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# Optimal treatment for women with a persisting pregnancy of unknown location, a randomized controlled trial: The ACT-or-NOT trial

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ABSTRACT

*Objective:* Pregnancy of unknown location (PUL) is not a diagnosis but a transient state used to classify a woman when she has a positive pregnancy test without definitive evidence of an intra-uterine or extra-uterine pregnancy on transvaginal ultrasonography. Management of a persisting PUL varies substantially, including expectant or active management. Active management can include uterine cavity evacuation or systemic administration of methotrexate. To date, no consensus has been reached on whether either management strategy is superior or non-inferior to the other.

*Design:* Randomized controlled trial.

*Setting:* Academic medical centers.

*Patients:* We plan to randomize 276 persisting PUL-diagnosed women who are 18 years or older from Reproductive Medicine Network clinics and additional interested sites, all patients will be followed for 2 years for fertility and patient satisfaction outcomes.

*Interventions:* Randomization will be 1:1:1 ratio between expectant management, uterine evacuation and empiric use of methotrexate. After randomization to initial management plan, all patients will be followed by their clinicians until resolution of the PUL. The clinician will determine whether there is a change in management, based on clinical symptoms, and/or serial human chorionic gonadotropin (hCG) concentrations and/or additional ultrasonography.

*Main outcome:* The primary outcome measure in each of the 3 treatment arms is the uneventful clinical resolution of a persistent PUL without change from the initial management strategy. Secondary outcome measures include: number of ruptured ectopic pregnancies, number and type of re-interventions (additional methotrexate injections or surgical procedures), treatment complications, adverse events, number of visits, time to resolution, patient satisfaction, and future fertility.

*Conclusion:* This multicenter randomized controlled trial will provide guidance for evidence-based management for women who have persisting pregnancy of unknown location.

## 1. Background

A woman with pain and bleeding in the first trimester of pregnancy is at risk for ectopic pregnancy (EP) and should be distinguished from a woman with an ongoing potentially viable intrauterine pregnancy (IUP) and from a woman with a miscarriage. EP is defined as the implantation

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of an embryo outside the uterus. EP is a major cause of maternal morbidity and is responsible for 6% of pregnancy-related deaths [1,2]. However, if diagnosed and treated early and before rupture, morbidity is limited and conservative management is preferred [3]. Early diagnosis allows for procedures that preserve fallopian tube function and fertility [4].

Diagnosis is straightforward if ultrasound evaluation definitively identifies a definitive IUP or EP [5]. However, ultrasound can be inconclusive in early pregnancy (no evidence of a gestation in the uterus or the adnexa) in up to 40% of women with a symptomatic first trimester pregnancy [6]. This clinical quandary is termed a 'pregnancy of unknown location' (PUL). A PUL is not a diagnosis but a transient state in the diagnostic process of a woman at risk for EP [7]. The management of a woman with a PUL necessitates close follow up and repeated diagnostic testing until a definitive diagnosis is reached. This can include serial serum human chorionic gonadotropin (hCG) concentrations, repeat ultrasound, or uterine evacuation. While the final diagnosis is either an early viable intrauterine pregnancy (IUP), miscarriage, or a visualized ectopic pregnancy, there is a clinical dilemma regarding when or if intervention is needed to make a definitive diagnosis. [8–10]. In addition, when (hCG) values are not declining spontaneously, there is no consensus regarding when or if intervention is necessary [8–10].

During the course of evaluation of a woman with a PUL, up to one third of women will be found to have serial (hCG) values that neither rise nor decline in a pattern suggesting an ongoing viable gestation or a spontaneously resolving pregnancy loss; termed a persisting pregnancy of unknown location (PPUL). These women are at high risk for ectopic pregnancy. While it is important to diagnose an ectopic pregnancy early, the desired goals for a woman with a PPUL may vary, but usually include wishing to minimize intervention, time lost from work, inconvenience, and psychological trauma as she undergoes further evaluation and possible pregnancy loss. These competing priorities have resulted in controversies regarding the utility and role of uterine evacuation, when (or if) presumptive treatment with methotrexate is warranted, and the role of expectant management.

Surgical exploration in the form of uterine evacuation (dilation and curettage) is often performed to confirm the location of the persistent trophoblastic tissue. If trophoblastic tissue is found at the time of uterine evacuation, then a miscarriage has been diagnosed and treated. If the (hCG) concentration does not decline after uterine evacuation, trophoblastic tissue is presumed to be outside of the uterine cavity and an ectopic gestation is indirectly confirmed [7]. This 'nonvisualized' ectopic pregnancy can then be treated medically with methotrexate (MTX), [8,9,11], if appropriate criteria are met.

Some though have advocated that it is not necessary to perform a uterine evacuation to determine the location of the gestation; the PPUL can simply be treated with methotrexate [12]. Alternatively, both early miscarriage and early ectopic pregnancy can be managed expectantly, [13–17] and one multicenter randomized controlled trial demonstrated no difference in the primary treatment success of either single-dose methotrexate versus expectant management [18]. Often the strategy of choice for the management of a PPUL is based on geographic location and training [19].

The goal of this pragmatic randomized controlled trial is to determine if active management (uterine evacuation or MTX) of women with a PPUL is superior to expectant management, if two common active management strategies of a women are non-inferior to each other, and to determine which management strategies are optimal based on cost, number of procedures, side effects, patient preference, and time to resolution.

## 2. Materials and methods

The ACT or NOT trial is a multi-center randomized clinical trial designed to identify the optimal management for a woman with a PPUL. Study participants will be recruited from the clinics of the Reproductive Medicine Network and affiliated entities after obtaining written informed consent. The protocol was approved by the University of Pennsylvania IRB which served as a central IRB (IRB # 815013), performed under IND # 65407 and clinical trials registration number NCT02152696.

### 2.1. Population

For inclusion, participants must be > 18 years old, hemodynamically stable, and identified to have a PPUL. A PPUL is defined as no definitive ultrasound evidence of an intra-uterine or extra-uterine gestation and serial (hCG) confirming non-viability. Ultrasound findings may include a normal uterus and adnexa or nonspecific hypoecchoic area in the uterus (without a yoke sac) or a nonspecific adnexal mass [7]. Prior to enrolment, a second opinion confirming that the pregnancy is non-viable is required. Ultrasound must be performed within 7 days prior to randomization.

Persistence of (hCG) consistent with a nonviable gestation is defined as at least 2 consecutive hCG values (over 2–14 days), showing < 15% rise/day, or < 50% fall between the first and last value. This abnormal pattern of serial (hCG) confirms that the gestation is nonviable. A minimal rise for a viable intrauterine pregnancy is 23% per day or 53% for two days [4]. A maximum rise per day (15%) was calculated and conservatively rounded to accommodate ease of determination of hCG value over a 7-day period: i.e. criteria are 30% or less for hCG values 2 days apart, 50% or less for values 3 days apart, 75% or less for 4 days, 100% or less for 5 days, 130% or less for 6 days, and 166% or less for values 7 days apart.

Exclusion criteria include the following: A definitive sign of gestation including ultrasound visualization of a gestational sac with a yolk sac, with or without an embryo, in the uterus or adnexa [7], the most recent hCG > 5000 mIU/mL, patient obtaining care in relation to a recently completed pregnancy (delivery, spontaneous or elective abortion), diagnosis of gestational trophoblastic disease, participant unwilling or unable to comply with study procedures, known hypersensitivity to MTX, presence of clinical contraindications for treatment with MTX, prior medical or surgical management of this gestation and participant unwilling to accept a blood transfusion. The presence of free fluid visualized by pelvic ultrasound was not an exclusion criterion.

### 2.2. Randomization

After confirming eligibility and informed consent, participants will be randomized by a central randomization office utilizing an internet-based program at the data coordinating center. Block randomization of 3 and 6 were used with the chances being 2:1 between the two choices. Randomization will be 1:2 between expectant management and active management, and 1:1 between active management A and active management B (thus randomization will be 1:1:1 into the three management arms). (See below and Fig. 1).

The arms will be: 1) Expectant management which consists of close monitoring of the PPUL without any intervention. 2) Active management A: consists of a uterine evacuation (or D&C) followed by MTX (50 mg/m$^2$) for those who do not have a drop in hCG suggesting trophoblastic tissue was removed from the uterus. (Fig. 2). 3) Active management B: consists of empiric treatment with MTX. (See Fig. 3.)

#### 2.2.1. Expectant management

In this arm the plan is to expectantly manage the PPUL with close clinical surveillance of signs and symptoms, and serial serum (hCG) concentrations. The frequency of follow up was at least every 4–7 days from randomization, and more often if clinically indicated. Success is defined as complete elimination of (hCG) from the serum, without medical or surgical intervention. Failure is defined as the need for surgical or medical intervention to treat a persistent or ruptured ectopic