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Effect of an Active vs Expectant Management Strategy on Successful Resolution of Pregnancy Among Patients With a Persisting Pregnancy of Unknown Location

The ACT or NOT Randomized Clinical Trial

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IMPORTANCE Women with an early nonviable pregnancy of unknown location are at high risk of ectopic pregnancy and its inherent morbidity and mortality. Successful and timely resolution of the gestation, while minimizing unscheduled interventions, are important priorities.

OBJECTIVE To determine if active management is more effective in achieving pregnancy resolution than expectant management and whether the use of empirical methotrexate is noninferior to uterine evacuation followed by methotrexate if needed.

DESIGN, SETTING, AND PARTICIPANTS This multicenter randomized clinical trial recruited 255 hemodynamically stable women with a diagnosed persisting pregnancy of unknown location between July 25, 2014, and June 4, 2019, in 12 medical centers in the United States (final follow up, August 19, 2019).

INTERVENTIONS Eligible patients were randomized in a 1:1:1 ratio to expectant management (n = 86), active management with uterine evacuation followed by methotrexate if needed (n = 87), or active management with empirical methotrexate using a 2-dose protocol (n = 82).

MAIN OUTCOMES AND MEASURES The primary outcome was successful resolution of the pregnancy without change from initial strategy. The primary hypothesis tested for superiority of the active groups combined vs expectant management, and a secondary hypothesis tested for noninferiority of empirical methotrexate compared with uterine evacuation with methotrexate as needed using a noninferiority margin of −12%.

RESULTS Among 255 patients who were randomized (median age, 31 years; interquartile range, 27-36 years), 253 (99.2%) completed the trial. Ninety-nine patients (39%) declined their randomized allocation (26.7% declined expectant management, 48.3% declined uterine evacuation, and 41.5% declined empirical methotrexate) and crossed over to a different group. Compared with patients randomized to receive expectant management (n = 86), women randomized to receive active management (n = 169) were significantly more likely to experience successful pregnancy resolution without change in their initial management strategy (51.5% vs 36.0%; difference, 15.4% [95% CI, 2.8% to 28.1%]; rate ratio, 1.43 [95% CI, 1.04 to 1.96]). Among active management strategies, empirical methotrexate was noninferior to uterine evacuation followed by methotrexate if needed with regard to successful pregnancy resolution without change in management strategy (54.9% vs 48.3%; difference, 6.6% [1-sided 97.5% CI, −8.4% to ∞]). The most common adverse event was vaginal bleeding for all of the 3 management groups (44.2%-52.9%).

CONCLUSIONS AND RELEVANCE Among patients with a persisting pregnancy of unknown location, patients randomized to receive active management, compared with those randomized to receive expectant management, more frequently achieved successful pregnancy resolution without change from the initial management strategy. The substantial crossover between groups should be considered when interpreting the results.

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Supplemental content

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Diagnosis of an early pregnancy failure is often straightforward when ultrasound definitively identifies an intrauterine or extrauterine pregnancy.[1-3] However, ultrasound does not definitively identify pregnancy location in up to 40% of women presenting for evaluation. This transient state is termed a *pregnancy of unknown location*.[4] During surveillance, up to one-third of women will have serial human chorionic gonadotropin (hCG) concentrations in a pattern suggesting neither an ongoing viable gestation nor a spontaneously resolving pregnancy loss; this scenario is termed a *persisting pregnancy of unknown location*. These women are at high risk of an ectopic pregnancy.[1-4] There is currently no consensus regarding the optimal strategy for the management of women with a persisting pregnancy of unknown location, and management currently appears to vary among clinics and clinicians.[2,3,5]

Uterine evacuation can confirm an intrauterine pregnancy loss (miscarriage) by the presence of chorionic villi on pathology. If the serum hCG concentration does not decline after uterine evacuation, the pregnancy is presumed to be extrauterine and can be treated medically with methotrexate (a competitive inhibitor of dihydrofolate reductase).[4] Medical management of ectopic pregnancy with methotrexate is common and it has also been advocated to use methotrexate empirically to treat a woman with a persisting pregnancy of unknown location.[2,3] Both early miscarriage and ectopic pregnancy can be managed expectantly in selected populations.[6-11] Small randomized clinical trials have failed to demonstrate differences between single-dose methotrexate and expectant management for women with a persisting pregnancy of unknown location or ectopic pregnancy.[6-8]

The goals of this pragmatic randomized clinical trial were to determine (1) if active management of women with a persisting pregnancy of unknown location is more effective than expectant management, and (2) if empirical treatment with methotrexate is noninferior to uterine evacuation followed by use of methotrexate (if needed) with regard to achieving successful pregnancy resolution.

Key Points

Question When a woman has an early nonviable pregnancy and the location is unknown, does an active management strategy (with either methotrexate alone or uterine evacuation with methotrexate as needed) more frequently lead to successful resolution of the pregnancy compared with an expectant management strategy?

Findings In this randomized clinical trial involving 255 women, a significantly greater percentage of patients randomized to receive active management than those randomized to receive expectant management experienced a successful resolution of the pregnancy without change from the initial management strategy (51.5% vs 36.0%, respectively).

Meaning Among patients with a persisting pregnancy of unknown location, an initial active management strategy, compared with an expectant management strategy, more frequently resulted in successful pregnancy resolution without change from the initial strategy, although the large proportion of patients who declined the management strategy to which they were originally randomized should be considered when interpreting the trial results.

Methods

The ACT or NOT trial was a multicenter randomized clinical trial designed and performed by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) clinical trials unit of the Reproductive Medicine Network and affiliated entities. The protocol was approved by a National Institutes of Health–appointed advisory board and a data and safety monitoring board (DSMB). The University of Pennsylvania served as the single Institutional review board (IRB, 815013). Written informed consent was obtained prior to randomization. The trial followed The Consolidated Standards of Reporting Trials (CONSORT) guidelines, and detailed methods of the trial can be found in the protocol (Supplement 1) and have been previously published.[12]

Participants

Hemodynamically stable pregnant women, 18 years or older, with no evidence of a definitive intrauterine or extrauterine gestation visualized with transvaginal ultrasound, and serial hCG values consistent with a nonviable gestation were invited to participate. Entry criteria required at least 2 consecutive hCG concentrations with less than 15% rise per day (compounded based on the number of days and rounded up) over 2 to 14 days (ie, <30% in 2 days, <50% in 3 days, <75% in 4 days, <100% in 5 days, <130% in 6 days, or <166% in 7 days).

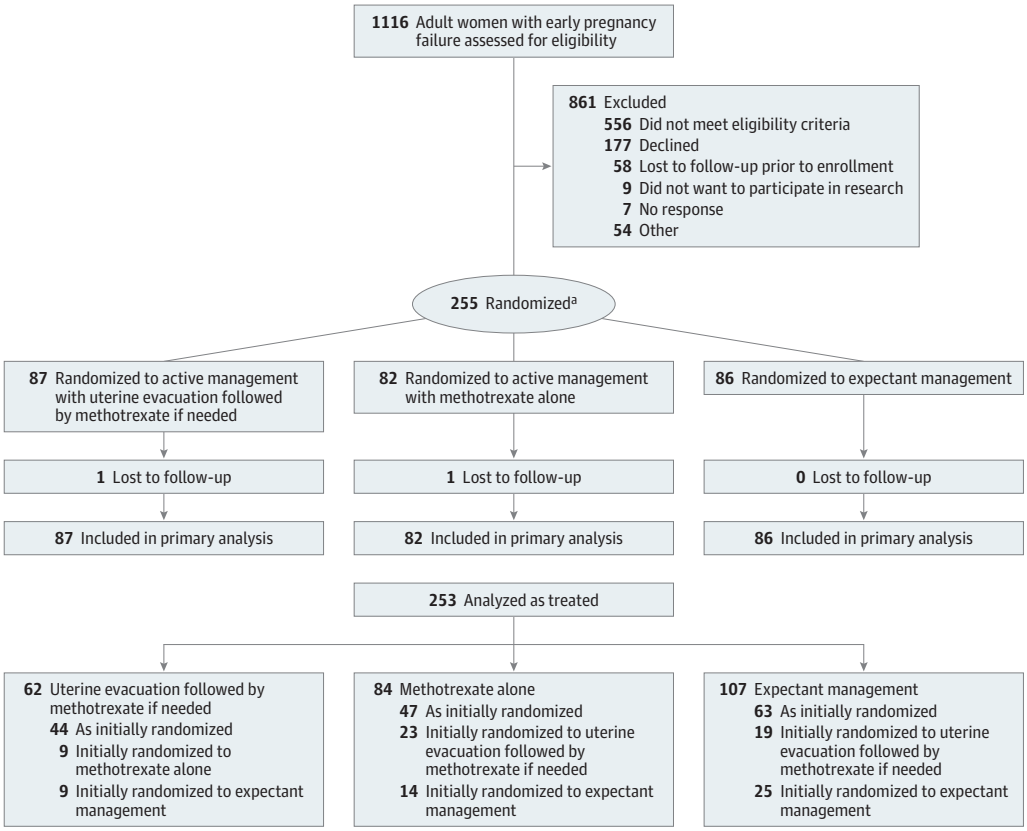
Exclusion criteria included ultrasound visualization of a yolk sac or embryo in a gestational sac in the uterus or adnexa, the most recent hCG value higher than 5000 mIU/mL, a decline of serial hCG values of more than 50% prior to enrollment, prior medical or surgical intervention, or contraindication to medical or surgical management. The presence of a nonviable gestation was confirmed by 2 clinicians prior to participants' consent and enrollment. Demographic information, medical history, and patients' self-reported race (based on fixed categories) were collected upon entry into the study to assess for balance and generalizability.

Randomization and Interventions

Participants were randomized using computer-generated numbers, with permuted varying block sizes (3 or 6) and stratified by sites, to expectant management, uterine evacuation with methotrexate as needed, or empirical methotrexate in a 1:1:1 ratio (**Figure**). Participants and clinicians were not masked to treatment strategy.

Expectant management consisted of close clinical surveillance and monitoring serial hCG values at least every 4 to 7 days. Uterine evacuation consisted of uterine evacuation within 3 days of randomization followed by methotrexate only for those who did not have a decline in hCG of at least 15% a day after the procedure. Empirical treatment with methotrexate consisted of initiation of methotrexate within 2 days of randomization. Methotrexate in both active

Figure. Eligibility, Randomization, and Follow-up of Patients With a Pregnancy of Unknown Location Participant Flow Through the ACT or NOT Randomized Clinical Trial



[a] Randomization was stratified by site.

treatment groups followed the 2-dose protocol with 2 intramuscular doses of 50 mg/m^2 given 3 days apart.[2,13] After initiation of each strategy, all women were followed up as outpatients until complete resolution of the pregnancy.

Outcomes

The primary outcome of the trial was successful resolution of the pregnancy without change from the initial strategy. Failure was defined as a need for unscheduled surgical or medical intervention to treat a progressing or ruptured ectopic pregnancy or to complete treatment of miscarriage.

Change in assigned strategy was classified as either voluntary or clinical. *Voluntary change in strategy (crossover)* was defined as a participant who immediately declined the assigned strategy. Participants who voluntarily changed strategies were followed up using the same study procedures. *Clinical change* was defined as the medical need for additional treatment based on pragmatic clinical decisions resulting from changes in signs or symptoms or by patient request after the initial treatment strategy had started.

Secondary outcomes included: number and type of unscheduled interventions, time until resolution, number of clinic visits (including visits for ultrasound or serum blood tests), adverse events (including ruptured ectopic pregnancy), patient acceptability, satisfaction, and preference. Secondary outcomes regarding clinical care were abstracted from medical records. Acceptability and satisfaction were assessed by standard questionnaires within 2 weeks of resolution of the gestation using categorical values (range, 1 totally unacceptable to 5 totally acceptable or range, 1 very dissatisfied to 5 very satisfied).

Sample Size

The sample size was designed to test 2 hypotheses. The primary hypothesis was that active management—which included random assignment to either uterine evacuation or empirical methotrexate—was superior to expectant management. We hypothesized an 18% difference based on estimates of 93% success for active management[13,14] and 75% success for expectant management.[6] A total of 160 women allocated to active and 80 to expectant management were necessary to detect a clinically important difference of 18% with 90% power. The secondary hypothesis was that use of empirical methotrexate was noninferior to uterine evacuation. A total of 80 participants in each active treatment group were required to test for a noninferiority margin of −12%, with 80% power, assuming a success rate of 92% vs 94% respectively. This estimate was based on the ranges of success rates

reported for the use of methotrexate to treat ectopic pregnancy.[13,14] The overall sample size was inflated to 276 to account for loss to follow up. Voluntary crossover was not considered when planning the sample size.

Statistical Analysis

In the primary analysis, success was considered as the resolution of the pregnancy in the absence of voluntary or clinical change in strategy. In the as-randomized population, all randomized patients were included in the analysis with the randomization group as the primary exposure. Patients who were lost to follow-up or dropped out of the study were assigned as not achieving the primary outcome.

A secondary analysis evaluated the population of patients according to the treatment as received (as treated). For this analysis, success represented resolution of the gestation in the absence of clinical change in strategy with, or without, a voluntary change. Post hoc analyses included a sensitivity analysis restricted to patients with no voluntary change, a post hoc–adjusted analysis according to treatment using an instrumental variable estimation, and an evaluation of subgroups based on clinical presentation. For the instrumental variable analysis, randomization treatment assignment was used as the instrument to estimate the rate ratio (RR) of success for the combined active groups vs the expectant management group via the 2-stage logistic regression model.[15] For the subgroup analysis, a test for the management strategy and subgroup interaction was used by adding this term and the subgroup as covariates in a general linear model.

Either a χ^2 or Fisher exact test was used for testing the difference between the 2 groups for categorical variables, and a Wilcoxon rank sum test or Kruskal-Wallis test was used for continuous variables. The Wald method and the Hodges-Lehman statistic were used for CI estimation for the difference in rate and median, respectively. A noninferiority test with a 1-sided 97.5% CI was used to test the noninferiority of methotrexate compared with uterine evacuation, with a noninferiority margin for a difference between groups of −12%. (The hypothesis in the protocol called for evaluation of whether the 2 active strategies were noninferior to each other, but given that empirical methotrexate was hypothesized to be slightly less effective but potentially more preferable due to less intervention, a test of noninferiority of methotrexate compared with uterine evacuation was deemed most appropriate.)

Because the trial was conducted at multiple sites, a generalized linear mixed-effects model with the stratification variable study site as a random effect was also performed as a post hoc analysis. For all the secondary outcomes, there was no imputation for missing data and 95% CIs were not adjusted for multiplicity. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. Data were analyzed with SAS software, version 9.4 (SAS Institute Inc). Except for the noninferiority test, all other tests were 2-tailed. $P < .05$ was considered significant for superiority.

Results

A total of 1116 participants were screened and 255 women consented between July 25, 2014, and June 4, 2019. The end date of patient follow-up was August 19, 2019. Outcome was determined for 253 participants; 2 were lost to follow-up (Figure). Baseline characteristics were generally balanced in the 3 treatment groups (**Table 1**). Of 255 participants, 99 (39%) declined the initially assigned strategy and elected an alternative strategy within the context of this study. Twenty-three women (26.7%) of 86 declined randomization to expectant management, 42 (48.3%) of 87 declined uterine evacuation, and 34 (41.5%) of 82 declined methotrexate ($P = .01$). Of those who declined their assigned regimen, a greater number crossed over to expectant management (n = 44) than to uterine evacuation (n = 18) or methotrexate (n = 37), $P = .01$ (eTable 1 and eTable 5 in Supplement 2). Outcomes based on voluntary and clinical change are represented in the eFigure in Supplement 2.

Randomization Group Comparisons

A higher percentage of women achieved the primary outcome of successful resolution of pregnancy with active management than expectant management (51.5% vs 36.0%; difference, 15.4% [95% CI, 2.8% to 28.1%]; RR, 1.43 [95% CI, 1.04 to 1.96]). Secondary outcomes included that women randomized to active management were less likely to undergo unscheduled surgery (12.7% vs 26.7%; difference, −14.1% [95% CI, −24.7% to −3.5%]; RR, 0.47 [95% CI, 0.28 to 0.80]), or receive unscheduled methotrexate (15.5% vs 46.5%; difference, −31.0% [95% CI, −42.9% to −19.2%]; RR, 0.33 [95% CI, 0.22 to 0.51]). The time to resolution and the total number of visits was not statistically significantly different for the active vs expectant management groups (**Table 2**).

The percentage of women with successful resolution with methotrexate was noninferior to uterine evacuation (54.9% vs 48.3%; difference, 6.6% [1-sided 97.5% CI, −8.4% to ∞]). Secondary outcomes included significantly fewer unscheduled surgeries (4.7% vs 21.0%; RR, 0.22 [95% CI, 0.08 to 0.64]; $P = .002$) and significantly more unscheduled methotrexate (30.2% vs 0%; difference, 30.2% [95% CI, 20.5% to 39.9%]; $P < .001$) in the uterine evacuation group. The time to resolution and the number of visits until resolution were not statistically significantly different (**Table 3**).

As-Treated Comparisons

Secondary analysis considered treatment as received. After accounting for voluntary change (crossover), the demographics of the population were still similar when defined by treatment received (eTable 2 in Supplement 2). The rate of successful resolution was higher in women who received active than who received expectant management; (94.5% vs 56.1%; difference, 38.4% [95% CI, 28.3% to 48.5%], RR, 1.69 [95% CI, 1.42 to 2.00]). There was a significant reduction in unscheduled surgical interventions 5.5% vs 21.5%; difference, −16.0% [95% CI, −24.6% to −7.4%]; RR, 0.25 [95% CI,

Table 1. Baseline Characteristics According to Randomization

	No./total (%)[a]		
	Uterine evacuation, methotrexate (n = 87)	Methotrexate (n = 82)	Expectant management (n = 86)
Age			
No.	86	82	86
Median (IQR), y	31.0 (27.0-36.0)	32.0 (27.0-36.0)	32.0 (28.0-36.0)
Ethnicity, No. (%)[b]			
Not Hispanic or Latino	75 (86.2)	74 (90.2)	80 (93.0)
Hispanic or Latino	8 (9.2)	6 (7.3)	3 (3.5)
Unknown	4 (4.6)	2 (2.4)	3 (3.5)
Race, No. (%)[c]			
White	40 (46.0)	39 (47.6)	41 (47.7)
Black	33 (37.9)	32 (39.0)	37 (43.0)
Asian	10 (11.5)	4 (4.9)	3 (3.5)
American Indian or Alaska Native	0	2 (2.4)	1 (1.2)
Native Hawaiian or other Pacific Islander	0	0	1 (1.2)
Unknown	4 (4.6)	5 (6.1)	2 (2.3)
Mixed race	0	0	1 (1.2)
Used assisted reproductive technology	26/84 (31.0)	26/80 (32.5)	34/85 (40.0)
Gravida[d]			
0	2/85 (2.4)	5/82 (6.1)	5/86 (5.8)
1	21/85 (24.7)	14/82 (17.1)	21 (24.4)
2	20/85 (23.5)	23/82 (28.0)	17 (19.8)
≥3	42/85 (49.4)	40/82 (48.8)	43 (50.0)
Para			
0	44/85 (51.8)	41/85 (50.0)	42/86 (48.8)
1	27/85 (31.8)	22/85 (26.8)	20/86 (23.3)
≥2	14/85 (16.5)	19/85(23.2)	24/86 (27.9)
≥1 prior spontaneous abortion	42/86 (48.8)	37 (45.1)	40 (46.5)
Prior ectopic pregnancy	7/85 (8.2)	7/85 (8.5)	13/86 (15.1)
Estimated gestational age at screening, wk[e]			
Median (IQR)	6.4 (6.0-7.4)	6.4 (5.6-7.3)	6.3 (5.3-7.0)
<6	19/83 (22.9)	26/80 (32.5)	34/85 (40.0)
6-7	38/83 (45.8)	32/80 (40.0)	30/85 (35.3)
>7	26/83 (31.3)	22/80 (27.5)	21/85 (24.7)
First hCG value at screening, mIU/mL			
Median (IQR)	347.0 (151.0-737.9)	320.0 (128.0-856.0)	413.0 (175.0-854.0)
<500, No. (%)	57 (65.5)	48 (58.5)	51 (59.3)
500-999, No. (%)	17 (19.5)	18 (22.0)	15 (17.4)
1000-1999, No. (%)	11 (12.6)	9 (11.0)	15 (17.4)
≥2000, No. (%)	2 (2.3)	7 (8.5)	5 (5.8)
Ultrasound findings			
Endometrial stripe thickness			
Median (IQR), mm	9.0 (6.0-14.0)	9.5 (5.1-14.0)	8.5 (6.0-13.0)
0-8, No. (%)	25/51 (49.0)	20/48 (41.7)	27/54 (50.0)
>8, No. (%)[f]	26/51 (51.0)	28/48 (58.3)	27/54 (50.0)
Hypoechoic area	9/77 (11.7)	8/73 (11.0)	4/79 (5.1)
Intrauterine only	7/9 (77.8)	4/8 (50.0)	4/4 (100.0)

(continued)

Table 1. Baseline Characteristics According to Randomization (continued)

	No./total (%)[a]		
	Uterine evacuation, methotrexate (n = 87)	Methotrexate (n = 82)	Expectant management (n = 86)
Adnexa only	2/9 (22.2)	2/8 (25.0)	0/4
Both intrauterine and adnexa	0/9 (0.0)	2/8 (25.0)	0/4
Adnexal mass	12/79 (15.2)	11/75 (14.7)	9/81 (11.1)
Free fluid in the cul-de-sac			
Mild	9/80 (11.3)	14/75 (18.7)	16/81 (19.8)
Moderate	5/80 (6.3)	0	2/81 (2.5)

Abbreviations: hCG, human chorionic gonadotropin; IQR, interquartile range.

[a] Percentages may not add to 100 due to rounding.

[b] Unknown was 1 category.

[c] Self-reported and based on fixed categories.

[d] Although it was not possible for a woman to be gravid 0 and be included in the trial, these results reflect data collected from patient history at baseline. To maintain consistency with other historical data, gravidity was not altered retrospectively.

[e] This was determined by last menstrual period, in vitro fertilization retrieval day, transfer day, or insemination date.

[f] A thick endometrial stripe may be associated with an intrauterine pregnancy.

Table 2. Primary and Secondary Outcomes for Combined Active Management Groups vs Expectant Management[a]

Outcome	No./total (%)		Absolute difference (95% CI), %	Risk ratio (95% CI)	*P* value
	Combined active management groups	Expectant management			
Primary					
Successfully resolved					
As-randomized population[b]	87/169 (51.5)	31/86 (36.0)	15.4 (2.8 to 28.1)	1.43 (1.04 to 1.96)	.02
As-treated population	138/146 (94.5)	60/107 (56.1)	38.4 (28.3 to 48.5)	1.69 (1.42 to 2.00)	<.001
Secondary					
As-randomized population					
Unscheduled treatments					
Surgery	21/166 (12.7)	23/86 (26.7)	−14.1 (−24.7 to −3.5)	0.47 (0.28 to 0.80)	.008
Dilation and curettage procedures	16/168 (9.5)	18/86 (20.9)	−11.4 (−21.1 to −1.7)	0.46 (0.24 to 0.85)	.02
Laparoscopy	7/168 (4.2)	9/86 (10.5)	−6.3 (−13.4 to 0.8)	0.40 (0.15 to 1.03)	.06
Administration of methotrexate	26/168 (15.5)	40/86 (46.5)	−31.0 (−42.9 to −19.2)	0.33 (0.22 to 0.51)	<.001
Randomization to resolution, median (IQR), d	22.0 (14.0 to 32.5)[c]	24.0 (12.0 to 35.0)	0.0 (−4.0 to 4.0)[d]	NA	.99
Total No. of all visits, median (IQR)	5.0 (4.0 to 7.0)	5.0 (4.0 to 7.0)	0.0 (−1.0 to 1.0)[d]	NA	.70
As-treated population					
Unscheduled treatments					
Surgery	8/146 (5.5)	23/107 (21.5)	−16.0 (−24.6 to −7.4)	0.25 (0.12 to 0.55)	<.001
Dilation and curettage	2/146 (1.4)	16/107 (15.0)	−13.6 (−20.6 to −6.6)	0.09 (0.02 to 0.39)	<.001
Laparoscopy procedure	6/146 (4.1)	10/107 (9.3)	−5.2 (−11.6 to 1.2)	0.44 (0.16 to 1.17)	.12
Administration of methotrexate	0	29/107 (27.1)	−27.1 (−35.5 to −18.7)	NA	<.001
Randomization to resolution, median (IQR), d	23.0 (14.0 to 34.0)	22.0 (13.0 to 33.0)[e]	0.0 (−3.0 to 4.0)[d]	NA	.78
Total No. of all visits, median (IQR)	5.0 (4.0 to 7.0)	5.0 (3.0 to 7.0)	0.0 (0.0 to 1.0)[d]	NA	.36
Treatment satisfaction					
Somewhat or totally acceptable[d]	64/90 (71.1)	41/57 (71.9)	−0.8 (−15.8 to 14.1)	0.99 (0.80 to 1.22)	.92
Satisfied or very satisfied[d]	73/90 (81.1)	45/57 (78.9)	2.2 (−11.2 to 15.5)	1.03 (0.87 to 1.21)	.75

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] The χ^2 or Fisher exact tests was used for testing the difference between the 2 groups for categorical variables, and the Wilcoxon rank sum test was used for continuous variables. All results were unadjusted.

[b] Patients lost to follow-up were treated as not achieving the primary outcome.

[c] Data were missing for 1 patient in combined active management groups (n = 168).

[d] Differences in medians were estimated with the Hodges-Lehmann method.

[e] Data were missing for 1 patient in expectant management group (n = 106).

Table 3. Primary and Secondary Outcomes for Uterine Evacuation Followed by Methotrexate vs Methotrexate Alone

Outcomes	No./total (%)		Absolute difference (95% CI), %	Risk ratio (95% CI)	*P* value
	Uterine evacuation followed by methotrexate	Methotrexate			
Primary					
As-randomized population	42/87 (48.3)	45/82 (54.9)	6.6 (−8.4 to ∞)[a]		.007[a]
As-treated population	57/62 (91.9)	81/84 (96.4)	4.5 (−4.6 to ∞)[a]		<.001[a]
Secondary[b]					
As randomized					
Unscheduled treatment					
Surgery	4/85 (4.7)	17/81 (21.0)	−16.3 (−26.2 to −6.3)	0.22 (0.08 to 0.64)	.002
Dilation and curettage procedures	0/86	16/82 (19.5)	−19.5 (−28.1 to −10.9)	NA	<.001
Laparoscopy procedure	4/86 (4.7)	3/82 (3.7)	1.0 (−5.0 to 7.0)	1.27 (0.29 to 5.51)	>.99
Administration of methotrexate	26/86 (30.2)	0	30.2 (20.5 to 39.9)	NA	<.001
Randomization to resolution, No.	87	81			
Mean (SD), d	22.5 (14.0)	28.3 (18.5)			
Median (IQR), d	21.0 (13.0 to 27.0)	23.0 (14.0 to 36.0)	−4.0 (−8.0 to 0.0)[c]	NA	.053
Total No. of all visits, median (IQR)	6.0 (4.0 to 7.0)	5.0 (3.0 to 7.0)	1.0 (0.0 to 1.0)[c]	NA	.09
For as-treated population					
Unscheduled treatment					
Surgery	5/62 (8.1)	3/84 (3.6)	4.5 (−3.4 to 12.3)	2.26 (0.56 to 9.10)	.29
Dilation and curettage	0	2/84 (2.4)	−2.4 (−5.6 to 0.9)	NA	.51
Laparoscopy	5/62 (8.1)	1/84 (1.2)	6.9 (−0.3 to 14.0)	6.77 (0.81 to 56.54)	.08
Administration of methotrexate	0	0	NA	NA	NA
Randomization to resolution, No.	62	84			
Mean (SD), d	21.4 (13.8)	29.5 (20.2)			
Median (IQR), d	20.5 (11.0 to 29.0)	23.0 (16.0 to 35.0)	−6.0 (−11.0 to −1.0)[c]	NA	.02
Total No. of all visits, median (IQR)	6.0 (4.0 to 8.0)	5.0 (4.0 to 7.0)	0.0 (0.0 to 1.0)[c]	NA	.27
Treatment satisfaction					
Somewhat or totally acceptable[d]	24/34 (70.6)	40/56 (71.4)	−0.8 (−20.2 to 18.5)	0.99 (0.75 to 1.30)	.93
Satisfied or very satisfied[d]	24/34 (70.6)	49/56 (87.5)	−16.9 (−34.5 to 0.7)	0.81 (0.64 to 1.02)	.05

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] For noninferiority; 1-side 97.5% CIs. Uterine evacuation followed by methotrexate is the reference group.

[b] For all the secondary outcomes, tests are for superiority; 2-sided *P* values. The χ^2 or Fisher exact test was used for testing the difference between the 2 groups for categorical variables, and the Wilcoxon rank sum test was used for continuous variables. All results were unadjusted.

[c] Differences in medians were estimated with the Hodges-Lehmann method.

[d] Details can be found in eTable 3 in Supplement 2.

0.12 - 0.55]) among women who received active management. The time to resolution and the number of visits until resolution were not statistically significantly different (Table 2).

The percentage of women with successful resolution with methotrexate was noninferior to uterine evacuation (96.4% vs 91.9%; difference, 4.5%; 1-sided 97.5% CI, −4.6% to ∞). The number of unscheduled interventions was not statistically significantly different between the 2 active management groups. The median time to resolution was 6 days shorter (interquartile range [IQR], −11.0 to −1.0 days) for women who received the uterine evacuation strategy than for women who received methotrexate (20.5 days [IQR, 11.0-29.0 days] vs 23.0 days [IQR, 16.0-35.0 days]; *P* = .02; Table 3).

Post Hoc Analysis

Instrumental variable adjustment of the as-treated analysis with randomization assignment as the instrument also demonstrated a greater likelihood of successful resolution with active management (RR, 1.99 [95% CI, 1.35-2.94]) than expectant management. A sensitivity analysis restricted to patients with no voluntary change demonstrated an RR of 1.89 (95% CI, 1.32-2.70) in favor of active management.

Results were similar with no statistically significant interaction regarding the magnitude and direction of the RR for successful resolution and time to resolution in as-treated populations after stratification by gestational age, hCG concentration, hCG pattern (rise or fall), endometrial thickness, use of assisted reproductive technologies, the

Table 4. Serious Adverse Events and Adverse Events by Treatments as Randomized and as Treated

Event	No. (%)					
	As randomized			As treated		
	Uterine evacuation followed by methotrexate (n = 87)	Methotrexate (n = 82)	Expectant management (n = 86)	Uterine evacuation followed by methotrexate (n = 62)	Methotrexate (n = 84)	Expectant management (n = 107)
≥1 Serious adverse event	6 (6.9)	1 (1.2)	2 (2.3)	5 (8.1)	2 (2.4)	2 (1.9)
Hospitalization	3 (3.4)	1 (1.2)	0	3 (4.8)	1 (1.2)	0
Ruptured ectopic pregnancy	3 (3.4)	0	2 (2.3)	2 (3.2)	1 (1.2)	2 (1.9)
≥1 Adverse event[a]	53 (60.9)	46 (56.1)	44 (51.2)	35 (56.5)	54 (64.3)	54 (50.5)
Vaginal bleeding	46 (52.9)	39 (47.6)	38 (44.2)	28 (45.2)	48 (57.1)	47 (43.9)
Pelvic pain	42 (48.3)	38 (46.3)	37 (43.0)	27 (43.5)	47 (56.0)	43 (40.2)
Fatigue	38 (43.7)	36 (43.9)	38 (44.2)	23 (37.1)	46 (54.8)	43 (40.2)
Nausea	32 (36.8)	31 (37.8)	22 (25.6)	19 (30.6)	38 (45.2)	28 (26.2)
Loss of appetite	28 (32.2)	23 (28.0)	25 (29.1)	18 (29.0)	27 (32.1)	31 (29.0)
Dizziness or weakness	27 (31.0)	17 (20.7)	18 (20.9)	12 (19.4)	26 (31.0)	24 (22.4)
Headaches	25 (28.7)	27 (32.9)	31 (36.0)	17 (27.4)	31 (36.9)	35 (32.7)
Diarrhea	21 (24.1)	13 (15.9)	9 (10.5)	5 (8.1)	24 (28.6)	14 (13.1)
Shoulder or back pain	18 (20.7)	12 (14.6)	14 (16.3)	7 (11.3)	19 (22.6)	18 (16.8)
Heart burn/ indigestion	12 (13.8)	5 (6.1)	7 (8.1)	5 (8.1)	9 (10.7)	10 (9.3)
Vomiting	11 (12.6)	10 (12.2)	2 (2.3)	5 (8.1)	14 (16.7)	4 (3.7)
Hair loss	9 (10.3)	6 (7.3)	4 (4.7)	3 (4.8)	11 (13.1)	5 (4.7)
Mouth sores	6 (6.9)	6 (7.3)	5 (5.8)	5 (8.1)	7 (8.3)	5 (4.7)
Persistent dry cough	5 (5.7)	5 (6.1)	3 (3.5)	2 (3.2)	10 (11.9)	1 (0.9)
Any other adverse effects	4 (4.6)	3 (3.7)	6 (7.0)	2 (3.2)	10 (11.9)	1 (0.9)

[a] Not including serious adverse events.

presence or absence of a hypoechoic area in the uterus or adnexa, moderate fluid in the cul-de-sac, and presence of an adnexal mass (eTable 4 in Supplement 2). When including the stratification variable study site as random effect, the RR for successful resolution for active management groups to expectant management was 1.49 (95% CI, 1.09-2.05), and 1.69 (95% CI, 1.42-2.00) for the as-randomized and as-treated patients, respectively.

Adverse Events

Five women were diagnosed with a ruptured ectopic pregnancy (2 randomized to expectant management; 3, to uterine evacuation; 2 women's actual treatment expectant management; 2, uterine evacuation; and 1, methotrexate). All were successfully treated with laparoscopy. One patient received a transfusion of 1 unit of packed red blood cells.

Four additional women were hospitalized. Three of these women were randomized to (and received) uterine evacuation. One woman was hospitalized for an influenza infection, 1 for assessment of coagulation status prior to laparoscopy, and 1 for observation for pain after receiving methotrexate. The fourth patient was randomized to (and received) methotrexate and was hospitalized for severe stomatitis.

The most common adverse event was vaginal bleeding for all of the 3 management groups (44.2%-52.9%). The number and type of adverse event in each group in the as randomized and the as-treated population of patients are presented in **Table 4**.

One participant, randomized to expectant management, was later noted to have a growing intrauterine pregnancy. She conceived following use of clomiphene citrate and intrauterine insemination and was enrolled at 4 weeks' and 5 days' gestation with an abnormal rise in serial hCG values; 7% in 2 days (86 mIU/mL vs 92 mIU/mL) and 24% over 4 days (92 mIU/mL vs 107 mIU/mL). Subsequent hCG values rose normally: 348 mIU/mL at 5 weeks' gestation, 803 mIU/mL at 5 weeks' and 2 days' gestation, and 2477 mIU/mL at 6 weeks' gestation. All assays were performed at the same laboratory. A singleton pregnancy with embryonic cardiac activity was diagnosed at 6 weeks' and 5 days' gestation. She delivered at term without complication. This case was considered a successful resolution according to the treatment plan and was judged to be unanticipated by the DSMB and IRB.

Patient-Reported Acceptability, Satisfaction, and Preferences

More than 70% of women found the treatment they received to be somewhat or totally acceptable and were satisfied or very satisfied. There were no statistically significant differences in the distribution of responses regarding acceptability

and satisfaction across the active and expectant management groups. However, participants' expressed desire for the treatment they received if they were to experience another pregnancy of unknown location varied, with 70.0% of those in the active management groups and 78.6% of those in the expectant management group indicating that they would probably or absolutely desire the same treatment with a future pregnancy (eTable 3 in Supplement 2).

Discussion

In this randomized clinical trial, active management was more effective than expectant management in achieving resolution of a persistent pregnancy of unknown location without a change in initiated management strategy. Differences from previous studies that failed to demonstrate superiority of active management over expectant management may be due to the use of more effective active management and greater power in the present study.

It is possible the use of the 2-dose protocol and the use of uterine evacuation contributed to higher success of active management in this trial. In a meta-analysis, the 2-dose methotrexate protocol used in this study was associated with better outcomes than with single-dose methotrexate for the medical management of ectopic pregnancy.[16] This study was powered to detect an 18% difference between active and expectant management but found a smaller difference of 15%, perhaps because the success rate in the as-randomized population was lower than expected in both groups and because loss to follow-up was lower than anticipated. The difference in resolution between the active and expectant management was greater in the as-treated population. Successful resolution in the as-treated population for active treatment (94.5%) was higher than in previous trials (range, 74%-90%).[6-8] In this study a total of 56% of women achieved uneventful successful resolution with expectant management. This was lower than the 74% to 100% found in previous studies.[6-8]

This is the first randomized trial, to our knowledge, to compare uterine evacuation to empirical methotrexate. Active management with empirical administration of methotrexate was noninferior to a dilation and evacuation followed by methotrexate as needed. A large decrease in hCG levels after uterine evacuation is more consistent with failed intrauterine pregnancy than ectopic pregnancy. A threshold that demarcates elimination of surveillance of hCG to distinguish the 2 has not been defined.[2,17,18] In this study, methotrexate was administered 24 hours after uterine evacuation only if hCG concentration failed to decline less than 15% to maximize resolution without further treatment. This strategy resulted in shorter time to resolution than empirical methotrexate, likely because 44% (27 of 62) of women who received uterine evacuation needed no further treatment. Removal of trophoblast cells from a nonviable intrauterine pregnancy will result in a more rapid clearance of hCG because any residual production has been eliminated.[19]

The criteria used to define a persisting pregnancy of unknown location were derived from international consensus[4] to include only women who presented a therapeutic dilemma. Current clinical standards, and conservative standards used in this trial, may not eliminate the possibility that the current pregnancy is viable. Despite conservative inclusion criteria to confirm a nonviable gestation, 1 participant randomized to expectant management eventually had a live birth. The clinical course of this participant emphasizes the need to ensure a gestation is nonviable before active intervention that will result in termination or possible teratogenicity.[20] The American College of Obstetricians and Gynecologists and NICE defines an increase of hCG levels of more than 49% (for initial values <1500 mIU/mL) and more than 63% over 48 hours as potentially viable, respectively.[2,3] However, a rise below these thresholds, which are based on probabilistic models using serial hCG measurements, does not define nonviability.[21] A live birth has been noted with hCG increase as low as 35% over 48 hours.[22] A decline in initial hCG values before a viable pregnancy was diagnosed has been noted in 3 women who conceived with IVF.[23]

In this study, a majority of women found the treatment they received satisfactory and acceptable. Distribution of serious events was not unexpectedly different across groups. The most commonly reported adverse events were vaginal bleeding and those consistent with known adverse effects of methotrexate.[24] Ruptured ectopic pregnancy was not chosen as a primary outcome because it was considered unethical to refrain from additional treatment until rupture in the face of progression of disease.[12]

Limitations

This study has several limitations. First, the study included a large percentage of women with early gestational age and low hCG levels, and a high percentage using assisted reproductive technology. Second, the clinicians and patients were not blinded to the treatment that was allocated or received. Choice of management for some women may have been influenced by clinical presentation. Although study power was limited to assess subgroups or interactions, findings did not appear to be different based on these characteristics. Third, the study had a high rate of crossover, which can introduce bias into a randomized clinical trial.[25] Women preferentially crossed over to, and expressed a stronger preference for, expectant management. It was not possible to distinguish if this decision was influenced by the patient, the clinician, or both. It is possible that women would prefer a chance at resolution without active management and find an increased need for unscheduled intervention an acceptable trade-off.[26,27] The RR was modestly stronger in the as-treated analysis. Fourth, women's cases were managed in a tertiary care setting, which may limit generalizability of findings to other clinical settings. Fifth, recruitment for this study was very difficult due to strong patient preferences regarding choice of management strategies; more than 75% of patients approached were not eligible or declined participation.

Conclusions

Among patients with a persisting pregnancy of unknown location, patients randomized to receive active management, compared with those randomized to receive expectant management, more frequently achieved successful pregnancy resolution without change from the initial management strategy. The substantial crossover between groups should be considered when interpreting the results.

ARTICLE INFORMATION

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REFERENCES

1. Barnhart KT. Ectopic pregnancy. *N Engl J Med*. 2009;361(4):379-387. doi:10.1056/NEJMcp0810384

2. ACOG Practice Bulletin. Tubal ectopic pregnancy. *Obstet Gynecol* 2018;131(3):e91-e103. doi:10.1097/AOG.0000000000002560

3. National Institute for Health and Care Excellence (NICE). Ectopic pregnancy and miscarriage: diagnosis and initial management. Updated November 2019. Accessed April 20, 2021. https://www.nice.org.uk/guidance/ng126

4. Barnhart K, van Mello NM, Bourne T, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril*. 2011;95(3):857-866. doi:10.1016/j.fertnstert.2010.09.006

5. Parks MA, Barnhart KT, Howard DL. Trends in the management of nonviable pregnancies of unknown location in the United States. *Gynecol Obstet Invest*. 2018;83(6):552-557. doi:10.1159/000488760

6. van Mello NM, Mol F, Verhoeve HR, et al. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? a randomized comparison. *Hum Reprod*. 2013;28(1):60-67. doi:10.1093/humrep/des373

7. Jurkovic D, Memtsa M, Sawyer E, et al. Single-dose systemic methotrexate vs expectant management for treatment of tubal ectopic pregnancy: a placebo-controlled randomized trial. *Ultrasound Obstet Gynecol*. 2017;49(2):171-176. doi:10.1002/uog.17329

8. Silva PM, Araujo Júnior E, Cecchino GN, Elito Júnior J, Camano L. Effectiveness of expectant management versus methotrexate in tubal ectopic pregnancy: a double-blind randomized trial. *Arch Gynecol Obstet*. 2015;291(4):939-943. doi:10.1007/s00404-014-3513-0

9. Mavrelos D, Nicks H, Jamil A, Hoo W, Jauniaux E, Jurkovic D. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. *Ultrasound Obstet Gynecol*. 2013;42(1):102-107. doi:10.1002/uog.12401

10. Helmy S, Mavrelos D, Sawyer E, et al. Serum human chorionic gonadotropin (β-hCG) clearance curves in women with successfully expectantly managed tubal ectopic pregnancies: a retrospective cohort study. *PLoS One*. 2015;10(7):e0130598. doi:10.1371/journal.pone.0130598

11. Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. *Ultrasound Obstet Gynecol*. 2004;23(6):552-556. doi:10.1002/uog.1061

12. Barnhart KT, Sammel MD, Stephenson M, et al; NICHD Cooperative Reproductive Medicine Network. Optimal treatment for women with a persisting pregnancy of unknown location, a randomized controlled trial: the ACT-or-NOT trial. *Contemp Clin Trials*. 2018;73:145-151. doi:10.1016/j.cct.2018.09.009

13. Barnhart K, Hummel AC, Sammel MD, Menon S, Jain J, Chakhtoura N. Use of "2-dose" regimen of methotrexate to treat ectopic pregnancy. *Fertil Steril*. 2007;87(2):250-256. doi:10.1016/j.fertnstert.2006.06.054

14. Barnhart KT, Gosman G, Ashby R, Sammel M. The medical management of ectopic pregnancy: a meta-analysis comparing "single dose" and "multidose" regimens. *Obstet Gynecol*. 2003;101(4):778-784. doi:10.1097/00006250-200304000-00028

15. Rassen JA, Schneeweiss S, Glynn RJ, Mittleman MA, Brookhart MA. Instrumental variable analysis for estimation of treatment effects with dichotomous outcomes. *Am J Epidemiol*. 2009;169(3):273-284. doi:10.1093/aje/kwn299

16. Alur-Gupta S, Cooney LG, Senapati S, Sammel MD, Barnhart KT. Two-dose versus single-dose methotrexate for treatment of ectopic pregnancy: a meta-analysis. *Am J Obstet Gynecol*. 2019;221(2):95-108.e2. doi:10.1016/j.ajog.2019.01.002

17. Shaunik A, Kulp J, Appleby DH, Sammel MD, Barnhart KT. Utility of dilation and curettage in the diagnosis of pregnancy of unknown location. *Am J Obstet Gynecol*. 2011;204(2):130.e1-130.e6. doi:10.1016/j.ajog.2010.11.021

18. Rivera V, Nguyen PH, Sit A. Change in quantitative human chorionic gonadotropin after manual vacuum aspiration in women with pregnancy of unknown location. *Am J Obstet Gynecol*. 2009;200(5):e56-e59. doi:10.1016/j.ajog.2008.10.013

19. Barnhart KT, Bader T, Huang X, Frederick MM, Timbers KA, Zhang JJ. Hormone pattern after misoprostol administration for a nonviable first-trimester gestation. *Fertil Steril*. 2004;81(4):1099-1105. doi:10.1016/j.fertnstert.2003.08.041

20. Fridman D, Hawkins E, Dar P, et al. Methotrexate administration to patients with presumed ectopic pregnancy leads to methotrexate exposure of intrauterine pregnancies. *J Ultrasound Med*. 2019;38(3):675-684. doi:10.1002/jum.14751

21. Barnhart KT, Senapati S, Sammel MD. Declaring a gestation nonviable: when 99% certainty is not enough. [published online October 13, 2020]. *Am J Obstet Gynecol*. 2021;224(2):232-233. doi:10.1016/j.ajog.2020.10.016

22. Seeber BE, Sammel MD, Guo W, Zhou L, Hummel A, Barnhart KT. Application of redefined human chorionic gonadotropin curves for the diagnosis of women at risk for ectopic pregnancy. *Fertil Steril*. 2006;86(2):454-459. doi:10.1016/j.fertnstert.2005.12.056

23. Shamonki MI, Frattarelli JL, Bergh PA, Scott RT. Logarithmic curves depicting initial level and rise of serum beta human chorionic gonadotropin and live delivery outcomes with in vitro fertilization: an analysis of 6021 pregnancies. *Fertil Steril*. 2009;91(5):1760-1764. doi:10.1016/j.fertnstert.2008.02.171

24. Gaies E, Jebabli N, Trabelsi S, et al Methotrexate side effects: review article. *J Drug Metab Toxicol*. 2012;3(4):1-5. doi:10.4172/2157-7609.1000125

25. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med*. 2017;377(14):1391-1398. doi:10.1056/NEJMsm1605385

26. Miller CA, Roe AH, McAllister A, Meisel ZF, Koelper N, Schreiber CA. Patient experiences with miscarriage management in the emergency and ambulatory settings. *Obstet Gynecol*. 2019;134(6):1285-1292. doi:10.1097/AOG.0000000000003571

27. Richardson A, Raine-Fenning N, Deb S, Campbell B, Vedhara K. Anxiety associated with diagnostic uncertainty in early pregnancy. *Ultrasound Obstet Gynecol*. 2017;50(2):247-254. doi:10.1002/uog.17214