



Approach to the patient with pregnancy of unknown location

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Literature review current through: **Feb 2025**.

This topic last updated: **Jan 21, 2025**.

INTRODUCTION AND DEFINITION

Pregnancy of unknown location (PUL) is a term used to describe the clinical scenario in which a patient with a positive pregnancy test has a transvaginal ultrasound (TVUS) that shows neither an intrauterine pregnancy (IUP) nor an ectopic pregnancy [1]. Importantly, this term is not a final diagnosis, but rather an entity that requires continued evaluation until a final diagnosis (ie, live intrauterine pregnancy, early pregnancy loss, ectopic pregnancy) is obtained [2,3].

Although the natural history of most PULs is an eventual IUP (either a live pregnancy or pregnancy loss), some pregnancies will be ectopic and can result in organ rupture and massive hemorrhage [4-8]. Thus, distinguishing between these entities is paramount as inappropriately early intervention could result in interruption of a desired ongoing IUP and delay in diagnosis of an ectopic pregnancy can result in severe maternal morbidity and even mortality.

The clinical manifestations, diagnosis, evaluation, and management of PUL are reviewed here. Related topics are discussed in detail separately and include:

- Diagnosis of ectopic pregnancy (see "Ectopic pregnancy: Clinical manifestations and diagnosis")
- Imaging of PUL (see "Ultrasonography of pregnancy of unknown location")
- Management of ectopic pregnancy (see "Ectopic pregnancy: Choosing a treatment")
- Management of pregnancy loss (see "Recurrent pregnancy loss: Management")

NATURAL HISTORY

The natural history of a PUL is difficult to ascertain due to global differences in the diagnostic approach and management of such patients. Historically, final diagnoses among patients with PUL are as follows [2]: ectopic pregnancy (6 to 20 percent) [4-8], intrauterine pregnancy (IUP; live or nonviable; 30 to 47 percent) [7-10], and pregnancies where the location is never confirmed (50 to 70 percent) [5-8,11].

Patients in whom the location is never confirmed will either have a **spontaneously** resolving PUL (where human chorionic gonadotropin [hCG] concentrations normalize without surgical or medical intervention) or a **persisting** PUL (where hCG concentrations do not normalize). Like the term PUL, persisting PUL is not a final diagnosis and possible final outcomes include [2]:

- Nonvisualized ectopic pregnancy: Rising or persistent hCG after uterine evacuation.
- Histologic IUP: Chorionic villi on pathology after uterine evacuation.
- Treated persistent PUL: Those treated medically without transvaginal ultrasound (TVUS) confirmation of pregnancy location, or surgically (including uterine evacuation).
- Resolved persistent PUL: Resolution of hCG after expectant management (ie, no medical or surgical therapy) or uterine evacuation without chorionic villi on pathology.

CLINICAL PRESENTATION

Patients with a PUL may present with symptoms of early pregnancy (eg, nausea, vomiting, fatigue, breast tenderness) or those more consistent with ectopic pregnancy (eg, irregular vaginal bleeding, abdominal pain). (See "Clinical manifestations and diagnosis of early pregnancy", section on 'Signs and symptoms' and "Ectopic pregnancy: Clinical manifestations and diagnosis".)

However, some patients may be asymptomatic and a diagnosis of PUL is made incidentally during evaluation of another medical problem or during routine laboratory testing after embryo transfer or other assisted reproductive technology treatment.

DIFFERENTIAL DIAGNOSIS

Because the term PUL can encompass any clinical scenario in which a patient has a positive pregnancy test but no visualized pregnancy, the differential diagnosis is quite broad and includes:

- Early intrauterine pregnancy (IUP; either live or demised) (see "Clinical manifestations and diagnosis of early pregnancy" and "Pregnancy loss (miscarriage): Clinical presentations, diagnosis, and initial evaluation")
- Ectopic pregnancy (see "Ectopic pregnancy: Clinical manifestations and diagnosis")
- Molar pregnancy (see "Hydatidiform mole: Epidemiology, clinical features, and diagnosis")
- Rare entities
 - Malignancy (eg, invasive mole, choriocarcinoma) (see "Gestational trophoblastic neoplasia: Epidemiology, clinical features, diagnosis, staging, and risk stratification")
 - Pituitary human chorionic gonadotropin (hCG) production (menopausal patients, rare genetic mutations) (see "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Pituitary hCG')
 - Heterophilic antibodies (see "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Interferents causing mostly false positive or falsely elevated results')
 - Laboratory error (see "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Analytical causes of erroneous results; antibody-related interference')

INITIAL EVALUATION

History and physical examination — A menstrual history is taken to estimate the gestational age (calculator 1). Risk factors for ectopic pregnancy are elicited, including prior ectopic pregnancy, prior tubal pathology (eg, pelvic inflammatory disease) or surgery (eg, tubal ligation), current use of an intrauterine device, and in vitro fertilization (IVF) (table 1). (See "Ectopic pregnancy: Epidemiology, risk factors, and anatomic sites", section on 'Risk factors'.)

Abdominal and pelvic examinations are performed. Although there are no distinct findings that are specific to PUL, findings suggestive of a possible ectopic pregnancy (eg, adnexal mass) or impending intrauterine pregnancy (IUP) loss (eg, bleeding from the cervix and an open cervical os), may prompt more expedited evaluation and management. (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'Step one: History and physical examination' and "Pregnancy loss (miscarriage): Clinical presentations, diagnosis, and initial evaluation", section on 'Perform physical and laboratory examinations'.)

Imaging — Transvaginal ultrasound (TVUS) is the mainstay of both the initial and subsequent evaluations in patients in whom PUL is suspected and its use in the assessment of a PUL cannot be overstated. A detailed review of ultrasound findings in PUL (including nonspecific findings such as a pseudosac or decidual cyst) is provided separately. (See "Ultrasonography of pregnancy of unknown location".)

Interpretation of TVUS findings should always consider the gestational age (if known with reasonable certainty) and the serum human chorionic gonadotropin (hCG) level. A gestational sac is not expected to be visualized in pregnancies less than five weeks [12].

The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) suggests that practices maintain a PUL detection rate of <15 percent [11]. However, rates of detection vary widely, and diagnostic performance is highly dependent on operator experience and the population evaluated. For example, studies have shown that 5 to 42 percent of patients undergoing TVUS during early pregnancy will be classified as having a PUL [4-6,13,14]; this range is narrowed to 8 to 10 percent in practices with specialized training [7,15]. Rates are typically lower in early pregnancy units (also referred to as early pregnancy assessment clinics) and low-risk populations (eg, no risk factors for ectopic pregnancy (table 1), regular menses with known last menstrual period [LMP]), and higher in patients in whom the gestational age is unknown or in emergency department evaluations where early pregnancy ultrasound experience may be more limited.

Categorization of findings — In 2011, an international panel of experts issued a consensus statement with suggested categories for classification of TVUS findings for patients undergoing evaluation for PUL [2]:

- Category 1: Definite ectopic pregnancy – Extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)
- Category 2: Probable ectopic pregnancy – Inhomogeneous adnexal mass or extrauterine sac-like structure
- Category 3: PUL – No signs of either ectopic pregnancy or IUP
- Category 4: Probable IUP – Intrauterine echogenic sac-like structure
- Category 5: IUP – Intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)

If given the classification of categories 1 or 5, a definitive diagnosis is made and PUL is excluded. By contrast, if given the classification of categories 2, 3, or 4, further diagnostic workup is needed. (See 'Subsequent testing in selected patients' below.)

Laboratory testing

- **Serum hCG concentration** – An initial serum quantitative hCG value serves to confirm pregnancy and inform subsequent TVUS findings. A single value of hCG does **not** confirm if a pregnancy is viable nor its location (ie, intrauterine or ectopic). As such, a single hCG value is not used to make management decisions.

The discriminatory zone, or the serum level of hCG where a gestational sac should be detected by TVUS if an IUP is present [16], should be used with caution, especially in patients with a desired pregnancy. This is described in detail separately. (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'hCG discriminatory zone' and "Ultrasonography of pregnancy of unknown location", section on 'Absence of findings'.)

- **Other** – Other laboratory testing may include complete blood count (in the setting of heavy bleeding and concern for symptomatic anemia), and renal and liver function tests (in the setting of suspected ectopic pregnancy and preparation for methotrexate treatment). (See "Ectopic pregnancy: Methotrexate therapy", section on 'Pretreatment evaluation').

Rh typing (for determination of need for anti-D immune globin) in early pregnancy is a point of active debate and is discussed in detail separately. (See "RhD alloimmunization: Prevention in pregnant and postpartum patients", section on 'Guidelines for prevention of anti-D alloimmunization (United States)' and "Pregnancy loss (miscarriage): Description of management techniques", section on 'Prevention of alloimmunization (RhD-negative patients)').

- **Limited role of serum progesterone** – In our practice, we do not routinely use serum progesterone as part of the diagnostic evaluation in patients with PUL. The use of serum progesterone in such patients is uncertain and cannot be used to distinguish pregnancy location (ie, intrauterine versus ectopic).

Furthermore, while serum progesterone was historically used to aid in determination of pregnancy viability, ranges of "normal" and "abnormal" levels (for live pregnancies) vary in the literature and predictive values of low progesterone in nonviable pregnancies differs among patients who conceive unassisted versus those who utilize assisted reproductive technologies [17]. In a meta-analysis including over 15,500 pregnant patients in early pregnancy with abdominal pain, uterine, cramping, or vaginal bleeding and evaluated with serum progestin levels, a level <6.3 ng/mL was consistent with a nonviable pregnancy (sensitivity 73 percent, specificity 99 percent) while a level ≥20 to 25 ng/mL was consistent with a confirmed live pregnancy (sensitivity 91 percent, specificity 75 percent) in the majority of patients [18]. Patients who utilized assisted reproductive technologies were excluded from the study.

The limited role of serum progesterone in patients with ectopic pregnancy and pregnancy loss is discussed in more detail separately. (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'Ancillary diagnostic tests' and "Pregnancy loss (miscarriage): Clinical presentations, diagnosis, and initial evaluation", section on 'Perform physical and laboratory examinations'.)

- **Investigational** – Use of serum biomarkers has been described [19], and may be useful as ancillary testing along with serum hCG and TVUS. Further studies are needed before these can be integrated into clinical practice.

SUBSEQUENT TESTING IN SELECTED PATIENTS

Following initial evaluation, selected patients (eg, hemodynamically stable patients with a desired pregnancy) undergo subsequent testing with both serial serum human chorionic gonadotropin (hCG) and transvaginal ultrasound (TVUS) assessment. For patients with hemodynamic instability or in whom the pregnancy is undesired, management can be expedited, and subsequent testing may not be needed. (See 'Management' below.)

hCG testing

- **hCG rise** – Serial serum human chorionic gonadotropin (hCG) measurements are typically obtained every 48 hours to determine if a pregnancy is normal (ie, ongoing intrauterine pregnancy [IUP]) or abnormal (ie, nonviable IUP, ectopic pregnancy). For patients in whom an initial hCG level is <10,000 mIU/mL, the expected rate of rise is dependent on initial hCG level and should be at least 49 percent for an initial hCG level of <1500 mIU/mL, 40 percent for an initial hCG level of 1500 to 3000 mIU/mL, and 33 percent for an initial hCG level of >3000 mIU/mL, respectively [20]. However, serial hCG values alone (without TVUS) **cannot** confirm the location of a pregnancy.

The same laboratory should be used for serial measurements since hCG results vary across different assays and laboratories [21].

- **hCG ratio** – The ratio of serum hCG levels at 48 hours and 0 hours may also be utilized for subsequent testing. A ratio of >1.66 (ie, an hCG rise >66 percent at 48 hours) is predictive of a viable IUP [14], whereas a ratio of <0.87 (ie, an hCG decrease of >13 percent at 48 hours) is suggestive of spontaneous pregnancy resolution (sensitivity 92.7 percent, specificity of 96.7 percent) [22]. If the hCG ratio is outside these bounds (ie, if the ratio of hCG at 48 to 0 hours is ≤ 1.66 but ≥ 0.87), then the possibility of an ectopic pregnancy or persistent PUL increases [7].

In a meta-analysis including observational studies evaluating the use of hCG to predict outcomes in patients with PUL, strategies utilizing hCG ratio to predict an ectopic

pregnancy had a sensitivity of 74 to 100 percent and specificity of 28 to 97 percent [23].

- **Logistic regression models** – The use of mathematical models (eg, "M4," "M6-P") have also been described and may reduce the number of visits, laboratory draws, and ultrasound assessments in patients with PUL. However, external validation of such models in diverse populations is needed prior to implantation into clinical practice. As with any clinical model, clinical judgement should supersede model prediction.

The M4 model uses the hCG ratio and log of the average hCG level to predict PUL outcome by estimating the risk of an ectopic pregnancy. In a multicenter external validation study including over 1900 patients, patients with a PUL were classified into low- (risk of ectopic pregnancy <5 percent) and high-risk (risk of ectopic pregnancy ≥5 percent) groups [24]. Low-risk patients were further categorized as those most likely to have spontaneously resolving PULs or IUPs; such patients were followed with a urine hCG in two weeks (spontaneously resolving PUL) or a TVUS in one week (IUP). By contrast, high-risk patients were followed with serial serum hCG and TVUS performed every 48 hours until a final diagnosis was made. Overall, approximately 70 percent of patients were classified as low risk and this classification was correct in approximately 97 percent of patients.

Approximately 85 percent of ectopic pregnancies were correctly classified as high risk. Subsequent applications of this model in other populations have not demonstrated the same high rates of accuracy [25].

The M6-P model is another logistic regression model that was developed as an extension of the M4 model and utilizes a serum progesterone level prior to the application of the hCG ratio. If the serum progesterone level is ≤2 nmol/L, patients are classified as low risk for ectopic pregnancy and managed with a urine hCG test in two weeks. All other patients receive hCG serum draws at 0 and 48 hours and are managed similarly to the M4 model. In a study of 2753 patients with PUL, the first step (ie, obtaining a serum progesterone alone) classified 16.6 percent of cases as low risk, but 2.9 percent of ectopic pregnancies were also classified as low risk [26]. Utilizing the two-step method, 62 percent of cases were classified as low risk (negative predictive value: 98.6 percent, sensitivity: 92 percent). Overall, 7.9 percent of ectopic pregnancies were initially classified as low risk [26].

Serial TVUS — The optimal interval at which to repeat transvaginal ultrasound (TVUS) is unclear. In our practice, we typically repeat the TVUS at three- to four-day intervals to facilitate earlier diagnosis and decrease the risks associated with delayed diagnosis of an ectopic pregnancy.

While some providers may wait to perform a subsequent TVUS until the hCG reaches the "discriminatory zone," discriminatory levels are not always reliable and some viable gestations may not be seen on TVUS using thresholds of 1500 mIU/mL, 2500 mIU/mL, or

even 3500 mIU/mL [27-29]. (See 'Laboratory testing' above and "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'hCG discriminatory zone'.)

MANAGEMENT

In general, initial management of a patient with PUL (ie, ultrasound categories 2, 3, and 4 (see 'Categorization of findings' above)) depends on the patient's hemodynamic stability and if the pregnancy is desired or undesired.

In all cases, continued frequent re-evaluation and assessment should occur throughout management as patients may quickly progress from stable to unstable, necessitating a timely change in patient management. Additionally, the provider and patient must utilize shared decision-making to balance the potential morbidity from an expectantly managed ectopic pregnancy and the interruption of a desired viable intrauterine pregnancy (IUP).

Hemodynamically unstable patients — Hemodynamically unstable patients are those experiencing large volumes of blood loss most likely from a ruptured ectopic pregnancy, or, less commonly, a hemorrhage from an early IUP loss. Such patients require immediate fluid resuscitation and surgical intervention (ie, abdominal exploration [typically with laparoscopy] and/or uterine evacuation).

Both procedures may be necessary: laparoscopy to allow removal of the ectopic pregnancy and hemoperitoneum, and uterine evacuation to inform further management and counseling regarding recurrence risks. In this way, surgery will be both diagnostic and therapeutic. However, the use of uterine curettage as a diagnostic tool is limited by the potential for disruption of a live pregnancy. This is discussed in detail separately. (See "Ectopic pregnancy: Clinical manifestations and diagnosis", section on 'Diagnostic evaluation' and "Ectopic pregnancy: Choosing a treatment".)

Hemodynamically stable patients — In hemodynamically stable patients, shared-decision making is guided by factors such as whether the pregnancy is desired or undesired, and if the patient prefers expedited resolution (and reduced frequency of follow-up testing).

- **Desired pregnancy** – For patients with a desired pregnancy, expectant management is with human chorionic gonadotropin (hCG) assessment every 48 hours and periodic transvaginal ultrasound (TVUS) assessment provided the patient remains stable and until a final pregnancy outcome (ie, ectopic pregnancy, IUP, treated PUL, resolved PUL) is confirmed ( algorithm 1).

For patients in whom hCG concentration is rising at expected rates of a viable pregnancy (see 'hCG testing' above), TVUS should be repeated in approximately one week, or sooner if there is an exacerbation of symptoms.

For patients in whom hCG concentration is declining, TVUS should be repeated only as clinically necessary and is not needed to confirm pregnancy resolution. A fall in serum hCG of 21 to 35 percent (depending on initial hCG level) over 48 hours suggests that the PUL is not viable and may support continued expectant management [30]. For such patients, the provider should again discuss the advantages and disadvantages of further expectant management versus surgical or medical treatment. Randomized trials including patients with PUL and falling hCG levels have shown that up to 40 percent of expectedly managed patients will ultimately undergo medical or surgical management [31,32].

An algorithm discussing appropriate candidates for expectant management when ectopic pregnancy is highly suspected is discussed elsewhere. (See "Ectopic pregnancy: Choosing a treatment", section on 'Medical versus expectant management'.)

- **Undesired pregnancy** – For those with an undesired pregnancy, choices for management include both proactive (ie, expedited or active) and expectant management (algorithm 2). Proactive management may reduce the number of follow-up tests (eg, ultrasound and serum hCG levels) and decrease the risks associated with a progressing ectopic pregnancy (eg, tubal rupture).

For patients choosing proactive management, a diagnostic uterine evacuation (with or without a laparoscopy in patients with an adnexal mass [33]) is typically performed. If chorionic villi are present, an IUP is confirmed, and no further management is necessary. The absence of chorionic villi on pathology, however, does not confirm the presence of an ectopic pregnancy. The sensitivity of curettage in finding chorionic villi is only 70 percent [34]. Pipelle endometrial biopsy is even less sensitive than curettage for detection of villi; sensitivities reported in two small series were 30 and 60 percent [35,36].

Thus, serial hCG concentrations are followed after uterine evacuation to assess for further decline, plateau, or rise, but can be discontinued if chorionic villi are present on final pathology. A fall in serum hCG of at least 15 to 20 percent suggests the pregnancy was intrauterine and serial hCG levels can then be followed until undetectable [37]. For patients in whom the hCG rises or plateaus, methotrexate may be used for subsequent management (if no contraindication to methotrexate use). This is discussed in detail separately. (See "Ectopic pregnancy: Choosing a treatment", section on 'Methotrexate therapy').

While proactive management is typical with uterine evacuation, immediate management with mifepristone and misoprostol has been described [38]. In a randomized trial of 1504 patients seeking medication abortion at ≤ 6 0/7 weeks of gestation and with a TVUS consistent with PUL, those receiving mifepristone plus misoprostol before confirmation of an IUP (early-start group) compared with after an IUP was confirmed (standard-care group) had similar rates of complete abortion [39]. For those without a complete abortion,

the early-start group had higher rates of ongoing pregnancy (3 versus 0.1 percent) but lower rates of surgical intervention (1.8 versus 4.5 percent). One patient in the early-start group had a ruptured ectopic pregnancy 25 days after medication abortion. Further studies are needed.

Patients with an undesired pregnancy undergoing expectant management are managed the same as for those with desired pregnancy (above).

SPECIAL CONSIDERATIONS

Management of persistent PUL — The term persistent PUL is used to describe gestations that begin as a PUL but are never visualized and do not resolve spontaneously. Approximately 2 percent of patients with an initial asymptomatic persistent PUL will ultimately experience tubal rupture [37].

For such patients, active management rather than expectant management may result in more successful resolution of the pregnancy. In a randomized trial including 255 patients with a persisting PUL, more patients receiving uterine aspiration and/or methotrexate compared with expectant management experienced successful resolution of their pregnancy without change in their initial management strategy (95 versus 56 percent, absolute difference 38.4 percent [95% CI 28.3 to 48.5], risk ratio [RR] 1.69) [37]. Success rates were similar for patients receiving either uterine evacuation (with or without methotrexate) or methotrexate alone but time to resolution was six days shorter in the group who received uterine evacuation. Ectopic pregnancy rupture requiring laparoscopy for definitive treatment occurred in a total of five patients (2 percent). The study had a high cross-over rate with patients preferentially crossing over to the expectant management group. The success of active management was higher in this trial than other trials [31,32,40], likely due to the use of two-dose (rather than single-dose) methotrexate which has been demonstrated to achieve higher success rates in the treatment of ectopic pregnancy [41]. This is discussed in detail separately. (See "Ectopic pregnancy: Methotrexate therapy", section on 'Comparing single-versus multiple-dose therapy'.)

Subsequent post-hoc analyses of this trial demonstrated that expectant management was more cost effective than uterine evacuation, but had a higher rate of salpingectomy compared with either methotrexate or uterine evacuation [42,43].

Persistent hCG elevations due to rare entities — The distinction between patients with a persistent PUL and those with a nonpregnancy-related cause of persistently elevated human chorionic gonadotropin (hCG) concentrations can be difficult. (See 'Differential diagnosis' above.)

Subsequent workup for rare entities responsible for elevations in hCG should be considered when patients do not fit the typical picture for having a gestational source of hCG or when other specific characteristics are present. For example, patients who are menopausal, perimenopausal, or who have recently undergone chemotherapy may have pituitary production of hCG, especially when levels are between 7 and 15 mIU/mL. In these cases, measurements of luteinizing hormone in the menopausal range and/or decline of hCG with estradiol supplementation confirms the pituitary as the source of hCG production. Additionally, patients with low hCG levels and a history of animal exposure (eg, farmers, veterinarians) may have heterophilic antibodies causing a false-positive elevation. These patients are easily triaged with the use of contemporary assays (that routinely include animal immunoglobulin) or assessing urine hCG (as heterophilic antibodies are too large to be filtered by glomeruli). (See "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Nonpathologic causes of low-level hCG elevations' and "Human chorionic gonadotropin: Biochemistry and measurement in pregnancy and disease", section on 'Interferents causing mostly false positive or falsely elevated results'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ectopic pregnancy" and "Society guideline links: Pregnancy loss (spontaneous abortion)" and "Society guideline links: Ultrasound imaging in pregnancy".)

SUMMARY AND RECOMMENDATIONS

- **Definition** – Pregnancy of unknown location (PUL) is a term used to describe the clinical scenario in which a patient with a positive pregnancy test has a transvaginal ultrasound (TVUS) that shows neither an intrauterine pregnancy (IUP) nor an ectopic pregnancy. This term is not a final diagnosis, but rather an entity that requires continued evaluation until a final diagnosis (ie, live IUP, early pregnancy loss, ectopic pregnancy) is obtained. (See 'Introduction and definition' above.)
- **Natural history** – Final diagnoses among patients with PUL include ectopic pregnancy (6 to 20 percent), IUP (live or nonviable; 30 to 47 percent), and pregnancies where the location is never confirmed (50 to 70 percent). Patients in whom the location is never confirmed will either have a spontaneously resolving PUL (where human chorionic gonadotropin [hCG] concentrations normalize without surgical or medical intervention) or a persisting PUL (where hCG concentrations do not normalize). (See 'Natural history' above.)

- **Clinical presentation** – Patients may be asymptomatic or may present with symptoms of early pregnancy (eg, nausea, vomiting, fatigue, breast tenderness) or those more consistent with ectopic pregnancy (eg, irregular vaginal bleeding, abdominal pain). (See 'Clinical presentation' above.)

- **Initial evaluation**

- TVUS is the mainstay of both the initial and subsequent evaluations in patients in whom PUL is suspected. Interpretation of TVUS findings should always consider the gestational age (if known with reasonable certainty) and the serum hCG level. (See 'Imaging' above.)
- A single value of hCG does **not** confirm if a pregnancy is viable nor its location (ie, intrauterine or ectopic). As such, a single hCG value is not used to make management decisions. (See 'Laboratory testing' above.)

- **Subsequent testing** – Subsequent testing with both serial serum hCG and TVUS assessment is used for selected patients (eg, hemodynamically stable patients with a desired pregnancy). For patients with hemodynamic instability or in whom the pregnancy is undesired, management can be expedited, and subsequent testing may not be needed. (See 'Subsequent testing in selected patients' above.)

- **Management**

- **Hemodynamically unstable patients** – Hemodynamically unstable patients (eg, patients with ruptured ectopic pregnancy or hemorrhage from an early IUP loss) require immediate fluid resuscitation and surgical intervention (ie, abdominal exploration [typically with laparoscopy] and/or uterine evacuation). (See 'Hemodynamically unstable patients' above.)
- **Hemodynamically stable patients with a desired pregnancy** – Hemodynamically stable patients with a desired pregnancy can be expectantly managed. Expectant management consists of hCG assessment every 48 hours and periodic TVUS assessment until a final pregnancy outcome (ie, ectopic pregnancy, IUP, treated PUL, resolved PUL) is confirmed (☞ algorithm 1). (See 'Hemodynamically stable patients' above.)
- **Hemodynamically stable patients with an undesired pregnancy** – For hemodynamically stable patients with an undesired pregnancy, we suggest proactive intervention rather expectant management (**Grade 2C**). Intervention, typically with uterine evacuation (with or without laparoscopy in patients with an adnexal mass), may reduce the number of follow-up tests (eg, ultrasound and serum hCG levels) and decrease the risks associated with a progressing ectopic pregnancy (eg, tubal rupture). However, expectant management is also a reasonable choice and may be preferred by some patients (☞ algorithm 2). (See 'Hemodynamically stable patients' above.)

- **Special considerations** – Patients with persistent hCG elevations or those in whom a nonpregnancy-related cause of persistently elevated hCG concentrations (eg, pituitary production, heterophilic antibodies) is suspected may be managed differently. (See 'Special considerations' above.)

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Topic 134770 Version 8.0

GRAPHICS**Risk factors for ectopic pregnancy compared with pregnant controls**

Degree of risk	Risk factors	Odds ratio
High	Previous ectopic pregnancy	2.7 to 8.3
	Previous tubal surgery	2.1 to 21
	Tubal pathology	3.5 to 25
	Sterilization	5.2 to 19
	IUD	
	▪ Past use	1.7
	▪ Current use	4.2 to 16.4
	▪ Levonorgestrel IUD	4.9*
	In vitro fertilization in current pregnancy	4 to 9.3
Moderate	Current use of estrogen/progestin oral contraceptives	1.7 to 4.5
	Previous sexually transmitted infections (gonorrhea, chlamydia)	2.8 to 3.7
	Previous pelvic inflammatory disease	2.5 to 3.4
	In utero DES exposure	3.7
	Smoking	
	▪ Past smoker	1.5 to 2.5
	▪ Current smoker	1.7 to 3.9
	Previous pelvic/abdominal surgery	4
	Previous spontaneous abortion	3
Low	Previous medically induced abortion	2.8
	Infertility	2.1 to 2.7
	Age ≥40 years	2.9
	Vaginal douching	1.1 to 3.1

Age at first intercourse <18 years	1.6
Previous appendectomy	1.6

IUD: intrauterine device; DES: diethylstilbestrol.

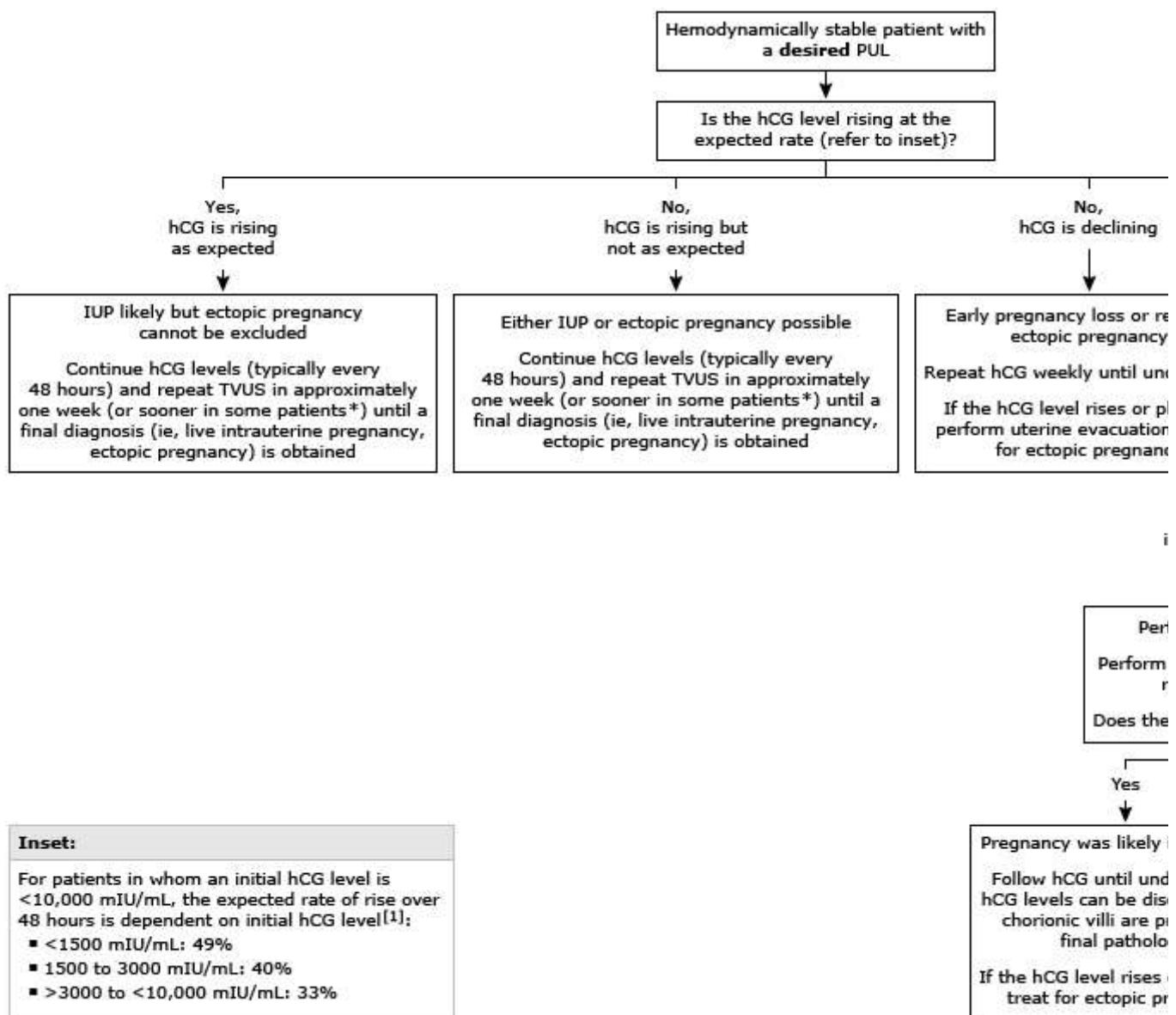
* Rates of ectopic pregnancy may be higher among those using the 13.5 mg compared with the 52 mg levonorgestrel IUD. This is discussed in related UpToDate content.

Data from:

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Graphic 82282 Version 10.0

Evaluation of PUL in a hemodynamically stable patient with a desired pregnancy



PUL is a term used to describe the clinical scenario in which a patient with a positive pregnancy test has a TVUS that shows neither an IUP nor an ectopic pregnancy. PUL may be asymptomatic or present with vaginal bleeding and/or abdominal pain. This algorithm does **not** apply to hemodynamically unstable patients or those with uncommon or rare etiologies including, but not limited to, the following: malignancy (eg, invasive mole, choriocarcinoma), pituitary hCG production, heterophilic antibodies. These are described in related UpToDate content. Patients with PUL and an undesired pregnancy are also managed differently.

PUL: pregnancy of unknown location; hCG: human chorionic gonadotropin; TVUS: transvaginal ultrasound; IUP: intrauterine pregnancy; MTX: methotrexate; IVF: in vitro fertilization.

* TVUS may be repeated sooner in patients with new or worsening symptoms or when the discriminatory zone is reached. The discriminatory zone is the serum hCG level above which a gestational sac should be visualized when an IUP is present. It varies by laboratory and institution and can range from 2000 to >3500 milli-international units/mL. Approximately 1% of IUPs will not be visualized on TVUS when the discriminatory zone is set at 3510 mIU/mL.

¶ Laparoscopy may also be performed in patients with an adnexal mass.

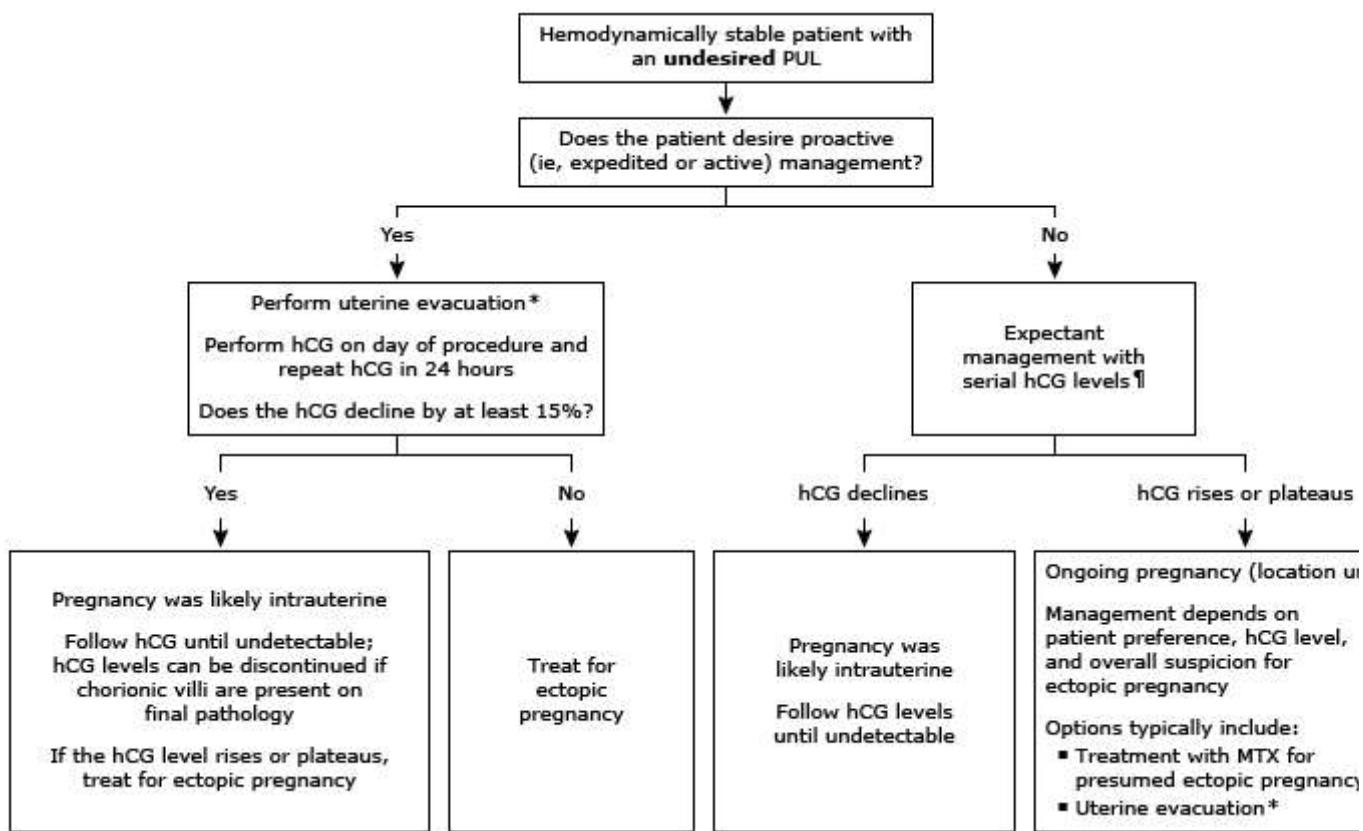
Δ Risk factors for ectopic pregnancy include, but are not limited to, prior ectopic pregnancy, prior tubal pathology or surgery (eg, pelvic inflammatory disease or tubal ligation), current use of an intrauterine device, and IVF.

Reference:

1. Barnhart KT, Guo W, Cary MS, et al. Differences in Serum Human Chorionic Gonadotropin Rise in Early Pregnancy by Race and Value at Presentation. *Obstet Gynecol* 2016; 128:504.
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Graphic 140926 Version 1.0

Evaluation of PUL in a hemodynamically stable patient with an undesired pregnancy



PUL is a term used to describe the clinical scenario in which a patient with a positive pregnancy test has a TVUS that shows neither an IUP nor an ectopic pregnancy. PUL may be asymptomatic or present with vaginal bleeding and/or abdominal pain. This algorithm does **not** apply to hemodynamically unstable patients or those with uncommon or rare etiologies including, but not limited to, the following: malignancy (eg, invasive mole, choriocarcinoma), pituitary hCG production, heterophilic antibodies. These are described in related UpToDate content. Patients with PUL and a desired pregnancy are also managed differently.

PUL: pregnancy of unknown location; hCG: human chorionic gonadotropin; TVUS: transvaginal ultrasound; IUP: intrauterine pregnancy; MTX: methotrexate.

* Laparoscopy may also be performed in patients with an adnexal mass.

¶ Serial hCG levels are typically obtained every 48 hours (initially) and may decrease in frequency depending on the rate of decline.

Graphic 140925 Version 1.0

Contributor Disclosures

Kurt T Barnhart, MD, MSCE No relevant financial relationship(s) with ineligible companies to disclose. **Kassie Bollig, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Courtney A Schreiber, MD, MPH** Patent Holder: Penn, Saul [Medical management of nonviable pregnancy]. Consultant/Advisory Boards: Exeltis [Advisory board, contraceptive technology R&D]. Other Financial Interest: American Board of Obstetrics and Gynecology [Member of Board of Directors, Chair of Division of Complex Family Planning]; Athenium Pharmaceuticals [Early pregnancy loss]. All of the relevant financial relationships listed have been mitigated. **Alana Chakrabarti, MD** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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