early treatment) for probable IUP and when hCG≥5000.

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 (1.4 %) ectopic pregnancies in the early group and six (0.8%) in the standard group (Table 1). Clinical details are shown in Table S5. SAEs were reported in 12/736 (1.6%) in the early start group and 5/718 (0.7%) in the standard group (p=0.10); most were

uncomplicated hospitalizations (≥24 hours) for treatment of ectopic pregnancy or incomplete abortion/ongoing pregnancy. (Table 4, Table S6)

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 IUP was non-inferior to delayed treatment following confirmed IUP with respect to completing abortion. Reasons for failed abortion differed between groups, with higher rates of surgical intervention for incomplete abortion after standard treatment and higher rates 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 similarly high rates of complete abortion for treatment with and without confirmed IUP. Yet more recent observational studies on medication abortion that were limited to pregnancy of unknown location showed a lower efficacy of early compared with delayed treatment.[12,13] Our study was not powered to detect non-inferiority within this subgroup. However, subgroup analyses involving our large population with pregnancy of unknown location likewise suggested the possibility of an advantage of delayed treatment in this subgroup (unlike the probable IUP group).

Findings for some secondary outcomes, such as duration of bleeding, pain, and post abortion infections, and patient preferences, 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 study, 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 and/or ultrasound.

Limitations of our trial should be recognized. Women with both pregnancy of unknown location or probable IUP were included, and the study was not designed to evaluate these

groups separately. Additionally, participants diagnosed with a pathological pregnancy were not followed for secondary outcomes such as bleeding, pain and acceptability of assigned treatment. Since we had underestimated the prevalence and imbalance of diagnosed pathological pregnancies between the groups, we have unbalanced groups for these analyses. Moreover, treatment outcome was assessed with hCG in the early group and according to local clinical practice in the standard group. In Nepal, the routine use of ultrasound for standard care patients might have led to "unnecessary" uterine aspirations for this group. To control for this, and other potential difference in clinical practice, we adjusted for country in our sensitivity analysis of the primary outcome and found consistent results.

Whereas patients in our study were included based on ultrasound findings, there has been a shift towards selective use of ultrasound only for those at high risk of pathological 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 study we determined success in the early treatment group on the basis of the fall in blood-hCG over seven days. It would be of value to evaluate if this could be determined with urine-hCG and/or sooner, especially for settings where abortion is restricted after 6 weeks of gestation.[12,13, 27] Also, we did not include procedural abortion which has shown potential to both offer rapid diagnosis of pregnancy location and to be highly effective.[13] Lastly, we did not collect data on race or ethnicity in our study population and hence cannot address generalizability of our findings according to these characteristics. (Table S3.)

In conclusion, results of this large multicenter trial indicate non inferiority of early start of medication abortion before confirmed IUP, as compared with the standard approach of delaying abortion until an IUP is confirmed.

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References

1. WHO Guidelines Approved by the Guidelines Review Committee. *Abortion care guideline*. World Health Organization
© World Health Organization 2022.; 2022.
2. Upadhyay UD, Coplon L, Atrio JM. Society of Family Planning Committee Statement: Abortion nomenclature. *Contraception*. Oct 2023;126:110094. doi:10.1016/j.contraception.2023.110094
3. Medication Abortion Up to 70 Days of Gestation: ACOG Practice Bulletin, Number 225. *Obstet Gynecol*. Oct 2020;136(4):e31-e47. doi:10.1097/aog.0000000000004082
4. Best practice in abortion care. Royal College of Obstetricians and Gynaecologists; First published 2015, updated 2022.
5. Bizjak I, Fiala C, Berggren L, Hognert H, Sääv I, Bring J, Gemzell-Danielsson K. Efficacy and safety of very early medical termination of pregnancy: a cohort study. *Bjog*. Dec 2017;124(13):1993-1999. doi:10.1111/1471-0528.14904
6. Kortsmit K, Nguyen AT, Mandel MG, Hollier LM, Ramer S, Rodenhizer J, Whiteman MK. Abortion Surveillance - United States, 2021. *MMWR Surveill Summ*. Nov 24 2023;72(9):1-29. doi:10.15585/mmwr.ss7209a1
7. Socialstyrelsen. *Statistik om aborter 2021*. 2022. https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/statistik/2022-6-8007.pdf
8. Fiala C, Bombas T, Parachini M, et al. Management of very early medical abortion-An international survey among providers. *Eur J Obstet Gynecol Reprod Biol*. Mar 2020;246:169-176. doi:10.1016/j.ejogrb.2020.01.022
9. Barnhart K, van Mello NM, Bourne T, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril*. Mar 1 2011;95(3):857-66. doi:10.1016/j.fertnstert.2010.09.006
10. Flynn AN, Schreiber CA, Roe A, Shorter JM, Frarey A, Barnhart K, Sonalkar S. Prioritizing Desiredness in Pregnancy of Unknown Location: An Algorithm for Patient-Centered Care. *Obstet Gynecol*. Nov 2020;136(5):1001-1005. doi:10.1097/aog.0000000000004124
11. Axelsson PB, Løkkegaard ECL, Helm P. [A ruptured ectopic pregnancy during early termination of pregnancy before ultrasound confirmation]. *Ugeskr Laeger*. Apr 20 2020;182(17)
12. Goldberg AB, Fulcher IR, Fortin J, et al. Mifepristone and Misoprostol for Undesired Pregnancy of Unknown Location. *Obstet Gynecol*. May 1 2022;139(5):771-780. doi:10.1097/aog.0000000000004756
13. Borchert K, Thibodeau C, Varin P, Wipf H, Traxler S, Boraas CM. Medication abortion and uterine aspiration for undesired pregnancy of unknown location: A retrospective cohort study. *Contraception*. Feb 16 2023:109980. doi:10.1016/j.contraception.2023.109980
14. Arey W, Lerma K, Beasley A, Harper L, Moayedi G, White K. A Preview of the Dangerous Future of Abortion Bans - Texas Senate Bill 8. *N Engl J Med*. Aug 4 2022;387(5):388-390. doi:10.1056/NEJMp2207423

15. Heller R, Cameron S. Termination of pregnancy at very early gestation without visible yolk sac on ultrasound. *J Fam Plann Reprod Health Care*. Apr 2015;41(2):90-5. doi:10.1136/jfprhc-2014-100924
16. Schaff EA, Fielding SL, Eisinger S, Stadalius L. Mifepristone and misoprostol for early abortion when no gestational sac is present. *Contraception*. May 2001;63(5):251-4. doi:10.1016/s0010-7824(01)00200-1
17. Goldstone P, Michelson J, Williamson E. Effectiveness of early medical abortion using low-dose mifepristone and buccal misoprostol in women with no defined intrauterine gestational sac. *Contraception*. Jun 2013;87(6):855-8. doi:10.1016/j.contraception.2012.10.013
18. Tai NQR, Reynolds-Wright JJ, Cameron S. Very early medical abortion: treatment with mifepristone and misoprostol before ultrasonographic visualisation of an intrauterine pregnancy. *BMJ Sex Reprod Health*. Nov 9 2022;doi:10.1136/bmjsrh-2022-201677
19. Brandell K, Reynolds-Wright JJ, Boerma C, et al. Medical Abortion before Confirmed Intrauterine Pregnancy: A Systematic Review. *Semin Reprod Med*. Jan 10 2023;doi:10.1055/s-0042-1760117
20. Fiala C, Safar P, Bygdeman M, Gemzell-Danielsson K. Verifying the effectiveness of medical abortion; ultrasound versus hCG testing. *Eur J Obstet Gynecol Reprod Biol*. Aug 15 2003;109(2):190-5. doi:10.1016/s0301-2115(03)00012-5
21. Whitehouse KC, Stifani BM, Duffy JMN, et al. Standardizing abortion research outcomes (STAR): Results from an international consensus development study. *Contraception*. Nov 2021;104(5):484-491. doi:10.1016/j.contraception.2021.07.004
22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. Apr 2009;42(2):377-81. doi:10.1016/j.jbi.2008.08.010
23. Schreiber CA, Creinin MD, Atrio J, Sonalkar S, Ratcliffe SJ, Barnhart KT. Mifepristone Pretreatment for the Medical Management of Early Pregnancy Loss. *N Engl J Med*. Jun 7 2018;378(23):2161-2170. doi:10.1056/NEJMoa1715726
24. Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. *N Engl J Med*. Aug 25 2005;353(8):761-9. doi:10.1056/NEJMoa044064
25. *Stata Statistical Software:*. StataCorp LLC; 2023.
26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine*. 2011;30(4):377-399. doi:https://doi.org/10.1002/sim.4067
27. Gilbert AL, Gelfand D, Fortin J, Roncari D, Goldberg AB. At-home urine pregnancy test assessment after mifepristone and misoprostol for undesired pregnancy of unknown location. *Contraception*. Apr 2023;120:109955. doi:10.1016/j.contraception.2023.109955

Figure Legend

Figure 1

Flowchart. Enrollment, Randomization, Received Treatment and Follow-up.

Table 1. Baseline Data All randomized participants without inclusion failure.

Characteristics	**EARLY START N=741**	**STANDARD N=724**
Age (years) mean ±SD	29.6±6.4	29.7±6.5
BMI mean ±SD*	24.9±4.8	24.9±4.9
Number of pregnancies n(%)		
1	167 (22.5)	179 (24.7)
2	132 (17.8)	116 (16.0)
≥3	442 (59.7)	429 (59.3)
Nulliparous n(%)	254 (34.3)	247 (34.1)
Previous miscarriage (≥1) n(%)	141 (19.0)	145 (20.0)
Previous ectopic (≥1) n(%) (exclusion criteria)	2 (0.3)	3 (0.4)
Previous abortion (≥1) n(%)	328 (44.3)	324 (44.8)
Current pregnancy		
Last menstrual period		
Certain n(%)	650 (87.7)	634 (87.6)
Uncertain n(%)	91 (12.3)	90 (12.4)
Gest. Length (days) according to LMP if known**Median (IQR)	37 (33-40)	36 (33-40)
Ultrasound* **		
PUL n(%)	241(32.5)	261/723 (36.1)
Probable IUP n(%)	500 (67.5)	462/723 (63.9)
Serum-hCG†		
Median (IQR)	2220 (747-5200)	1850 (707-5900)
Pathological pregnancy(total) n(%)‡	21 (2.8)	104 (14.4)
Early pregnancy loss n(%)	9 (1.2)	96 (13.3)
Molar pregnancy n(%)	1 (0.13)	1 (0.14)
Pregnancy of unknown location n(%)	1 (0.13)	1 (0.14)
Ectopic pregnancy n(%)	10 (1.4)	6 (0.8)

* Missing data on 14 participants in Standard arm and 5 in Early arm

**5 participants in the Standard arm and 1 participant in the Early arm had LMP-values outside of a reasonable range (0-100 days)

*** Baseline ultrasound missing for 1 participant in Standard arm

† Serum-hCG at baseline missing for 11 participants in Standard arm and 3 in Early arm

‡ Diagnosed after inclusion

Table 2. Primary outcome

Risk difference (RD) (STANDARD-Early) and risk ratio (RR) (STANDARD/Early), unadjusted on strict intention to treat (ITT) population and per protocol (PP) population. See supplemental for adjusted RD, RR and modified ITT-analysis.

Outcome ITT-population	**EARLY START** (n=729)	**STANDARD** (n=715)	**Primary analysis** Risk Difference (95% CI)‡	**Primary analysis** Risk Ratio (95% CI)‡	**p-value**	**Multiple Imputation Analysis** Risk Difference (95% CI)	**Multiple Imputation Analysis** Risk Ratio (95% CI)
Complete abortion* n(%)**	676/710 (95.2)	656/688 (95.3)	0.1 (-2.1,2.3)	1.00 (0.98,1.02)	0.90	0.2 (-2.0, 2.4)	1.00 (0.98, 1.02)
Ongoing pregnancy n(%)**	21/710 (3.0)	1/688 (0.1)	-2.8 (-4.0, -1.5)	20.3 (2.74, 151)†			
Surgical intervention for incomplete abortion*** n(%)	13/710 (1.8)	31/688 (4.5)	2.7 (0.8, 4.5)	0.41 (0.21, 0.77)†			
Outcome PP-population	**EARLY START (n=683)**	**STANDARD (n=574)**	**RD**	**RR**			
Complete abortion* n(%)	664 (95.8)	546 (95.1)	-0.7 (-3.0, 1.6)	1.01 (0.98, 1.03)			

* Outcome data missing for 19 and 27 participants in Early arm and Standard arm respectively

**Defined as no ongoing pregnancy *and* no need for surgical intervention for incomplete abortion (includes surgical intervention for spontaneous abortion and missed abortion) within 30 days after abortion.

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

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

‡Complete case analyses without data imputation

Table 3. Secondary outcomes in the mITT-population.

	EARLY START (n=719)	**STANDARD (n=618)**	**/ M Primary analysis** Risk Ratio (95% CI)	**Primary analysis** Median difference (95% CI)	**Multiple Imputation Analyses**Risk Ratio (95% CI)	**Multiple Imputation Analyses** Median difference (95% CI)
Additional abortion treatment (total)* n(%)	49/700 (7.0)	52/591 (8.8)	0.80 (0.55, 1.16)†		0.82 (0.56, 1.19)†	
-Surgical n(%)	17/700 (2.4)	28/591 (4.7)	0.51 (0.28,0.93)†			
-Misoprostol n(%)	24/700 (3.4)	29/591 (4.9)	0.70 (0.41, 1.19)†			
-Mifepristone and misoprostol n(%)	15/700 (2.1)	3/591 (0.5)	4.22 (1.23, 14.5)†			
Bleeding days Median(IQR) (missing=103/96)	5(3,7)	6 (4,8)		-1 (-1.62, -0.37)†		-1 (-1.56, -0.44)†
Severe Pain ** n(%)	125/622 (20.1)	131/528 (24.8)	0.81 (0.65, 1.01)†		0.80 (0.64, 1.01)†	
Infection*** n(%)	11/646 (1.7)	25/543 (4.6)	0.37 (0.18, 0.74)†		0.40 (0.20, 0.80)†	
Unscheduled telephone contacts ≥1 n(%)	114/648 (17.6)	98/543 (18.1)	0.97 (0.76, 1.25)†		1.02 (0.87, 1.33)†	
Unscheduled visits ≥1 n(%)	85/646 (13.2)	65/543 (12.0)	1.10 (0.81, 1.49)†		1.18 (0.86, 1.63)†	
Satisfaction with treatment n(%)	568/612 (92.8)	446/521 (85.6)	1.08 (1.04, 1.13)†		1.08 (1.04, 1.13)†	
Preference						
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 (17.1)				
Recommendation‡						
STANDARD	9/615 (1.5)	150/520 (28.9)				
EARLY START	524/615 (85.2)	241/520 (46.4)				
Unsure	82/615 (13.3)	129/520 (24.8)				

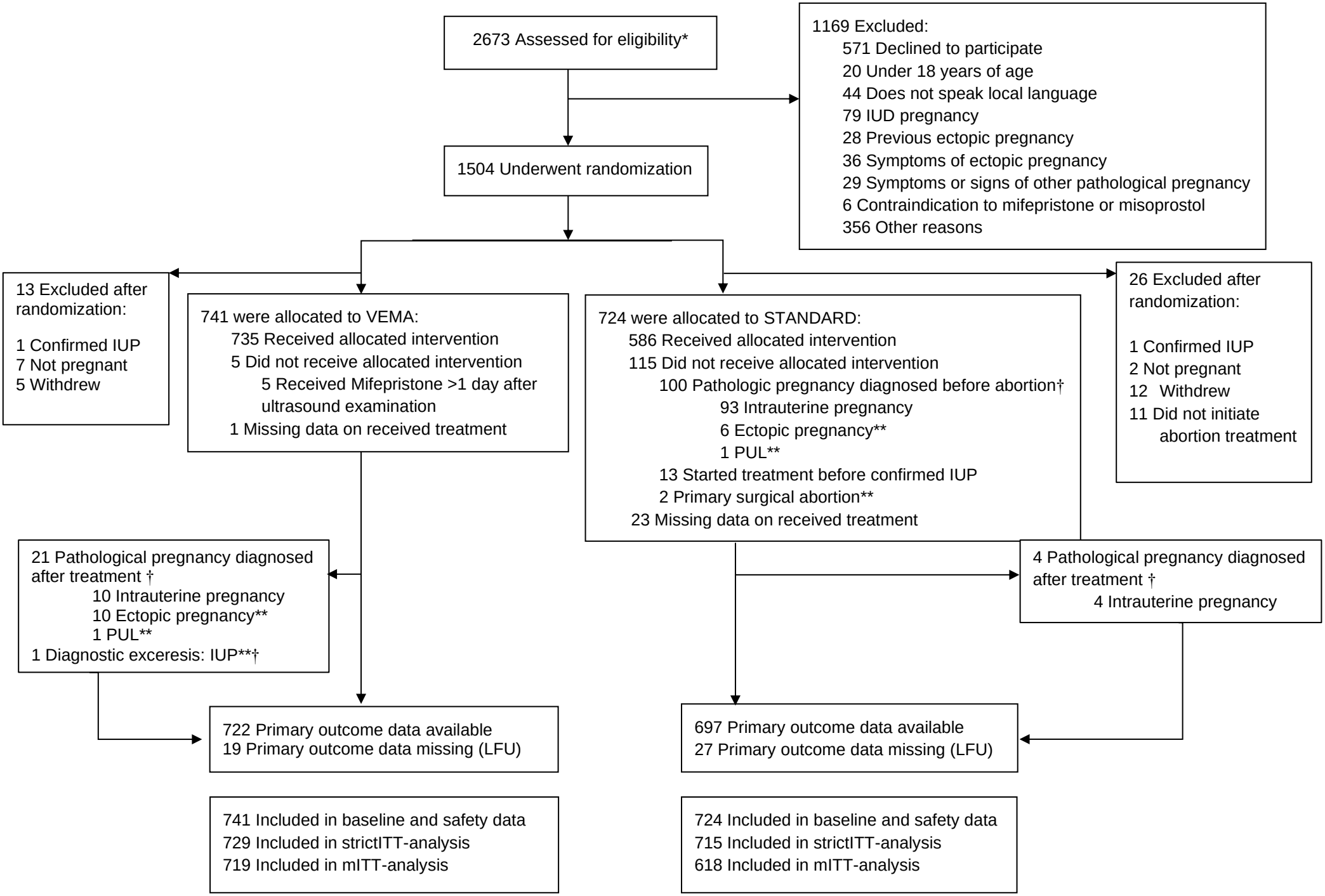
* for ongoing pregnancy or incomplete abortion Participants can receive a combination of additional treatments
**NRS = numerical (integer) rating scale 0-10,
***Treated with antibiotics

**** Proportion ≥ 5, measured on a scale 0-6, 0=dissatisfied and 6=very satisfied**.**
†Analyses not adjusted for multiplicity and should not be used for hypothesis testing.
‡ Which treatment would be recommended to a friend

Table 4. Safety outcomes. All randomized participants without inclusion failure

	EARLY START (n=741)	**STANDARD (n=724)**	**p-value**
Adverse events*, ** n(%) of participants with ≥1 AE	15/737 (2.0)	35/718 (4.9)	0.003
Types of AE reported** (one participant can have ≥1 AE)			
Bleeding	0	10	
Pain	2	1	
Allergy	2	1	
Infection	11	23	
Other	1	5	
SAE*** no (%) of participants with ≥1 SAE	12/737 (1.6)	5/718 (0.7)	0.10
Types of SAE reported (one participant can have ≥1 SAE)			
Blood transfusion	1	1	
Bleeding no blood transfusion	3	0	
Infection (in-patient)	1	2	
Laparoscopy	6	2	
Laparotomy	0	1	
Uterine aspiration (in-patient)	3	0	
Medical treatment (in-patient)	0	1	

*Data missing on 6 participants in Standard arm and 4 in early arm
**Abortion or study related adverse events, SAEs not included and presented separately
***for details see Supplemental Table 6 Supplementary Appendix.



*Exclusion data missing from 1 sites (Södersjukhuset, Stockholm, Sweden) and linear approximation was used for exclusion data from Helsinki, Finland before 20220217.
** not included in strictITT-population
† not included in mITT