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Navigating Uncertainty: Expectant or Active Management for Persisting Pregnancy of Unknown Location?

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Abstract

Introduction: Up to 40% of patients presenting for evaluation of early pregnancy are diagnosed with a transient state called a pregnancy of unknown location (PUL). Management of PUL is dynamic and variable, with the ultimate goal of avoiding risks of ectopic pregnancy while balancing other factors, such as patient priorities. We compare active versus expectant management of persisting PUL to guide clinician counseling for PUL management.

Active Management: Active management involves either uterine evacuation or empiric methotrexate and has the clinical benefit of preventing ruptured ectopic pregnancy if clinical suspicion is high; it has been shown in prior studies to increase likelihood of successful pregnancy resolution compared to expectant management. Patient-specific factors are important to consider when thinking about active management, such as prior abdominal surgical history that may make emergent surgery for a downstream ectopic pregnancy more challenging and morbid, or challenges with follow-up required for expectant management. Patient priorities, such as pregnancy desiredness, are also important to center in these decisions.

Expectant Management: Expectant management involves serial HCG monitoring to use HCG trends to risk-stratify likelihood of ectopic pregnancy. Benefits include avoiding unnecessary interventions or disrupting a viable pregnancy, as well as avoiding risks of uterine evacuation or methotrexate. Patient preferences should similarly be prioritized in decision-making, such as desire for diagnostic certainty or concerns about future fertility.

Conclusion: Shared decision-making is critical in determining optimal management of persisting PUL, which is dynamic and individualized. Several patient-specific factors should be used to guide patient counseling and clinical practice.

Keywords: Pregnancy of unknown location; active management; expectant management

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Debate

Introduction

In up to 40% of patients presenting for evaluation of early pregnancy, ultrasound is unable to definitively identify an intrauterine pregnancy despite serum confirmation of pregnancy, a transient state called a pregnancy of unknown location (PUL) (1). Management of PUL is driven by multiple factors but often begins with serial human chorionic gonadotropin (HCG) monitoring to determine the likelihood of a PUL ultimately representing an intrauterine pregnancy, an early pregnancy loss, or an ectopic pregnancy [2]. When serial HCG trends do not appear consistent with either a viable intrauterine pregnancy or an early pregnancy loss, this can further be classified as a persisting PUL (1), where the suspicion for an ectopic pregnancy increases. One of the main clinical priorities in management of PUL is to avoid the risks and morbidities of a ruptured ectopic pregnancy (2), therefore the question of optimal strategy and timing of how to approach PUL management is of prime importance. However, the state of a PUL is one with inherent uncertainty that is mediated by multiple factors specific to each unique patient. Here, we aim to discuss and compare active versus expectant management of persisting PUL and identify relevant variables clinicians should consider in approaching PUL management.

Active Management

Active management of PUL involves using either uterine evacuation or empiric methotrexate to both treat PUL and potentially diagnose an intrauterine or extrauterine pregnancy (3). When uterine evacuation is used, the presence of chorionic villi on pathology can confirm an intrauterine pregnancy, while the lack of villi coupled with a stable or rising serum HCG is highly suspicious for an ectopic pregnancy that can subsequently be treated with methotrexate or laparoscopy. Empiric methotrexate, most commonly in a two-dose protocol, can alternatively be used as a medical management strategy, coupled with serial HCG monitoring to ensure appropriate decline.

When comparing active versus expectant management of PUL, several factors need to be considered. When clinical suspicion for ectopic pregnancy is high, the clinical priority is typically to achieve pregnancy resolution to prevent and avoid progression to a ruptured ectopic pregnancy. If patients are presenting with clinical symptoms or signs that are worrisome for ectopic pregnancy despite lack of ultrasound confirmation, such as unilateral abdominal pain, this could favor active management to avoid delays in diagnosis and treatment with expectant management.

In the setting of a persisting PUL, or a PUL where serial HCGs have not been consistent with a normal intrauterine pregnancy or an early pregnancy failure, the ACT-or-NOT trial, a randomized control trial (RCT) comparing active versus expectant management, showed that patients who underwent active management with uterine evacuation or empiric methotrexate were more likely to achieve successful pregnancy resolution (3). In that study, empiric methotrexate was also noninferior to uterine evacuation followed by methotrexate if needed for pregnancy resolution.
Another patient-specific factor to consider is the individual risk of an unscheduled surgery if an ectopic pregnancy is not detected and treated prior to rupture. For example, patients with significant prior abdominal surgeries undergoing unscheduled or emergency surgery for a ruptured ectopic pregnancy are at increased risk for bowel, bladder, or vascular injury. In the ACT-or-NOT trial, patients with a persisting PUL who underwent active management were shown to be significantly less likely to undergo unscheduled surgery—12.7% vs 26.7% compared to expectant management (3)—which could reasonably prompt clinicians to more strongly favor active management in these patients. Additionally, patients who may have challenges with prolonged periods of follow-up and returning for serial lab draws may not be optimal candidates for expectant management due to the risk of these patients being lost to follow-up and therefore potentially missing a life-threatening diagnosis. In these situations, active management with uterine evacuation may be preferred, as methotrexate would also require serial lab draws for HCG monitoring.

Patient values and preferences during management of PUL must also be considered and prioritized. Patients with a PUL have been shown to have a range of priorities surrounding their pregnancy and management options, including their own health, obtaining diagnostic certainty around the pregnancy, and the impacts of treatment interventions on their future fertility (4). First and foremost, pregnancy desiredness should be elicited and incorporated (5). In patients with an undesired pregnancy, active management is the most expedient way to achieve pregnancy resolution and may be favored in this population. The current literature describes both uterine aspiration and medical management with mifepristone and misoprostol as safe, effective strategies for low-risk

patients presenting with undesired PUL even in the absence of an established prior HCG trend (6-8).

This approach may benefit patients by decreasing unnecessary labs, ultrasounds, and appointments that may be challenging and triggering for this population. Conversely, some patients desiring immediate future conception may favor active management in the form of uterine aspiration to achieve more expeditious resolution of the PUL and return to ovulation. Patients whose main priority is their own health and avoiding the need for unplanned risks of a possible ectopic pregnancy should also prompt recommendation for active management. Similarly, for those who value having diagnostic certainty about the location of a PUL, uterine evacuation may be the best option for both diagnosis and management. Additionally, if an intrauterine pregnancy is identified on uterine aspiration, the products of conception can be sent for cytogenetic analysis to determine if chromosomal abnormalities were present.

Expectant Management

With expectant management of PUL, serial HCG monitoring is performed, typically every 2-7 days, and the HCG trend is used to determine if the PUL most likely represents an early intrauterine pregnancy, an early pregnancy failure or abnormal intrauterine pregnancy, or an ectopic pregnancy. The primary benefit of expectant management is the possibility to avoid interventions that may not be necessary and are associated with their own risks. Uterine evacuation, while a highly safe procedure, has a risk of uterine perforation (less than 0.3% (9)) or postoperative intrauterine adhesion formation (ranging from 8-30%), although these adhesions are not always clinically significant (10-13)). Methotrexate can have adverse effects such as mucositis, myelosuppression, and pulmonary, liver, and kidney toxicity (11).

If serial HCG values rise in a pattern suggestive of a viable intrauterine pregnancy—typically considered as a 50% rise over 2 days when the initial HCG value is <1,500 mIU/mL (2,15)—or decrease to suggest an early pregnancy failure, the suspicion for ectopic pregnancy is low and intervention is not needed. Even in cases where the HCG trend plateaus, this may represent an abnormal intrauterine pregnancy that will ultimately become an early pregnancy failure. Some ectopic pregnancies can also self-resolve without intervention and without rupturing, in which case serial HCG monitoring may reveal an ultimate drop in HCG after an initial plateau. Some studies have shown that in patients with a PUL or ectopic pregnancy with low-level plateaued HCG values (e.g. <2,000 mIU/mL), there is no difference in rate of pregnancy resolution between those expectantly managed with serial HCGs and those treated with single-dose methotrexate (9, 16-17). Therefore, the population of patients with a persisting PUL but who are asymptomatic and have low HCG levels may be appropriate candidates for expectant management.

Active management also poses the risk of interrupting a potentially viable intrauterine pregnancy, which can be an unacceptable risk to many patients. As previously discussed, patient preferences, beliefs, and values around PUL management should be prioritized. For patients with highly desired pregnancies, expectant management is often preferred to avoid intervening on a possibly viable intrauterine pregnancy, and these patients may have a higher tolerance for the risks of a potential ectopic pregnancy. Some patients may wish to defer intervention as long as possible until a greater level of diagnostic suspicion or certainty is achieved around concern for an ectopic pregnancy. Others may also prioritize avoiding upfront procedures or medications, like uterine evacuation or methotrexate, and therefore prefer expectant management; these patients should be counseled, however, on the risk of needing an unscheduled, potentially emergent, and oftentimes riskier procedure if a PUL ultimately becomes a ruptured ectopic pregnancy. Finally, in patients who prioritize future fertility or are attempting to conceive, some may wish to avoid empiric methotrexate due to the 3-5 month delay it imposes on attempting another pregnancy, or to avoid uterine evacuation due to risks of intrauterine adhesion formation, therefore preferring expectant management. However, for these patients, it is important to acknowledge the risks of requiring salpingectomy for a ruptured ectopic pregnancy with expectant management and the impact on future fertility, especially in those already with underlying tubal factors for infertility.

Conclusion

When considering management of persisting pregnancies of unknown location (PUL), shared decision-making toward active versus expectant management between clinicians and patients is driven by multiple factors. These factors primarily involve patient priorities surrounding the pregnancy, clinical symptoms, and patients' individual medical history. When counseling patients on management of a persisting PUL, we recommend the following guidelines:

1. Elicit and center patients' personal and clinical priorities around the pregnancy (including pregnancy desiredness), any interventions, and future pregnancies/fertility.
2. Obtain thorough medical and surgical history, with particular attention to history of prior abdominal surgeries and contraindications to medical management.
3. Ensure patients are fully counseled about risks and benefits of both active and expectant management, including anticipatory guidance and follow-up needs.

The following table can be used as a reference in determining if active or expectant management may be preferred for different patient scenarios:

Active	Expectant
Undesired pregnancy	**Highly desired pregnancy**
Challenges with long-term follow-up*	**Desire to avoid upfront intervention if not needed; desire to avoid surgical risks**
Significant prior surgical history	**Desire to avoid interrupting ongoing pregnancy**
Concerning clinical symptoms (unilateral abdominal pain, vaginal bleeding, etc.) or hemodynamic instability	**Low peak HCG levels (e.g. <2,000 mIU/mL)**
Underlying tubal disease and desired future fertility	**Prioritization of immediate future fertility/trying again to conceive (avoid methotrexate)**
Desire for increased diagnostic certainty*	

*Uterine evacuation may be preferred option

Persisting pregnancies of unknown location (PUL) and the ultimate management course for these patients continue to be dynamic and individualized, but we propose the above framework as a synthesis of existing literature and clinical expertise surrounding PUL management to guide clinical practice.

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