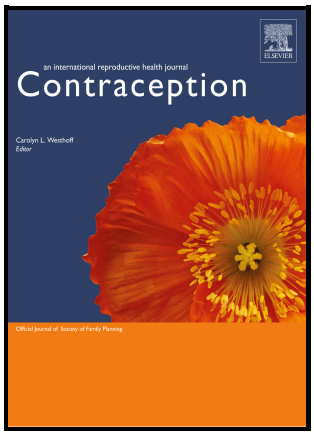

Society of Family Planning Clinical Recommendation: Management of undesired pregnancy of unknown location and abortion at less than 42 days of gestation

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Abstract

Pregnancy of unknown location is a condition in which a pregnancy test is positive, but no intrauterine or extrauterine pregnancy is visualized using transvaginal ultrasonography. We recommend using standardized nomenclature and definitions to describe intrauterine pregnancy (IUP), probable IUP, pregnancy of unknown location (PUL), probable ectopic pregnancy (probable EP), and ectopic pregnancy (EP) (Best Practice). Among abortion-seeking patients found to have a PUL, the incidence of ectopic pregnancy (EP) is 4-8%. We recommend clinical judgment in assessing the risk for EP in the setting of PUL; the absence of an intrauterine gestational sac (GS) or yolk sac should not delay care (GRADE 1B). In asymptomatic individuals with an undesired PUL who prefer to proceed with immediate treatment (medication or procedural management without delay) and have a low risk of EP, as determined by the clinician based on history, symptoms, and all other available data, we recommend medication management with mifepristone and misoprostol or procedural management via uterine aspiration and clear plans for ensuring pregnancy resolution in a timely fashion (GRADE 1B). While both medication and procedural management of undesired PUL are associated with earlier pregnancy resolution and identification of EP, the two main risks of inadequate follow-up include ongoing pregnancy and missing or delaying a subsequent diagnosis of EP. For individuals with PUL choosing immediate treatment with medication management, we recommend clinicians obtain a baseline serum quantitative hCG at the time of medication provision to aid in diagnosis and follow-up (GRADE 1A). Following medication management of PUL with mifepristone and misoprostol, we suggest a repeat serum quantitative hCG level, with pregnancy resolution defined as either a 50% decline or greater at 48-72 hours after misoprostol or an 80% decline or greater at seven days after mifepristone or 5-10 days after misoprostol (GRADE 2B). We recommend against direct extrapolation of follow-up recommendations from no-test abortion clinical protocols to individuals with a documented PUL treated with mifepristone and misoprostol, given the higher risk of EP among individuals with a known PUL (GRADE 1C). When uterine aspiration is performed at less than 42 days of gestation, including for individuals with PUL or probable IUP, and both chorionic villi and GS are not visualized, we recommend repeat ultrasonography (if an IUP or probable IUP was seen initially), serum

quantitative hCG follow-up, or both (GRADE 1B). When both chorionic villi and GS are not visualized after uterine aspiration and serial serum hCG follow-up is warranted, we recommend testing on the day of the procedure and 24-72 hours later, with pregnancy resolution defined as greater than 50% decline 24 hours after aspiration, greater than 70% by 48 hours, or greater than 80% by approximately 72 hours (GRADE 1B).

Keywords:

Ectopic pregnancy, Human chorionic gonadotropin, Medication abortion, Pregnancy of unknown location, Procedural abortion, Uterine aspiration

1. Background

Purpose

Pregnancy of unknown location (PUL) is a condition in which a pregnancy test is positive, but no intrauterine or extrauterine pregnancy is visualized using transvaginal ultrasonography. A PUL may be an expected finding 35 days or less after a sure last menstrual period (LMP). Most individuals with a PUL will eventually be diagnosed with an intrauterine pregnancy (IUP) with or without cardiac activity, or an early pregnancy loss (EPL) with a location that was never visualized on ultrasonography [1]. Between 6-27% of individuals with a PUL will be later found to have an ectopic pregnancy (EP) [2–4].

Data from a nonabortion-seeking population with PUL suggest that the incidence of EP is markedly lower if any intrauterine fluid collection is present [4]. Clinicians should formulate an individual management plan based on clinical factors and in consideration of available resources. When caring for individuals with an early pregnancy, clinicians should explicitly ask whether the pregnancy is desired, as this information impacts management decisions and prioritizes patient-centered care [5].

This Clinical Recommendation provides guidance for early abortion care, with a focus on managing an undesired PUL identified with routine ultrasound examination during in-clinic abortion care. This guidance does not apply to the care of patients receiving telemedicine medication abortion, without routine ultrasound examination. While these recommendations are intended to guide management for people with an undesired PUL, they may also be useful in caring for individuals with an undesired probable IUP (defined in Table 1).

Definitions

This document uses nomenclature aligned with Barnhart et al.'s [6] consensus statement regarding definitions (Table 1) and outcomes (Figure 1), which include visualized EP, visualized IUP, resolved persistent PUL, and treated persistent PUL as diagnostic classifications. It also incorporates language from the first-trimester ultrasonography consensus statement from the Society of Radiologists in Ultrasound [7], endorsed by the Society of Family Planning.

Outcomes of a PUL could include an IUP, EP, or spontaneously resolved PUL (decline in serum quantitative hCG levels without intervention; pregnancy location is never determined,

Figure 1). Nearly all individuals with intrauterine fluid collections (probable IUPs or intracavitary fluid collections) are eventually diagnosed with an IUP [4,8]. Clinicians can further classify an IUP as concerning for or diagnostic of EPL, if applicable, based on ultrasonography characteristics, or, when individuals undergo serial ultrasonography, time-based criteria (Table 2).

Many clinicians offer immediate treatment with mifepristone and misoprostol or uterine aspiration to individuals with an undesired pregnancy who have a probable IUP or PUL on ultrasonography after stratifying for risk by considering such clinical factors as a history of EP, presence of abdominal or pelvic pain, and bleeding [9–12]. When mifepristone and misoprostol are used for immediate treatment, this practice is known in Europe as "very early medication abortion" (VEMA) [9–11,13] and in the US as "same-day-start" or "immediate" medication abortion or management [14,15].

Immediate uterine aspiration can offer quick diagnosis and resolution of pregnancy [5]. Determining the location of a pregnancy may not be necessary to provide treatment [1]. The need for diagnosis may vary depending on individual risk factors for EP, whether the diagnosis affects the management of future pregnancies, and patient preference [16,17].

An individual with a PUL who chooses serial serum quantitative hCG measurements and further ultrasonography imaging prior to intervention (delay for diagnosis) often does so with the intent of seeking a diagnosis. Their intent to continue the pregnancy may be conditional on the diagnosis and prognosis, and may evolve over time [18]. If serum quantitative hCG remains elevated and no pregnancy is visualized, the individual is said to have a persisting PUL, a subclassification of PUL [6,19].

A persisting PUL is an abnormal pregnancy that is not visualized on transvaginal ultrasound and is neither progressing nor spontaneously resolving over time, with serum quantitative hCG levels that remain elevated. Evacuating the uterus with mifepristone and misoprostol or uterine aspiration in this circumstance does not meet the clinical definition of abortion [20]. The ultimate outcome of a persisting PUL depends on the response to medication or procedural management (Figure 1).

In the setting of PUL at the time of initial presentation, without intervention, approximately one quarter of patients will go on to experience early pregnancy loss or EP [14]. As such, evacuating the uterus before definitive diagnosis may or may not be an abortion.

To clarify these nuances, this document uses 'abortion' if an embryo with cardiac activity is present; when an intrauterine GS and yolk sac are present; and in the setting of 'probable IUP', when an intrauterine GS or fluid collection is present. We use 'medication management' or 'procedural management' or 'uterine aspiration' in the setting of PUL, persisting PUL, probable EP, EP, embryonic demise, or anembryonic pregnancy. Clinicians should be aware that legal definitions may vary, and insurance coverage may differ based on diagnosis.

Epidemiology

Much of the published literature on the epidemiology of individuals with PUL reports on patients seen for problems in early pregnancy, including bleeding, pain, or pre-existing risk factors for EP [1,2,21–31]. The reported prevalence of PUL in this population ranges from 3-42%, with most estimates under 11%. The population of individuals seeking an abortion is different from patients who present for problems in early pregnancy in that they are less likely to report pain or bleeding. Data from clinics where all patients underwent routine ultrasonography from 2014-2019, before the US Supreme Court's 2022 ruling in *Dobbs v. Jackson Women's Health Organization*, indicated that the proportion of people seeking abortion with pregnancies classified as PUL was 3% among *all* patients seeking abortion (Borchert) and 8% among those seeking abortion who reported a last menstrual period (LMP) of 42 days of gestation or less (Goldberg) [14,15].

It is not known whether EP risk should be assigned differently for asymptomatic individuals with a certain LMP less than 35 days (when PUL might be expected) compared with asymptomatic individuals with an LMP of 35 days or more. With the use of no-test medication abortion protocols [32], fewer people will undergo routine ultrasonography; in these circumstances, PUL may be diagnosed less frequently. One study that compared routine ultrasonography screening to a telemedicine-hybrid medication abortion protocol (where imaging was obtained only if indicated) found no difference in the identification of EPs between

groups; however, it is important to note that ultrasonography was performed in 39% of those in the telemedicine-hybrid group [33].

Legal Climate

Clinicians, particularly those in states where abortion is banned, should understand that clinical definitions do not always align with legal definitions. They should be familiar with institutional, local, and state regulations that impact abortion provision, as well as institutional resources. National and regional resources can be helpful in areas where gestational duration limits or other restrictions exist.

Considerations for patient preferences and health equity

Both immediate treatment, with medications or uterine aspiration, and delay-for-diagnosis approaches are safe and reasonable management options for individuals with a PUL without concerning symptoms or major risk factors for EP. Individuals may prefer to end the pregnancy on the day of presentation for care, or delay intervention in favor of waiting for a diagnosis of IUP or EP (expectant management). Utilizing shared decision-making regarding management preferences promotes patient-centered care. Patient preferences can change over time as individuals receive more information about the pregnancy [18] and should weigh heavily in this decision.

When providing care to individuals with a PUL, clinicians should clearly communicate a plan of care, which usually includes subsequent assessment of serum quantitative human chorionic gonadotropin (hCG) levels or ultrasonography or both, how patients will be contacted with results, and how follow-up care will be provided. In formulating the plan, clinicians should engage in shared decision-making and consider patient safety as well as potential difficulties with accessing care.

Ultimately, the decision for immediate or delayed treatment should primarily lie with the patient. The inability to choose one's preferred management option in a timely fashion exacerbates health inequities and likely worsens outcomes, as immediate management facilitates rapid diagnosis and treatment of both undesired and ectopic pregnancies.

2. Clinical Questions

Diagnosis Considerations

2.1 How can clinicians differentiate between intrauterine pregnancy (IUP), probable IUP, pregnancy of unknown location (PUL), probable ectopic pregnancy (probable EP), ectopic pregnancy (EP), and early pregnancy loss (EPL)?

We recommend using standardized nomenclature and definitions to describe intrauterine pregnancy (IUP), probable IUP, pregnancy of unknown location (PUL), probable ectopic pregnancy (probable EP), and ectopic pregnancy (EP) (Best Practice) (Table 1, Table 2). Barnhart et al. [6] and Doubilet et al. [34] published widely-used consensus statements defining PUL and related ultrasonography classifications (Table 1), and criteria for EPL, respectively. In the setting of abortion care, individuals may undergo ultrasonography because they do not meet the criteria to undergo a no-test medication abortion [35], as part of a protocol or state-level requirement that includes routine ultrasonography, or per patient preference. Gestational duration and serum quantitative hCG levels correlate with transvaginal ultrasonography findings, and a GS is usually seen 35 days after the last menstrual period [36].

In the setting of a desired pregnancy, clinicians use an intentionally conservative high serum quantitative hCG threshold of 3,500 mIU/mL to avoid the potential for misdiagnosis and interventions that could potentially compromise a developing IUP [37]. Doubilet's diagnostic criteria for EPL do not incorporate an assessment of the desirability of the pregnancy nor optimal approaches in cases of an undesired pregnancy, including an undesired PUL. Given the relatively higher risk of EP in individuals with a PUL compared with probable IUP, it is appropriate to use a lower threshold when the pregnancy is undesired. Based on a convenience sample of 126 patients, **we suggest using 2,000 mIU/mL as the serum quantitative hCG threshold for when an intrauterine pregnancy will typically be visualized on transvaginal ultrasonography (GRADE 2C)** [38].

When transvaginal ultrasonography is not conclusive, a single serum quantitative hCG measurement does not predict whether an IUP with cardiac activity will develop. Trends in serum quantitative hCG consistent with pregnancy progression or EPL are well characterized. However, those for EP can be variable and overlap with IUP and EPL [39,40]. Most reports on these trends prioritize nonintervention out of concern for interrupting a desired pregnancy. For

example, a 35% rise in serum quantitative hCG for two values obtained over 48 hours occurs for 99% of individuals with IUPs [41]. Using this conservative guideline minimizes the risk of misclassifying an early pregnancy that would have developed normally as an EPL. Additionally, slower increases are anticipated when initial values are high [42]. Clinicians should take these considerations into account when interpreting and making management decisions based on serial measurements of serum quantitative hCG levels in the setting of undesired PUL.

2.2 When is it acceptable to treat before a definite intrauterine pregnancy or ectopic pregnancy diagnosis?

Clinicians should first confirm if the pregnancy is desired, undesired, or if the patient is undecided [43–45]. If undesired and the patient is certain that they would like an abortion, the clinician should inquire if the patient prefers to proceed with immediate treatment or to delay and determine a definitive diagnosis.

In a systematic review and meta-analysis, Schmidt-Hansen et al. [46] looked at outcomes when initiating medication or procedural abortion for individuals with PUL or probable IUP, versus initiation for those with a confirmed IUP. In two studies of medication abortion initiation, there were no differences in ongoing pregnancy, complete abortion, or missed diagnosis of EP among 1,244 individuals with probable IUP and PUL classifications at treatment [47,48]. Similarly, in a third study of procedural abortion (n=1,530), there were no missed diagnoses of EP among a subgroup of 153 individuals without an identifiable GS on transvaginal ultrasonography [49]. Although the authors assigned a GRADE quality of evidence rating of very low for all reported outcomes, the National Institute for Health and Care Excellence (NICE) guidelines state to "consider abortion before there is definitive ultrasound evidence of an intrauterine pregnancy (a yolk sac) for women who do not have signs or symptoms of an ectopic pregnancy" based on these findings [50]. **We recommend clinical judgment in assessing the risk for ectopic pregnancy in the setting of PUL; the absence of an intrauterine gestational sac or yolk sac should not delay care (GRADE 1B).**

The National Abortion Federation [51] and Planned Parenthood Federation of America [52] also state that abortion care should be offered to patients with PUL, with verification and documentation of pregnancy resolution when medication abortion or uterine aspiration is

initiated. Initiation of abortion with close follow-up identifies EP more rapidly than if treatment is delayed for diagnosis [14,15]. **In asymptomatic individuals with an undesired PUL who prefer to proceed with immediate treatment (medication or procedural management without delay) and have a low risk of ectopic pregnancy, as determined by the clinician based on history, symptoms, and all other available data, we recommend medication management with mifepristone and misoprostol or procedural management via uterine aspiration and clear plans for ensuring pregnancy resolution in a timely fashion (GRADE 1B) (Figure 2).**

2.3 What are the key prerequisites for offering treatment of PUL, before a definite intrauterine pregnancy or ectopic pregnancy diagnosis?

Clinicians should have the capacity to confirm pregnancy resolution and exclude ectopic pregnancy through tissue examination, follow-up ultrasonography, or monitoring serial serum quantitative hCG levels (Best Practice).

Factors that influence how to complete the evaluation and management include follow-up visit type (in-person versus asynchronous or synchronous telemedicine), how patients can obtain laboratory and imaging tests (including serum qualitative or quantitative hCG, and ultrasonography), and timing (see the Confirmation of Pregnancy Resolution section for further information). Clinicians should minimize the impact of socioeconomic inequity when considering how to proceed with diagnosis and management, as the resources available to an individual will vary. Management should be individualized to optimize access to care, while ensuring patient safety.

Medication Management

2.4 When is medication management appropriate for the management of undesired PUL?

Most data supporting the use of mifepristone and misoprostol in patients with undesired PUL come from retrospective studies evaluating data from clinical services where medication abortion is offered to those presenting very early in pregnancy. Clinical protocols reported in these studies often specified that offering mifepristone and misoprostol for early abortion was reserved for those without ectopic risk factors or symptoms [12,14,15,53]. A recent prospective, randomized controlled trial (RCT) evaluated outcomes for individuals receiving mifepristone and

misoprostol at up to 42 days from LMP who had PUL or probable IUP on transvaginal ultrasound, and specifically excluded patients with bleeding or unilateral pain, previous EP, or IUD in place [13].

Before 2020, there were limited published data on the practice of providing mifepristone and misoprostol in the setting of undesired PUL. Much of the early data on medication abortion efficacy before 42 days of gestation combines patients with a confirmed IUP, probable IUP, or PUL before initiation of the abortion. Subsequent studies have examined outcomes for individuals with PUL who initiate immediate treatment with medication management and those who delay for diagnosis. Available evidence suggests that rates of treatment success may be lower when mifepristone and misoprostol are initiated for individuals with PUL, compared with probable IUP or IUP (Table 3). No published data specifically compare mifepristone and misoprostol to misoprostol only for PUL.

While current mifepristone labeling lists EP as a contraindication as it is not effective alone in the management of EP, there does not appear to be evidence of harm in inadvertently administering mifepristone and misoprostol to patients who are later diagnosed with an EP. Two studies specifically looked at using mifepristone as an adjunctive therapy with methotrexate for EP treatment, with mixed results. One suggested some potential benefit [54] and the other did not [55], but neither identified harms.

The most serious risk of initiating medication management in the setting of PUL is the potential for delaying diagnosis and treatment of EP, which can result in significant morbidity and mortality. Goldberg et al. [14] found diagnostic benefit (shortened time to diagnosis) with immediate treatment of PUL with mifepristone and misoprostol, compared with delay for diagnosis using serial serum quantitative hCG testing (median 4.5 days vs 8.0 days, p=0.004) while Borchert et al. [15] did not (median three days vs four days, p=0.3).

2.5 How does medication management of PUL differ from medication abortion management recommendations?

While the majority of individuals seeking abortion with a PUL will ultimately have an IUP, published data demonstrate a 4-8% incidence of EP in this group [10,12,14,15], compared with a <1-2% incidence across all reported pregnancies [56,57]. Given the higher risk of EP in

individuals with a PUL, these patients should be followed more closely and in a shorter interval than the general population undergoing medication abortion.

Regimens used for medication abortion may also be used for medication management of PUL. Available evidence indicates that there may be a higher risk of ongoing pregnancy when initiating mifepristone and misoprostol among individuals with PUL, compared with those who have a definite IUP (Table 3), and thus close follow-up is warranted. To date, there is no evidence to support an alternate interval between mifepristone and misoprostol or routine repeat doses of misoprostol amongst patients with PUL [58].

Clinicians should consider likely diagnosis (IUP versus EP), potential toxicity, need for and availability of follow-up care, and considerations related to cost in choosing a course of medication treatment. In the setting of persisting PUL, primary treatment with methotrexate is well-studied and may also be considered. An RCT demonstrated shorter time to resolution and fewer surgical interventions for individuals with persistent PUL who received primary methotrexate, or methotrexate after uterine aspiration when indicated, compared with delay for diagnosis [59].

As with medication abortion for a definite IUP, there is no evidence-based regimen of medications taken after medication management of a PUL or probably IUP that can "reverse" an abortion. "Medication abortion reversal", or the theory that mifepristone antagonization with progesterone could prevent medication abortion, is not evidence-based and may introduce additional clinical risks [60–62]. This document focuses on individuals with an undesired PUL, and while those seeking abortion care generally have a high degree of decision certainty [63], if an individual expresses uncertainty about their pregnancy desire, clinicians can use shared decision-making to offer delay for diagnosis.

Procedural Management

2.6 When is procedural management via uterine aspiration appropriate for the management of undesired PUL?

When logistically and legally available and desired, uterine aspiration is the most rapid management approach in the setting of undesired PUL. Procedural management is part of the diagnostic evaluation of EP for individuals at risk for this condition [37,64,65]. Chung et al. [66]

reported on a retrospective cohort of 321 individuals considered to be at risk for EP, who met any of the following criteria and underwent diagnostic dilation and curettage: 1) no visible IUP by ultrasonography and serum quantitative hCG greater than 2,000 mIU/mL; 2) abnormal serum quantitative hCG trend (< 50% increase in two days); or 3) abnormal fall in serum quantitative hCG level (< 20% decline in two days). In this cohort, 73.2% had an EP and 26.8% had an EPL. For those with EPL, procedural management confirmed the diagnosis and avoided unnecessary exposure to methotrexate. Borchert's 2023 study [15] examined median days to diagnosis for low-risk PUL patients. Among 19,151 abortion encounters, of which 501 (2.6%) had a low-risk PUL (asymptomatic and without ultrasonography findings concerning for EP), median days to diagnosis of pregnancy location were significantly lower in the immediate treatment via uterine aspiration group (two days, IQR 1-3 days) compared with the delay for diagnosis group (three days, IQR 2-10 days, p<0.001).

Confirmation of Pregnancy Resolution

2.7 What are the best approaches to confirm pregnancy resolution and exclude ectopic pregnancy when managing undesired pregnancy of unknown location and abortion at less than 42 days of gestation?

With both medication and procedural management of undesired PUL, there are two main risks: ongoing pregnancy and missing or delaying a subsequent diagnosis of EP. Mitigating these risks will depend on whether the individual undergoes medication or procedural management.

Medication management

For individuals with PUL choosing immediate treatment with medication management, we recommend clinicians obtain a baseline serum quantitative hCG at the time of medication provision to aid in diagnosis and follow-up (GRADE 1A). Following medication management of PUL with mifepristone and misoprostol, we suggest a repeat serum quantitative hCG level, with pregnancy resolution defined as either a 50% decline or greater at 48-72 hours after misoprostol or an 80% decline or greater at seven days after mifepristone or 5-10 days after misoprostol (GRADE 2B, Figure 2).

For individuals with a probable intrauterine pregnancy choosing immediate treatment with medication management, we suggest that clinicians obtain a serum quantitative hCG for any individuals at higher risk of ectopic pregnancy (ie, those with risk factors or symptoms) (GRADE 2B); serum quantitative hCG levels are expected to be above discriminatory zones in the setting of probable intrauterine pregnancy and a repeat measurement can confirm pregnancy resolution. When a repeat serum quantitative hCG level is not available in the setting of medication management of PUL or probable intrauterine pregnancy with a baseline hCG level less than 2,000 mIU/mL, we suggest confirmation of pregnancy resolution with alternative approaches, which may include home urine pregnancy tests at approximately 14 days after mifepristone (GRADE 2C). When criteria are not met to confirm completed abortion, repeat ultrasonography can be used to evaluate for IUP or EP. Table 3 summarizes selected studies that used serum quantitative hCG trends to determine medication abortion success, but few report trends separately for individuals with PUL.

Fiala [67] and Honkanen [68] describe serum quantitative hCG decreases from baseline consistent with complete abortion with mifepristone and misoprostol. Multiple studies define complete abortion or successfully treated PUL as a 50% serum quantitative hCG decline at 48-72 hours after misoprostol or an 80% serum quantitative hCG decline by seven days after mifepristone [10,13–15,67,69,70]. Two additional studies examining the utility of home urine pregnancy tests in the setting of PUL found that patients with a baseline hCG level less than 2,000 mIU/mL and complete abortion uniformly had negative urine hCG tests 14 days after medication administration [69,71]. Following serum quantitative hCG levels to zero is not required for asymptomatic individuals who meet these criteria; however, clinicians should use judgment if offering medication management under higher risk circumstances (eg, individuals with risk factors for EP) or if the patient develops symptoms concerning for EP.

Available data guide evaluation and management for individuals found to have a PUL identified during in-clinic abortion care. **We recommend against direct extrapolation of follow-up recommendations from no-test abortion clinical protocols to individuals with a documented PUL treated with mifepristone and misoprostol, given the higher risk of ectopic pregnancy among individuals with a known PUL (GRADE 1C).**

Procedural management

Studies from the 1990s and 2000s have shown an ongoing pregnancy rate of approximately 1.5% after procedural abortion at less than 42 days of gestation [72,73]. Amongst people who are confirmed pregnant, manual or electric aspiration has been shown to be safe and effective for procedural abortion at these gestational durations [74].

Immediate uterine aspiration may diagnose EP more quickly and allow for earlier treatment compared with serial serum quantitative hCG monitoring for patterns suspicious for this diagnosis [59,66]. Based on the evidence summarized below, **we recommend mitigating the risk of ongoing pregnancy following procedural abortion at less than 42 days gestation with careful examination of fresh aspirate for chorionic villi and a gestational sac (GRADE 1A).**

In Paul's [72] study of 1,132 individuals with probable IUP, two had EPs identified through serial serum quantitative hCG monitoring, initiated because presence of a GS and villi could not be confirmed on tissue examination.

In Edwards and Carson's [49] cohort of 1,530 individuals undergoing procedural abortion at less than 42 days of gestation, nine of 81 (11%) individuals with PUL and no gestational tissue on fresh aspirate had EPs. Five had serum quantitative hCG levels greater than 1,700 mIU/mL and were referred for further treatment on the day of presentation. Given the risk of EP among patients with PUL, early treatment allows rapid progression through a diagnostic pathway.

2.8 If pregnancy resolution cannot be confirmed after medication or procedural management of PUL, what are the appropriate next steps?

Clinicians should evaluate for EP and treat as indicated, given the risk for EP in individuals with PUL.

When individuals with PUL do not meet the criteria for pregnancy resolution after initial medication management, we recommend continued evaluation with serial serum quantitative hCG, ultrasonography, uterine aspiration, empiric treatment with methotrexate, or some combination of these interventions (GRADE 1C). Patients may need continued monitoring with serial serum quantitative hCG levels or empiric treatment with methotrexate [59], and such evaluation and treatment must be individualized based on the post-treatment index of suspicion

for EP, suspicion for retained intrauterine pregnancy tissue, patient factors (eg, ability to obtain additional evaluation and treatments), and available clinical resources.

When uterine aspiration is performed at less than 42 days of gestation, including for individuals with pregnancy of unknown location or probable intrauterine pregnancy, and both chorionic villi and gestational sac are not visualized, we recommend repeat ultrasonography (if an intrauterine pregnancy or probable intrauterine pregnancy was seen initially), serum quantitative hCG follow-up, or both (GRADE 1B). A thin stripe or 'empty uterus' on ultrasonography after suction—without identification of a gestational sac in the aspirate—is not adequate to exclude ongoing pregnancy in the setting of early uterine aspiration**. When both chorionic villi and gestational sac are not visualized after uterine aspiration and serial serum quantitative hCG testing follow-up is warranted, we recommend testing on the day of the procedure and 24-72 hours later, with pregnancy resolution defined as greater than 50% decline 24 hours after aspiration, greater than 70% by 48 hours, or greater than 80% by approximately 72 hours (GRADE 1B, Figure 2).** This recommendation is consistent with Planned Parenthood Federation of America's Medical Standards and Guidelines [52]. It is also consistent with the National Abortion Federation's Clinical Policy Guidelines for Abortion Care [51], which extrapolated from data on the initial rapid serum quantitative hCG decline based on a serum hCG half-life of five to nine hours and a slower phase half-life of 22-32 hours [75], and supported by recent data from Baldwin et al. [76].

3. Summary of Recommendations

- We recommend using standardized nomenclature and definitions to describe intrauterine pregnancy (IUP), probable IUP, pregnancy of unknown location (PUL), probable ectopic pregnancy (probable EP), and ectopic pregnancy (EP) (Best Practice).
- We suggest using 2,000 mIU/mL as the serum quantitative hCG threshold for when an intrauterine pregnancy will typically be visualized on transvaginal ultrasonography (GRADE 2C).

- We recommend clinical judgment in assessing the risk for ectopic pregnancy in the setting of PUL; the absence of an intrauterine gestational sac or yolk sac should not delay care (GRADE 1B).
- In asymptomatic individuals with an undesired PUL who prefer to proceed with immediate treatment (medication or procedural management without delay) and have a low risk of ectopic pregnancy, as determined by the clinician based on history, symptoms, and all other available data, we recommend medication management with mifepristone and misoprostol or procedural management via uterine aspiration and clear plans for ensuring pregnancy resolution in a timely fashion (GRADE 1B).
- Clinicians should have the capacity to confirm pregnancy resolution and exclude ectopic pregnancy through tissue examination, follow-up ultrasonography, or monitoring serial serum quantitative hCG levels (Best Practice).
- For individuals with PUL choosing immediate treatment with medication management, we recommend clinicians obtain a baseline serum quantitative hCG at the time of medication provision to aid in diagnosis and follow-up (GRADE 1A).
- Following medication management of PUL with mifepristone and misoprostol, we suggest a repeat serum quantitative hCG level, with pregnancy resolution defined as either a 50% decline or greater at 48-72 hours after misoprostol or an 80% decline or greater at seven days after mifepristone or 5-10 days after misoprostol (GRADE 2B).
- For individuals with a probable intrauterine pregnancy choosing immediate treatment with medication management, we suggest that clinicians obtain a serum quantitative hCG for any individuals at higher risk of ectopic pregnancy (ie, those with risk factors or symptoms) (GRADE 2B); serum quantitative hCG levels are expected to be above discriminatory zones in the setting of probable intrauterine pregnancy and a repeat measurement can confirm pregnancy resolution.
- When a repeat serum quantitative hCG is not available in the setting of medication management of PUL or probable intrauterine pregnancy with a baseline hCG level less than 2,000 mIU/mL who undergo medication management, we suggest confirmation of

pregnancy resolution with alternative approaches, which may include home urine pregnancy tests at approximately 14 days after mifepristone (GRADE 2C).

- We recommend against direct extrapolation of follow-up recommendations from no-test abortion clinical protocols to individuals with a documented PUL treated with mifepristone and misoprostol, given the higher risk of ectopic pregnancy among individuals with a known PUL (GRADE 1C).
- We recommend mitigating the risk of ongoing pregnancy following procedural abortion at less than 42 days gestation with careful examination of fresh aspirate for chorionic villi and a gestational sac (GRADE 1A).
- When individuals with PUL do not meet criteria for pregnancy resolution after initial medication management, we recommend continued evaluation with serial serum quantitative hCG, ultrasonography, uterine aspiration, empiric treatment with methotrexate, or some combination of these interventions (GRADE 1C).
- When uterine aspiration is performed at less than 42 days of gestation, including for individuals with pregnancy of unknown location or probable intrauterine pregnancy, and both chorionic villi and gestational sac are not visualized, we recommend repeat ultrasonography (if an intrauterine pregnancy or probable intrauterine pregnancy was seen initially), serum quantitative hCG follow-up, or both (GRADE 1B).
- When both chorionic villi and gestational sac are not visualized after uterine aspiration and serial serum hCG follow-up is warranted, we recommend testing on the day of the procedure and 24-72 hours later, with pregnancy resolution defined as greater than 50% decline 24 hours after aspiration, greater than 70% by 48 hours, or greater than 80% by approximately 72 hours (GRADE 1B).

4. Recommendations for Future Research

- Effectiveness of mifepristone and misoprostol for individuals with PUL versus probable IUP. Few published studies compare these two groups, though some report outcomes combining them.
- Relative effectiveness of mifepristone and misoprostol for individuals with PUL based on LMP and serum quantitative hCG level.

- Effectiveness of mifepristone and misoprostol versus misoprostol only for individuals with PUL to inform clinical practice where mifepristone is not available.
- Safety and efficacy of different strategies (eg, serial serum quantitative hCG measurements, high-sensitivity and semi-quantitative urine pregnancy tests) to confirm resolution of pregnancy among individuals with PUL who undergo uterine aspiration; receive mifepristone and misoprostol; or receive misoprostol only.
- Whether exposure to mifepristone and misoprostol amongst patients with a PUL who are subsequently diagnosed with an EP are less likely to rupture or require surgical treatment.

5. Sources

A series of clinical questions was developed by the authors and reviewed by representatives from the Society of Family Planning's Clinical Affairs Committee. We searched PubMed, Ovid Medline, Cochrane Library of Clinical Trials, Embase, and the TRIP database to identify relevant articles published since 2003 in English. Search terms included, but were not limited to: abortion, induced; chorionic gonadotropin; pregnancy, ectopic; ultrasonography, prenatal; mifepristone; misoprostol. The search was restricted to articles published in the English language. We also reviewed guidelines published by organizations or institutions, such as the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the Society of Family Planning, as well as relevant product labels. We located additional studies by reviewing references of identified articles. When reliable research was not available, expert opinion from complex family planning clinicians was used. A comprehensive systematic review was not performed.

6. Intended Audience

This Clinical Recommendation is intended for Society of Family Planning members, family planning and sexual and reproductive health service clinicians, family planning and reproductive health researchers, consumers of family planning care, and policymakers.

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Authorship

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Conflict of Interest

The authors have no conflicts of interest to report. The Society of Family Planning receives no direct support from pharmaceutical companies or other industries for the production of clinical recommendations.

Disclaimer

This publication is designed as a resource to assist clinicians in providing family planning care. It should not be considered inclusive of all proper treatments or serve as the standard of care. It is not intended to substitute for the independent professional judgment of the treating clinician. Variations, taking into account individual circumstances, may be appropriate. This publication reflects the best-available evidence at the time of publication, recognizing that continued research or major changes in the practice environment may impact future recommendations and should be evaluated for incorporation into care. Clinical guidance, grounded in evidence-based research, are distinct from legal requirements and restrictions governing family planning care. Medical recommendations do not vary based on practice location. However, abortion is not legal in all states and circumstances, and this document is not intended to aid in unlawful care. Any updates to this document can be found on https://www.societyfp.org/clinical-guidance/. The Society and its contributors provide the information contained in this publication

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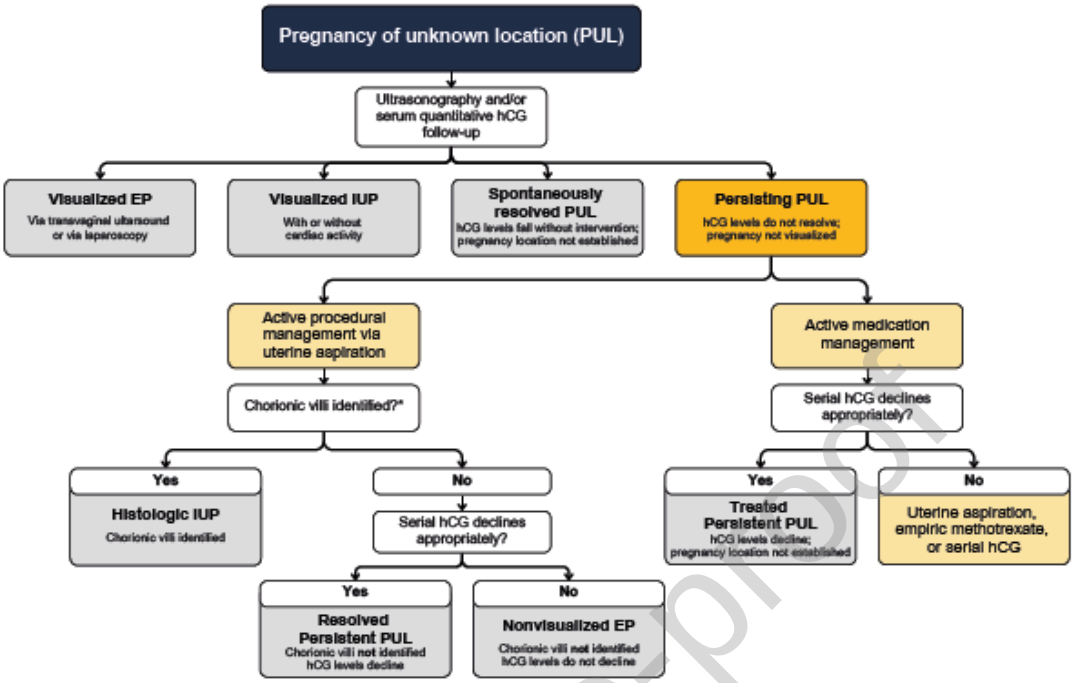


Figure 1. Definitions of outcomes for individuals with a pregnancy of unknown location initially managed expectantly. EP, ectopic pregnancy; hCG, beta human chorionic gonadotropin; IUP, intrauterine pregnancy. Adapted from Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. Fertil Steril 2011;95:857–66. *When confirming pregnancy resolution following uterine aspiration <42 days, both chorionic villi and a gestational sac should be visualized. However, a gestational sac is unlikely to be seen on examination of fresh aspirate in the setting of persisting PUL.

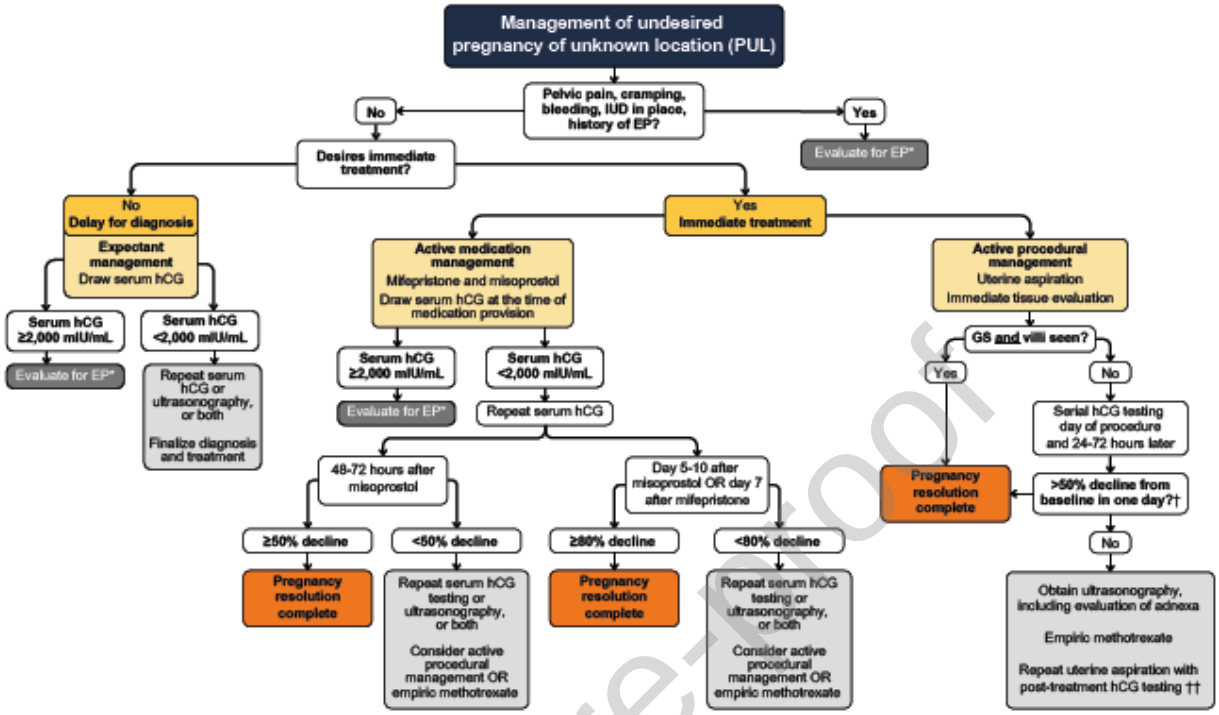
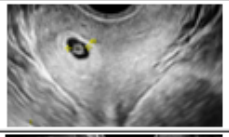
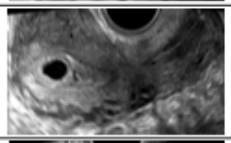
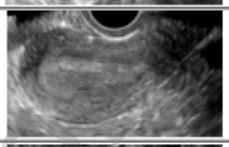
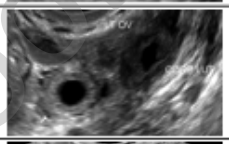
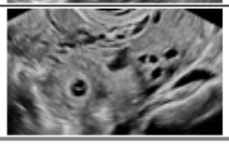


Figure 2. Management of undesired pregnancy of unknown location. EP, ectopic pregnancy; GS, gestational sac; hCG, beta human chorionic gonadotropin, IUD, intrauterine device. *Includes ultrasonography evaluation of adnexa, initial serum hCG and repeat hCG in 48 hours. Refer to hospital for worsening pelvic pain, presyncope, syncope, or abnormal hCG rise. A suggested normal hCG rise at 48 hours is at least 49% if initial value is less than 1,500 mIU/mL; 40% if between 1,500 and 3,000 mIU/mL; 33% if greater than 3,000 mIU/mL [42]. †In one study, minimum declines from baseline to day one, day two, and day three after procedural management via uterine aspiration were 56%, 77%, and 83% [76]. ††Further monitoring with serial hCG testing and expectant management may be considered on a case-by-case basis.

Table 1. Definitions for ultrasonography findings in the setting of a positive pregnancy test.

IUP	Intrauterine gestational sac with a yolk sac or embryo (cardiac activity present or absent) implanted in a normal uterine location	
Probable IUP	Round or oval fluid collection in a normal uterine location	
PUL	No IUP or EP on transvaginal ultrasonography	
Probable EP	Inhomogeneous adnexal mass or extrauterine sac-like structure	
Definite EP	Extrauterine gestational sac with a yolk sac or embryo (cardiac activity present or absent)	

IUP, intrauterine pregnancy; PUL, pregnancy of unknown location; EP, ectopic pregnancy
Adapted from Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, et al. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. Fertil Steril 2011;95:857–66.
Images courtesy of Shuchi K. Rodgers, MD

Table 2. Key for GRADE recommendations. [a]

Symbol	Meaning
1	Strong recommendation
2	Weaker recommendation
A	High quality evidence
B	Moderate quality evidence

C	Low quality evidence, clinical experience, or expert consensus
Best Practice	A recommendation in which either (1) there is an enormous amount of indirect evidence that clearly justifies a strong recommendation, direct evidence would be challenging and inefficient use of time and resources to bring together and carefully summarize, or (2) a recommendation to the contrary would be unethical

[a] Society of Family Planning clinical recommendations use a modified GRADE system. The GRADE system is described in several publications, with a comprehensive set of articles in the Journal of Clinical Epidemiology (J Clin Epidemiology, (2011) 64:383-394, 64:395-400, 64:401-406, 64:407-415, 64:1277-1282, 64:1283-1293, 64:1294-1302, 64:1303-1312, 64:1311-1316, (2013) 66:140-150, 66: 151-157, 66:158-172, 66:173-183, 66:719-725, 66:726-735).

Table 3. Selected studies of mifepristone and misoprostol effectiveness in early pregnancy

Study and setting	Population	Intervention	Confirmation of abortion completion	Comparison/outcome
Schaff 2001 [77] Single center pilot study in New York, US	n=30 with PUL Positive pregnancy test and desired abortion; no GS on transvaginal ultrasonography	Mifepristone 200 mg orally and misoprostol 800 µcg vaginally one day later	hCG* level up to four days after misoprostol > 50% decrease, weekly urine pregnancy test until negative < 50% decrease, 2nd dose misoprostol and return visit 1-15 days later	Completed abortion, 25/30 (83.3%) Ongoing pregnancy, 2/30 (6.7%) EP, 2/30 (6.7%)
Fiala 2003 [67] Single center prospective study comparing hCG level and ultrasonography to confirm completed	n=217 Amenorrhea ≤ 49 days of gestation and desired medication abortion n=6 with PUL n=44 with probable IUP	Mifepristone 600 mg orally and misoprostol 400 µcg orally	Ultrasonography and hCG level 6-18 days after mifepristone 80% hCG decrease: PPV of 0.995	Completed abortion, 213/217 (98.2%) Outcomes not reported separately for PUL and probable IUP

medication abortion in Austria	n=167 with IUP			
Goldstone 2013 [53] Retrospective multicenter observational study in Australia	n=13,413 Amenorrhea ≤ 63 days of gestation and desired medication abortion n= 56 with PUL n=12 with probable IUP n=13,345 with IUP	Mifepristone 200 mg orally and misoprostol 800 µcg buccally	> 50% decrease in hCG level 5-7 days after treatment	PUL/probable IUP group, 1/68 (1.5%) Continuing pregnancies in PUL/probable IUP group, 5/67 (7.5%) Continuing pregnancies in IUP group, 83/13,345 (0.6%) *p*<0.001
Li 2017 [69] Randomized controlled trial of hospital- versus self-administered medication abortion in China	n=735 Amenorrhea ≤ 35 days of gestation and desired medication abortion n=520 with PUL n=215 with probable IUP	Mifepristone 75 mg and misoprostol 400 µcg orally	Hospital-administered medication abortion: hCG level three days after misoprostol if no histologic evidence of abortion > 50% decrease at three days followed weekly < 50% decrease followed every three days Self-administered medication abortion: urine hCG self-detection	Hospital-administered medication, 370 PUL, 260 Probable IUP, 110 Unconfirmed EP, 1 Ongoing pregnancies, 5 Complete abortion, 365/370 (98.6%) Self-administered medication, 365 PUL, 260 Probable IUP, 105 Unconfirmed EP, 2 Ongoing pregnancies, 3 Completed abortion, 357/365 (97.8%) Outcomes not reported separately for PUL and probable IUP
Bizjak 2017 [48] Retrospective case-note review in Austria (2004-2014) and Sweden (2012-2015)	n=2643 Gestations ≤ 49 days and desired medication abortion n=153 with PUL	Mifepristone 600 mg orally and misoprostol 400 µcg orally (Austria) Mifepristone 200 mg orally and	PUL/probable IUP group: > 50% decrease in hCG level seven days after treatment	Completed abortion in PUL group, 143/153 (93.5%) Complete abortion in probable IUP group, 977/988 (98.9%)

	n=988 with probable IUP n=1502 with IUP	misoprostol 800 µcg vaginally (Sweden)	IUP group: low-sensitivity urine pregnancy test 14-28 days after treatment	Complete abortion in IUP group, 1458/1502 (97.1%)
Jar-Allah 2022 [10] Retrospective case-note review in Austria (2004-2014) and Sweden (2012-2013)	n=682 Gestations ≤ 49 days and desired medication abortion n=106 with PUL n=576 with probable IUP	Mifepristone 600 mg orally and misoprostol 400 µcg orally (Austria) Mifepristone 200 mg orally and misoprostol 800 µcg vaginally (Sweden)	Austria: follow-up transvaginal ultrasonography and negative semiquantitative urine pregnancy test Sweden: > 80% decrease in hCG level 5-10 days after mifepristone	EP in PUL group, 5/106 (4.7%) Complete abortion in PUL group, 94/101 (93.1%) EP in probable IUP group, 1/576 (0.2%) Complete abortion in probable IUP group, 566/575 (98.4%)
Goldberg 2022 [14] Retrospective cohort study at an ambulatory clinic in Massachusetts, US	n=452 with PUL Last menstrual period of ≤ 42 days	Mifepristone 200 mg orally and misoprostol 800 µcg buccally OR Delay for diagnosis	50% decrease in hCG level 48-72 hours after misoprostol or 80% decrease by seven days after mifepristone	Took mifepristone, n=209 Unknown pregnancy outcome, n=39 Chose delay for diagnosis, n=122 Chose same-day medication abortion, n=48 Successful medication abortion, delay for diagnosis, 118/122 (96.7%) Successful medication abortion, same-day 41/48 (85.4%) *p*=0.013
Borchert 2023 [15] Retrospective cohort study at an ambulatory clinic in Minnesota, US	n=501 with PUL	Immediate uterine aspiration OR Mifepristone 200 mg orally and misoprostol 800 µcg buccally	Immediate uterine aspiration: visualization of gestational sac; if not seen, > 50% decrease in hCG level between baseline on	Chose immediate aspiration, n=109 Follow-up nonadherence, 19/109 (17.4%)

	OR Delay for diagnosis	day of aspiration and second measurement in 24-48 hours Same-day medication abortion and baseline hCG level < 2000 mIU/mL: > 50% decline 48-72 hours after misoprostol Delay for diagnosis: spontaneous decline by > 50% from baseline in 48-72 hours	EP, 8/109 (7.3%) Initial success, 80/109 (73.4%) IUP with initial treatment failure, 2/109 (1.8%) Chose same-day medication abortion, n=244 Follow-up non-adherence, 62/244 (25.4%) EP, 13/244 (5.3%) Initial treatment success, 144/169 (85.2%) IUP with initial treatment failure 25/244 (10.2%) Chose delay for diagnosis, n=148 Follow-up nonadherence, 56/148 (37.8%) EP, 10/148 (6.8%) Spontaneously resolved PUL, 65/148 (43.9%) Delayed treatment, 17/148 (11.5%, with 100% abortion completion) Lower abortion completion rate for same-day medication abortion (85.2%) vs immediate aspiration (97.6%), *p*=0.003

Tai 2023 [12] Retrospective database review at an abortion service in Edinburgh, UK	n=181 with PUL	VEMA or delayed treatment	≥ 80% decrease in hCG level seven days after mifepristone	VEMA group, 77/181 (42.5%) Delayed treatment group, 104/181 (57.5%) Lost to follow-up (entire cohort), 11/181 (6.1%) Similar EP rate for VEMA (2.6%) and delayed treatment group (5.8%), p=0.305 Similar abortion completion rate for VEMA (93.3%) and delayed treatment group (97.6%), *p*=0.256
Brandell 2024 [13] Multicenter noninferiority randomized controlled trial	n=1504 Gestations ≤ 42 days with probable IUP or PUL and desired medication abortion	Mifepristone 200 mg orally and misoprostol 800 µcg vaginally, sublingually ('early start'), or buccally or delayed treatment until IUP seen ('standard')	≥ 80% decrease in hCG level seven days after mifepristone	Intention to treat analysis n=729, early start 19, missing primary outcome data Complete abortion, 676/710 (95.2%) Ongoing pregnancy, 21/710 (3.0%) Surgical intervention for incomplete abortion, 13/710 (1.8%) n=715, standard 27, missing primary outcome data Complete abortion, 656/688 (95.3%) Ongoing pregnancy, 1/688 (0.1%)

		Surgical intervention for incomplete abortion, 31/688 (4.5%) Between-group difference -0.1 percentage points (95% CI -2.4 to 2.1, consistent with noninferiority) Outcomes not reported separately for PUL and probable IUP

CI, confidence interval; EP, ectopic pregnancy; GS, gestational sac; hCG, human chorionic gonadotropin; IUP, intrauterine pregnancy; PUL, pregnancy of unknown location; VEMA, very early medication abortion

*For this table, hCG refers to serum quantitative hCG.