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REVIEW

Updates in the Management of Pregnancy of Unknown Location: A Focus on Expediting and Streamlining Care

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Abstract

Purpose of Review This review will highlight advances in pregnancy of unknown location (PUL) management and advocate for incorporating desiredness and triaging of low-risk patients to less intensive follow-up when possible.

Recent Findings After the initial diagnosis of a PUL, fluid is sometimes seen inside the uterine cavity on transvaginal ultrasound. A retrospective study looked at the incidence of ectopic pregnancy in patients who have intrauterine fluid collections and found that the risk of ectopic pregnancy in this population is very low. For patients with PUL and an intrauterine fluid collection, a follow-up ultrasound in 1 week can be offered. For patients with undesired PULs, mifepristone and misoprostol can be given and has been shown to lead to shorter time to diagnosis and pregnancy resolution compared to establishing a final diagnosis prior to initiating medication abortion. However, abortion efficacy is lower in patients with undesired PULs. Therefore, medication abortion can be initiated in this population in the carefully selected patient and with close interval follow-up. Multiple algorithms exist and are available for clinicians to use to risk stratify patients with PUL; the M4 model was found in a systematic review to outperform other models. For patients with persistent PULs, active management is more successful at pregnancy resolution than expectant management.

Summary Clinicians should provide active management to patients with undesired pregnancy of unknown location. Selected patients at low risk of ectopic pregnancy can be triaged to less intensive follow-up in order to reduce unnecessary blood-draws and visits.

Keywords Pregnancy of unknown location · Ectopic pregnancy · Pregnancy desires

Introduction

A pregnancy of unknown location (PUL) is a transient state in which a pregnancy is confirmed by a urinary pregnancy test and/or a serum beta-human chorionic gonadotropin (HCG) level, but a pregnancy is not visualized by transvaginal ultrasound. A PUL is not a final diagnosis. A PUL can ultimately become a normal intrauterine pregnancy, a miscarriage, or an ectopic pregnancy. The goal of the clinician is to arrange follow-up in order to rule out an ectopic pregnancy and establish a final diagnosis. An ectopic pregnancy is defined as a pregnancy located outside of the uterus, most commonly in the fallopian tube, and it can be life threatening if not identified and treated [1]. Ectopic pregnancy occurs in 2% of all pregnancies but can occur in up to 18% of pregnancies in patients presenting to the emergency room with bleeding or cramping [2], which is often how PULs are identified. In order to rule out an ectopic pregnancy, PULs need to be followed closely by providers. Follow-up usually includes serial beta HCG levels, repeat ultrasounds, and can include medical management or surgical procedures. This article will highlight the advances in management of PULs and advocate for expedited triage of patients and treatment when indicated.

Diagnosis and Management of Pregnancy of Unknown Location

When a PUL is initially diagnosed, the clinicians will have the patient's clinical history, vital signs, single beta-HCG value, possibly a progesterone level, and an ultrasound. A true PUL on ultrasound will show no signs of an ectopic

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pregnancy or an intrauterine pregnancy, while a probable ectopic pregnancy may show an inhomogeneous adnexal mass or extrauterine sac-like structure [2]. However, one meta-analysis of 2216 patients with an ectopic pregnancy found that seeing an adnexal mass that was separate from the ovary on transvaginal ultrasound has a sensitivity of 84.4% and specificity of 98.9% [3]. Therefore, ultrasound cannot usually be used alone to diagnose an ectopic pregnancy.

On the other hand, ultrasound will sometimes show fluid in the endometrial canal or even a gestational sac without internal landmarks of intrauterine pregnancy (IUP), for example, a yolk sac or embryo. A pseudosac occurs when there is fluid in the endometrial canal or a small sac like structure without definitive land marks of an IUP [4]. In a retrospective cohort study of patients presenting with a PUL, pelvic pain, and bleeding researchers sought to establish an incidence and relative rate of intrauterine fluid collection among ectopic pregnancies and IUPs [5•]. This study found that the presence of an intrauterine fluid collection had a relative risk (RR) of 0.08 (0.04–0.16) for ultimately being diagnosed with an ectopic pregnancy [5•]. Given these findings, patients without major risk factors for ectopic pregnancy and who are identified as having an intrauterine fluid collection can likely be followed with interval ultrasound rather than serial beta-HCG. This gives clinicians an opportunity to streamline care and reduce unnecessary intensive follow-up for patients who present with intrauterine fluid collections.

A new point of care (POC) testing assessment shows promise in ruling out ectopic pregnancy in patients presenting with vaginal bleeding in the first trimester. Investigators sought to validate a POC test strip known as ROM plus, which detects alpha-fetoprotein (AFP) and insulin-like growth factor binding protein 1 (IGFBP-1). In this prospective cohort study of patients presenting in early pregnancy with vaginal bleeding, all vaginal blood samples from the patients diagnosed with ectopic pregnancy ($n=12$), threatened miscarriage ($n=4$), and complete miscarriage ($n=4$) tested negative for fetal tissue using the test strip [6•]. They had 16 individuals experiencing an active miscarriage of which 14 had positive test result for fetal tissue. Including controls, the test strip ultimately had a sensitivity of 95.7% for detecting embryonic/fetal tissue in vaginal blood and a specificity of 97.7% [6•]. The ROM plus POC test shows promise at helping to triage patients who present with vaginal bleeding in early pregnancy into high or low risk for ectopic pregnancy. In the case of a positive result, intensive serial beta-HCG testing is likely not necessary.

Assessing Desiredness

After being diagnosed with a PUL, most stable patients will undergo follow-up with a gynecology provider. One way to expedite follow-up and treatment for patients diagnosed with PUL is to assess their pregnancy desires. This should be done at the initial diagnosis of a PUL. Pregnancy desiredness exists on a spectrum and can be assessed with different questions but generally open ended questions are best [7]. If the patient has an undesired pregnancy, then the clinician can offer the patient active management, with the goal of ruling out ectopic pregnancy but also resolving the pregnancy [8]. In this situation, there is no reason to recommend extended follow-up to establish a final diagnosis prior to intervening. However, if the patient is uncertain or has a desired pregnancy, a short-interval follow-up assessment is best. A recent qualitative study of patients diagnosed with PUL found that patients' priorities were dynamic and changed throughout the course of management [9]. Therefore, patients' pregnancy desires and desire for active management should be reassessed throughout their follow-up.

Active Management of Undesired PUL

Active management can be offered at first presentation to patients with an undesired PUL through a diagnostic uterine aspiration, diagnostic laparoscopy, medical management with methotrexate, or medical management with mifepristone and misoprostol. For a patient with an intrauterine fluid collection and no adnexal mass, a diagnostic uterine aspiration or medical management with mifepristone and misoprostol may be most appropriate. Whereas for a patient with an adnexal mass and no intrauterine fluid collection, empiric methotrexate or diagnostic laparoscopy may be most appropriate. There is no single best treatment option, so clinicians should consider the clinical scenario and use a shared decision-making approach in counseling patients on these options.

In a recent retrospective cohort study, patients requesting a medication abortion with a last menstrual period of 42 days or less and a diagnosis of a PUL were either given mifepristone followed by misoprostol (while simultaneously excluding ectopic pregnancy with serial beta-HCG [same-day-start group]), or recommended to have short-term follow-up to establish a diagnosis with serial beta-HCG tests before medication abortion treatment was initiated (delay-for-diagnosis group) [10•]. This study found that the same-day start group had a shorter time to diagnosis (median 5 days vs 9 days) with no difference in emergency room visits or nonadherence with follow-up. They also had shorter time to complete abortion (median 5 days vs 19 days). Those patients in the

same-day-start group had lower rate of successful medication abortion compared to the delay-for-diagnosis group (85% vs 96%), and the rate of ongoing pregnancy was also higher in the same-day-start group (10% vs 2.5%) [10•]. Given these findings, medication abortion can be offered to patients with undesired PUL. However, the necessity of follow-up should be emphasized both to exclude an ectopic pregnancy and to exclude the possibility of an ongoing pregnancy. This study recruited patients from a Planned Parenthood where the incidence of ectopic pregnancy is lower than patients seen in the emergency room, and thus, its generalizability to patients presenting in the ED with bleeding or cramping is likely limited [11]. Using mifepristone and misoprostol for management of PUL will likely lead to faster diagnosis and resolution of pregnancies, but patients should be carefully selected and the importance of follow-up should be emphasized.

Conservative Management of Desired PUL

In stable patients who have desired pregnancies, clinicians should manage conservatively with short-interval follow-up. Follow-up often involves a repeat beta-HCG along with assessment of clinical signs and repeat ultrasounds. There is no universally accepted protocol for ruling out ectopic pregnancy or risk stratifying PULs. Some clinicians follow PULs with serial HCG until a viable pregnancy or miscarriage can be ruled out while others advocate for a single progesterone level to help with diagnosis. However, most often beta-HCGs will be trended in some fashion.

Assessing Beta-HCG Patterns in Patients with PUL

For a patient with a desired pregnancy the goal is to avoid interrupting a viable intrauterine pregnancy. The conservative cutoff for a minimal rise in beta-HCG over 2 days can be as slow as 35% in a viable intrauterine pregnancy [12]; however, the majority of viable pregnancies will have a percent rise above this conservative cut off. A secondary analysis of a prospective multi-center study of patients diagnosed with a PUL who presented to an Early Pregnancy Unit sought to evaluate the predictive value of progesterone, beta-HCG, and beta-HCG ratio (beta-HCG at 48 h/initial beta-HCG) cut offs that could be used to exclude a viable IUP. This study found that a progesterone level below 2 and a beta-HCG ratio below 0.87 was unlikely to be associated with viability but did not definitively rule out the possibility of a viable IUP [13].

Another way to confirm that a pregnancy will not be viable is to establish a trend suggestive of a spontaneous abortion. When trending beta-HCG in patients with confirmed spontaneous abortion, the slowest rates of decline (as represented by the 95th percentile) ranged from 21 to 35% reduction in 2 days and 60 to 84% in 7 days [14]. However, because of the overlap in beta-HCG patterns between spontaneous abortions and ectopic pregnancies, these patients should still have follow-up to confirm resolution of the pregnancy. One retrospective study of a cohort of patients diagnosed with a PUL found that a beta-HCG drop of 85% within 4 days or a drop of 95% within 7 days can rule out an ectopic pregnancy [15]. Therefore, in patients with this trajectory, the clinician can assume the final diagnosis is a resolving PUL and stop intensive follow-up with serial beta-HCGs.

When assessing the percent change in beta-HCG for ectopic pregnancy, typically clinicians will encounter a plateau in the beta-HCG. The majority of ectopic pregnancies (71%) will have a percent change in the initial beta-HCG follow-up that is outside the normal range for a patient experiencing a spontaneous abortion or viable intrauterine pregnancy [16]. However, 20% of ectopic pregnancies can have an increase of 53% or more in 48 h. Thus, while most ectopic pregnancies will not follow a traditional pattern for a viable pregnancy or miscarriage, there is still considerable overlap. This highlights the importance of active management in undesired pregnancies and ongoing surveillance in desired pregnancies. In a multicenter cohort study, investigators used a 35% increase and a 2-day decrease of 36–47% and achieved 83% sensitivity and 70.8% specificity to predict ectopic pregnancy. However, 16.8% of ectopic pregnancies and 7.7% of IUP would be misclassified using serial beta-HCG alone. A third beta-HCG and early US decreased IUP misclassification to 2.7% [17]. Therefore, in stable pregnancies that are desired, a third beta-HCG is likely to improve diagnostic prediction and reduce the chance of misclassifying an IUP.

Treatment Algorithms

Multiple studies and researchers have attempted to create treatment algorithms for PULs. However, there is not one universally accepted algorithm for patients diagnosed with a PUL. These algorithms include using a single beta-HCG level, a beta-HCG ratio (beta-HCG at 48 h/initial beta-HCG), single progesterone cut-off levels, and logistic regression models based on clinical data. In a systematic review with metanalysis, investigators found that the M4 logistic regression model (which uses the initial beta-HCG and beta-HCG ratio) performed best at predicting the final outcome of ectopic pregnancy, with a calculated area under the curve (AUC) of 0.87 [18•]. Thus, using a logistic regression model like the M4 may help clinicians to risk stratify patients and reduce unnecessary intensive follow-up for low-risk patients.

An updated version of the M4, the M6 model, consists of a single progesterone, the initial beta-HCG level, and a beta-HCG ratio [19]. A prospective multicenter study with

the goal of validating the M6 model was conducted. In this study, they used a two-step approach. First, if the initial progesterone was less than 2 mmol/L, then the patient was scheduled for a urine pregnancy test in 2 weeks. If it was greater than 2, then the patient underwent a repeat beta-HCG at 48 h. In this second assessment, the beta-HCG ratio was put into the M6 model and patients were assigned a percent risk of ectopic pregnancy and were defined as high risk if their percent risk was > 5%. In this study, 320 patients were diagnosed with an ectopic pregnancy or persistent PUL. Of those patients, only 15 were misclassified as low risk [20]. The M6 model is available online and through phone applications. Therefore, clinicians could consider using this free risk prediction model to help triage patients diagnosed with PUL. In another recent study, the authors sought to verify the performance of an online algorithm for diagnosing ectopic pregnancies in a cohort of patients presenting to an emergency room in Brazil. This study's calculator considers risk of ectopic pregnancy based on clinical data, transvaginal ultrasound findings, and beta-HCG levels. They found that the accuracy, sensitivity, and specificity of the proposed algorithm was 98.9% [21]. However, their ectopic pregnancy incidence was only 8.5% which may limit generalizability. This calculator is also available online and could be utilized by clinicians.

Management of a Persistent PUL

During the surveillance of a PUL, up to one-third of people will have serial beta-HCG, suggesting neither ongoing viable nor spontaneously resolving pregnancy. This clinical scenario is referred to as a persistent PUL. In this scenario, where a definitive ectopic pregnancy is not visualized, it can be challenging to counsel patients on specific management strategy. A multicenter randomized control trial attempted to answer whether active management was more effective at pregnancy resolution (defined as pregnancy resolution without a change in treatment from initial strategy) than expectant management in patients with a persistent PUL [22••]. The trial investigated if empiric two-dose methotrexate was non-inferior to uterine evacuation followed by methotrexate if needed for pregnancy resolution. Investigators randomized 255 people to either expectant management, uterine evacuation followed by methotrexate if indicated, or empiric methotrexate. Of note, 39% of trial participants declined their initially assigned treatment strategy. Active management led to successful pregnancy resolution 51% of the time compared to 36% of the time with expectant management (RR, 1.43 [95% CI, 1.04 to 1.96]) 22••. However, the time to resolution and total number of visits were not different. This study also found that the percentage of patients with successful resolution of pregnancy with empiric methotrexate was

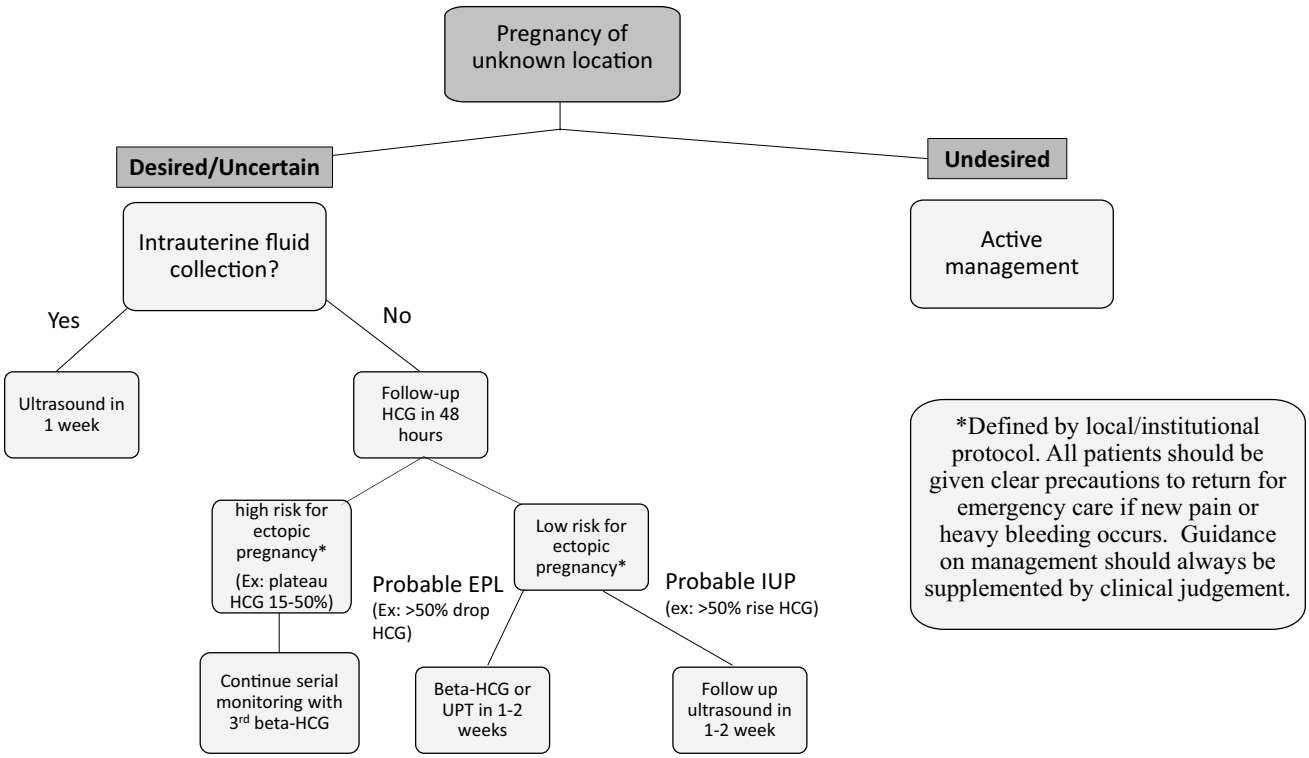

Fig. 1 Algorithm incorporating recent research findings to triage patients who are diagnosed with pregnancy of unknown location. EPL, early pregnancy loss; IUP, intrauterine pregnancy

noninferior to uterine evacuation (54.9% vs 48.3%). Therefore, in a patient identified as having a persistent PUL, this trial supports active management as more likely to successfully resolve the abnormal pregnancy than expectant management. They also found that either aspiration followed by methotrexate if needed or empiric methotrexate can be offered as options for active management. When clinicians are applying this to practice, it is important to note that this study used the two-dose methotrexate protocol, and thus, this non-inferiority may not be generalizable to the single-dose methotrexate protocol.

Conclusion

At present, there have been advances in how to manage PULs and how to effectively triage patients as high and low risks for ectopic pregnancy. However, there is not a gold-standard protocol for doing so. There are risk stratifying algorithms in existence that are available and could be used by clinicians to help triage patients through this management process. Because the follow-up for PUL can be labor-intensive for patients, with multiple short interval blood tests, clinicians should strive to provide active management to patients experiencing undesired pregnancies and identify patients at low risk for ectopic pregnancy, such as those with intrauterine fluid collections or beta-HCG patterns consistent with resolved PUL or viable IUP to triage them to less intensive follow-up (Fig. 1). Future research should focus on validating available algorithms in diverse populations and finding ways to reduce burden on patients in order to streamline care during the management of PULs.

Compliance with Ethical Standards

Conflict of Interest Dr. Flynn has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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