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Pregnancy of unknown location: A consensus statement of nomenclature, definitions and outcome

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Abstract

Objective—To improve the interpretation of future studies in women who are initially diagnosed with a pregnancy of unknown location (PUL), we propose a consensus statement with definitions of population, target disease and final outcome.

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Capsule:
Careful definition of populations and classification of final outcomes of women with a pregnancy of unknown location should enhance interpretation of research and lead to improved clinical care.

Methods—A review of literature and a series of collaborative international meetings were used to develop a consensus for definitions and final outcomes of women initially diagnosed with a PUL.

Results—Global differences were noted in populations studied and in the definitions of outcomes. We propose to define initial ultrasound classification of findings into five categories: definite ectopic pregnancy (EP), probable EP, PUL, probable intrauterine pregnancy (IUP), and definite IUP. Patients with a PUL should be followed and final outcomes should be categorized as visualized EP, visualized IUP, spontaneously resolved PUL and persisting PUL. Those with the transient condition of a persisting PUL should ultimately be classified as non-visualized EP, treated persistent PUL, resolved persistent PUL, or histological IUP. These specific categories can be used to characterize the natural history or location (intra- vs. extrauterine) of any early gestation where the initial location is unknown.

Conclusions—Careful definition of populations and classification of outcomes should optimize objective interpretation of research, allow objective assessment of future reproductive prognosis and hopefully lead to improved clinical care of women initially identified to have a PUL.

Keywords

Nomenclature; pregnancy of unknown location; international consensus; ectopic pregnancy

INTRODUCTION

Ectopic pregnancy (EP) occurs in about 1-2% of pregnant women and may compromise a woman's health and future fertility (1). The most common clinical complaints suggestive for EP are symptoms of abdominal pain and/or vaginal bleeding. Unfortunately, these symptoms are neither sensitive nor specific for the diagnosis of EP and some women remain asymptomatic for a long portion of the disease progression. Practice guidelines, derived from evidence based literature, aim for an accurate and early diagnosis of EP to limit the morbidity and mortality resulting from this condition (1-5). If diagnosed early, an EP can be treated medically with systemic methotrexate (MTX) or with minimally invasive surgery (6).

There is a worldwide consensus regarding the utility of transvaginal ultrasound (TVS) and (serial) quantitative serum human chorionic gonadotrophin (hCG) concentrations in the diagnosis of EP. Diagnosis can be straightforward when TVS definitively identifies an intrauterine pregnancy (IUP) or EP (1,6-13). However, the location of a gestation after TVS can be inconclusive in a substantial number of women (10,13-15). This situation is termed a pregnancy of unknown location (PUL), necessitating further diagnostic tests and follow-up to achieve a final diagnosis (10).

Protocols using various diagnostic algorithms have been published to predict the pregnancy outcome and ultimately diagnose women who are initially classified as having a PUL (8,14,16-25). In 2006, a consensus statement was published regarding the diagnosis and management of women with a PUL (10). However, in practice, differences and controversies in the approach and management of PUL still remain, likely due to differences in definitions of the population at risk and the classifications of final outcomes. To improve the ability to generalize future study findings of women who are initially diagnosed with a PUL, we propose a consensus statement with definitions of population, target disease and final outcome.

METHODS

To formulate this consensus statement, we conducted a review of recent literature and collected data regarding populations in preparation for collaborative meetings in London (January 2009), Hamburg (September 2009), and Atlanta (October 2009). We developed a consensus for definitions and descriptions of populations.

RESULTS

The results of the review are presented in Tables 1 and 2 and summarized below.

Global differences in diagnostic strategy

There are differences in the diagnostic strategy based on geography. In the UK and mainland Europe, it has been advocated that the use of two serum hCG concentrations assessed 48 hours apart, expressed as a ratio, can predict the outcome of women with a PUL with good accuracy (7,8,27,29). The strategy in the USA is to follow serial serum hCG concentrations until these levels deviate from what is expected for a potential viable gestation or miscarriage (33-35). Others have advocated the use of serum progesterone as an adjuvant in the diagnostic process (17,26,36,37). Condous *et al*. demonstrated that additional use of clinical signs and symptoms upon presentation does not improve the accuracy of prediction based on the initial two serum hCG concentrations (38). In contrast in the USA, Barnhart *et al.* have demonstrated very good prediction of final outcome of women at risk for EP solely from presenting clinical signs and symptoms (39,40). The American strategy for the diagnosis of women at risk for EP is relatively aggressive, advocating intervention and at times uterine curettage to distinguish a nonviable IUP from an EP (32). The UK and European strategy is more conservative, relying more on ultrasound diagnosis, and advocating more extended follow up of women with a PUL without intervention (41-44). In order to objectively compare strategies, it is important to first ensure that the nomenclature and definitions of final outcomes are consistent internationally.

Populations studied in the literature

Inclusion criteria for the populations studied in various manuscripts are often not clearly specified and there is a large degree of variation. Differences include dissimilarities in initial point of contact, evaluation and referral to other healthcare providers, as well as the diagnostic ultrasound criteria. Many manuscripts originating from the USA report the evaluation of women who have presented to an emergency department and do not receive a definitive diagnosis at presentation. This includes women with an ultrasound suggestive of, but not definitive of, an intrauterine or extrauterine gestation or with inconclusive scans. The TVS is usually performed by a radiologist covering the emergency department. Women without a definitive diagnosis are then referred to a gynecologist for follow up (18,35).

The populations evaluated in the manuscripts from the UK and European countries are often symptomatic and asymptomatic women who are evaluated within specialized early pregnancy units (45-47). The initial contact is with a gynecologist or clinical nurse specialist who performs both the clinical evaluation and the TVS and arranges any further review. Because criteria for diagnosis of an IUP or EP are more liberal, more women may be diagnosed at the initial scan. Follow up is therefore limited to women who meet a more strict definition of a PUL (48,49).

Definitions used in the literature

In many cases the final diagnostic outcome of a PUL, such as an IUP or EP, is made by TVS instead of histology. The ultrasound criteria used to make the diagnosis differ in the

manuscripts published and this affects both the population evaluated (as described above) as well as the classification of final outcome.

○ **Pregnancy of Unknown Location—**PUL is a descriptive term applied to women with a positive pregnancy test who have no evidence of either an IUP or EP on TVS. However, this term is a classification and not a final diagnosis. PUL is not always defined consistently in the literature (Table 1), but there is consensus that women with a PUL should be followed until a final diagnosis can be made. A clinical dilemma is weighing the risk of morbidity due to an EP against the morbidity associated with interventions used to achieve a definitive diagnosis and treatment. However, a definitive location of a PUL cannot always be determined even with ultrasound follow up, because both a miscarriage and an EP may resolve without intervention. The final outcomes of women with a PUL in the literature originating from the USA have been categorized into three groups: IUP, EP and miscarriage or spontaneous abortion (SAB). The literature from the UK and European countries has stratified final outcomes into four categories: IUP, EP, failed PUL and persisting PUL.

○ **Intrauterine Pregnancy—**In studies originating from USA, the diagnosis of an IUP is usually considered definitive only when a yolk sac or embryo is identified within an intrauterine gestational sac (unless the woman has a certain nonviable intrauterine gestation including an empty sac (anembryonic gestation), early fetal demise (embryonic demise) or retained trophoblast tissue (incomplete miscarriage)) (50). These outcomes would all be classified as miscarriage or SAB. In studies originating from UK and European countries, the definition of IUP includes women with an identified intrauterine gestational sac regardless of the findings of a yolk sac or embryo, and regardless of viability.

○ **Miscarriage and Failed Pregnancy of Unknown Location—**In the USA, women with spontaneous resolution of serum hCG levels are classified as a completed miscarriage and are included in the spontaneous abortion (SAB) category. The outcome definition “miscarriage” also includes women who underwent dilation and curettage with histological identification of chorionic villi, or with negative chorionic villi but postoperative resolution of serum hCG. In the UK and European countries, women in whom the serum hCG resolved without intervention are diagnosed as having a failed PUL on the basis that the location of the pregnancy has never been confirmed. Intervention with uterine curettage is rarely reported in the literature originating from the UK and European countries (42).

○ **Ectopic Pregnancy and Persisting Pregnancy of Unknown Location—**In manuscripts originating from the USA, the ultrasound criteria to diagnose an EP include only the findings of an extrauterine gestational sac with the visualization of a yolk sac or embryo. Other diagnostic criteria for an EP are increasing serum hCG levels after uterine evacuation. In the manuscripts originating from UK and European countries, the ultrasound diagnosis of an EP is more liberal including the finding of an extrauterine inhomogeneous mass (blob sign), or an extrauterine empty gestational sac (bagel sign) (15,51). If no IUP or EP is visualized by TVS but women have a plateau or rise in serial serum hCG concentrations, the situation is classified as a persisting PUL. Some women with a persisting PUL are managed expectantly without surgical intervention or are treated with systemic MTX. The literature provides neither a precise definition for when to classify a persisting PUL nor when medical management versus expectant management is recommended. Practice varies in these regards.

Consensus Statement with Definitions of Population, Target Disease and Outcome

Differences in the criteria used to describe women with a PUL can result in potentially meaningful differences in populations reported in the literature. There was consensus that

the final outcomes of a woman with a PUL were not clearly and consistently used in all manuscripts. It was agreed that careful definition of populations and classification of final outcomes are essential so that both past and future research can be interpreted correctly.

Description of Population

A study population must be defined clearly if results are to be interpreted appropriately. It is proposed that study populations should be optimally described by listing the criteria used to make a diagnosis of IUP or EP, and clarifying which women were followed until a final diagnosis was made and which women were not evaluated further.

The following categorization for ultrasound diagnosis is proposed (Figure 1):

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

At presentation, a woman can be classified as being in one of the five categories based on ultrasound findings. When classified as Probable EP, PUL or Probable IUP (category 2, 3, or 4) a woman can shift to Definite EP or Definite IUP (category 1 or 5) during the diagnostic process. Categories 1 and 5 are considered definitive diagnostic classifications.

Another essential factor to include in the description of the population is information that may have an impact on the underlying risk of EP. For example, it should be stated if the population includes symptomatic women (abdominal pain and/or vaginal bleeding), women at risk for EP without clinical symptoms (such as women who have had a previous EP or tubal surgery, who have conceived with assisted reproduction techniques (ART), who have a tubal ligation or IUD in place, or have a history of salpingitis) (52), or asymptomatic, low risk women presenting for hyperemesis, dating, or reassurance.

Definition of final outcomes

There was consensus that final outcomes reported in manuscripts should be as definitive as possible, to avoid the use of active or present tense terms (i.e. failing, resolving) and to be as comprehensive as possible. It is important to specify the criteria used to make a diagnosis of EP or IUP so that the reader can judge the level of certainty. For example, the ultrasound criteria used to diagnose an EP or IUP should be clearly stated. Of additional importance is the documentation of the ultrasound criteria used to classify the various categories of a nonviable IUP (50,53).

The following categorization of final outcomes of women with a PUL is proposed (Figure 2):

1 A visualized EP; this is a confirmed EP identified by TVS or at the time of surgery. As there are differences in criteria used for ultrasound diagnosis, the criteria used should be explicitly stated in a manuscript.

2 A visualized IUP; this is a confirmed IUP identified by TVS, regardless of the viability. However, whenever possible this category should be further subdivided based on viability:

- ○ viable IUP (normal ultrasound milestones for gestational age)
- ○ IUP of uncertain viability (definitive ultrasonic evidence of an IUP but milestones are insufficient to state if the gestation is viable) or
- ○ nonviable intrauterine gestation (definitive ultrasonic evidence of empty sac, embryonic demise, or retained trophoblastic tissue).

3 A spontaneously resolved PUL; this term should be used for women who start as having a PUL but have a spontaneous resolution of serum hCG to undetectable levels without surgical or medical intervention. This definition takes into account that the exact location of the gestation is never identified.

A persisting PUL is used to describe a gestation that starts as a PUL that is followed with serial serum hCG levels and/or TVS but is neither visualized nor resolves spontaneously. Similar to the term PUL, the term persisting PUL is a classification and not a final diagnosis. The final outcome of a persisting PUL is dependent on intervention or therapy as per local standards. Final outcomes include:

4 A non-visualized EP is defined as a rising serum hCG level after uterine evacuation.

5 A treated persistent PUL is defined as those who are treated medically without confirmation of the location of the gestation by TVS, laparoscopy or uterine evacuation.

6 A resolved persistent PUL is defined as resolution of serum hCG levels after expectant management or after uterine evacuation (without medical therapy) without evidence of chorionic villi on pathology.

7 A histological IUP is defined as identification of chorionic villi in the contents of the uterine evacuation.

This proposed classification system was designed to reflect the natural history and diagnostic approach of women with a PUL. Ultimately, these definitions can be collapsed to best describe the final location of the gestation, which may better be used for the purposes of determining reproductive prognosis. When collapsed, the final categories are EP, IUP, treated PUL or failed PUL (Figure 3).

DISCUSSION

Around the globe, research is ongoing in women at risk for EP who are initially classified by TVS as having a PUL. Active research is focusing on the optimal surveillance, diagnostic criteria and treatment strategies in these women. New diagnostic procedures and predictors of final outcomes in women with a PUL have resulted in the earlier diagnosis of women with EP, reducing both morbidity and mortality of this disease. Not unexpectedly, differences in management and clinical care have arisen in different healthcare environments. There is consensus regarding the utility of quantitative serial serum hCG values and ultrasound for the diagnosis of EP in women initially classified as having a PUL. Serum progesterone measurements may also help to identify women at risk for EP, but the discriminative capacity is insufficient to diagnose EP with certainty (21,36).

The goal of this manuscript is not to advocate one specific strategy, but to highlight that differences in definitions of populations and final outcomes have made the interpretation of current medical literature regarding women with PUL problematic. As such, it has been difficult to validate and extrapolate study findings from one geographical area to clinical practice in another.

The specification of populations studied is important for clinical research. Differences in a priori risk of a disease and prevalence of a disease will affect the diagnostic test characteristics. It was only after face to face discussions between US, UK, and European research groups that fundamental differences in the populations under study were appreciated. For example, the populations studied in manuscripts from the USA have included women from ultrasound category 2, 3 and 4, while the populations under study from manuscripts from the UK have included only women in ultrasound category 3 (see Figure 1). Transparency and completeness in the description of study populations will limit future misinterpretation.

Defining final outcomes is also important for quality clinical research. There are still knowledge gaps and great variations in the natural history of miscarriage and EP. While it is recognized that it is not possible to definitively diagnose all women at risk for EP, a clear definition of final outcomes is pivotal for interpreting the findings of clinical research studies. The definitive ascertainment of ultimate viability of an IUP is beyond the scope of this manuscript. However, clear definitions and frequency of sub-outcomes of women with an IUP using suggested terms such as viable, nonviable or uncertain viability will allow objective comparison of the findings of future studies.

The definitions we have proposed are designed to reflect current diagnostic and surveillance strategies for women with a PUL. As the diagnostic process continues, the aim is that all women with an initial ultrasound classification of a PUL should have an ultimate diagnosis of an IUP, an EP or spontaneous resolution of a pregnancy which remains of unknown location. A second transient time point during the diagnostic process of women with a PUL is when a diagnosis is not apparent after serial evaluations and a woman is defined as having a persisting PUL. The approach to clinical care in different areas reflects how the clinician balances tolerance of potential morbidities from diagnostic measures against perceived risks of a delay in diagnosis or the need for a definitive diagnosis. The ability to determine the final outcome of a woman with a persisting PUL depends upon local thresholds for further diagnostic or therapeutic intervention.

The specificity of the final outcomes proposed was designed to allow investigators and clinicians to potentially reclassify outcomes to match their interests. If the goal is to develop a test or procedure to aid in determination of follow-up frequency for women at risk for tubal rupture, one may wish to compare women with a persisting PUL (and its subcategories) to situations where serial TVS is able to diagnose an IUP or EP. The definition of histological IUP captures inherent differences in the clinical course of a woman with a slow decline or plateau in the serial hCG levels who was found to have chorionic villi on uterine evacuation and a woman with rising serial hCG levels noted to have an IUP confirmed by TVS on a subsequent visit.

An alternate research interest may be to distinguish an IUP from an EP regardless of the time or steps necessary to make a definitive diagnosis. In this situation, the histological IUP category can be combined with the visualized IUP category. Similarly, the non-visualized EP category can be combined with the visualized EP category. Another important area of clinical research would be to establish criteria for expectant management of women with PUL. Research could focus on categories in which there is equipoise between expectant management and intervention. When such research confirms that expectant management is safe and accepted by women, diagnostic criteria can be adjusted and new studies can be started.

Research will continue to define the optimal approach to women at risk for EP. By using more precise and consistent language in the descriptions of patients, their risk factors and

their diagnoses, one can focus on strategies to identify women who need increased surveillance, as opposed to those whose pregnancies are likely to resolve spontaneously without intervention. Our proposed nomenclature will optimize objective interpretation of future research and the ability to objectively assess future reproductive prognosis. Ultimately, consensus should aid in the generalizability of study results and potentially lead to improved clinical care. It is strongly encouraged that from now on the frequency and percentage of women categorized into each initial classification group and subsequent final outcome and sub-outcome group should be included in each paper on women with a PUL.

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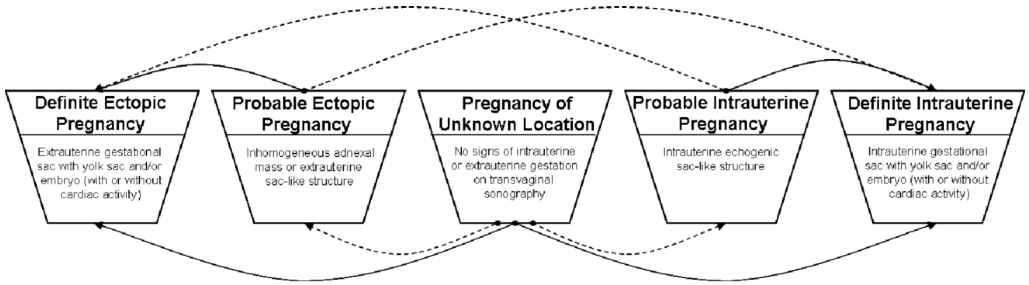

FIGURE 1.
Classification of ultrasound findings for a woman with a positive pregnancy test

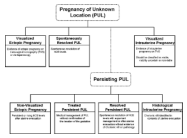

FIGURE 2.
Classification of final outcomes for women with an initial ultrasound classification of pregnancy of unknown location based on clinical management

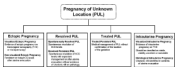

FIGURE 3.
Classification of final outcomes for women with an initial ultrasound classification of pregnancy of unknown location based on location

Table 1

Review of the literature on PUL: population, inclusion criteria and methods

First author	Year	Country	Setting	Data collection	n	Population	Inclusion criteria	Exclusion criteria	Diagnostic method
El bishry (26)	2008	UK	University hospital	Retrospective	126	Signs and symptoms suggestive of EP	TVS inconclusive scan	TVS: Intrauterine gestational sac/fetal pole TVS: Presence of EP	P < 16 hCG > 25 P 16-80 hCG > 25 P >80 hCG < 1000 P > 80 hCG > 1000
Kirk (27)	2007	UK	EPU	Prospective interventional	363	Vaginal bleeding, lower abdominal pain, unsure date, previous EP, spontaneous abortion, maternal anxiety	TVS no evidence IUP/ EP	Clinical instability or signs hemoperitoneum on TVS hCG > 10.000 IU/L (for modeling purposes)	Initial hCG > 1000 IU/L without history of heavy bleeding → repeat scan within 24h M4 logarithm of hCG average, hCG ratio and quadratic effect
Florio (28)	2007	Italy	Tertiary referral center for obstetric care	Prospective observational	536	Vaginal bleeding, pain, cramping	TVS no clear evidence of IUP, retained products of conception, or an EP	Clinical instability, hemoperitoneum, product of conception visualized on speculum examination	Expectant management, revision every 3 days, serial hCG. Surgical intervention based on hCG ratio over 48 h or clinical symptoms
Condous (29)	2007	UK	EPU	Prospective observational	376	lower abdominal pain, with or without vaginal bleeding, poor obstetric history, TVS to determine gestational age	Positive pregnancy test TVS no sign of IUP or EP or retained products of conception	TVS any evidence of intrauterine gestational sac, adnexal mass thought to be EP; endometrial thickness > 15mm with heterogeneous irregular tissues within the uterus; clinical instability or signs of intra abdominal bleeding or hemoperitoneum on TVS	Serial TVS and hCG monitoring
Hahlin (7)	1995	Sweden	University hospital	Prospective	80	Bleeding or mild pain Suspected pregnancy and risk factors for EP	TVS failure to identify location gestational sac	Clinical instability, indirect sign pregnancy location such as open cervical canal	Risk score EP according to Thorburn (1986); hCG measurement within 24-72h
Hajenius (8)	1995	NL	University hospital	Prospective study	265	Positive pregnancy test and vaginal bleeding ±	TVS no visible pregnancy and hCG < 1500 IU/L	-	Serial TVS and hCG monitoring every 48 h

First author	Year	Country	Setting	Data collection	n	Population	Inclusion criteria	Exclusion criteria	Diagnostic method
						abdominal pain and/or risk factors, and patients on routine examination.			
Rivera (30)	2009	USA	General hospital	Prospective cohort study	23	-	TVS no evidence IUP/EP and hCG > 2000 IU/L or hCG < 2000 IU/L with abnormal rising levels < 66% in 48 h	Clinical instability, TVS evidence of EP/IUP, heavy vaginal bleeding suggestive of passage of tissue, inability to tolerate outpatient manual vacuum aspiration	Manual vacuum aspiration
Dart (31)	2002	USA	University hospital	Prospective observational	635	Abdominal pain or vaginal bleeding	TVS indeterminate, not diagnostic of IUP nor suggestive or diagnostic of an EP	TVS complex adnexal mass separate from ovary, extra uterine sac-like structure, moderate to large amount of anechoic fluid or any echogenic fluid in cul de sac; Patient who recently delivered; passed definite products of conception; patient status after D&C	Serial TVS
Barnhart (32)	2002	USA	Tertiary care medical center	Retrospective cohort study	112	-	TVS no visible IUP/EP and hCG > 2000 IU/L or plateauing hCG < 2000 IU/L	-	D&C before treatment

PUL pregnancy of unknown location; IUP intrauterine pregnancy; EP ectopic pregnancy; P progesterone; TVS trans vaginal ultrasound; EPU early pregnancy unit; D&C dilation and curettage

Table 2

Review of the literature on PUL: final outcome definitions

First author		Country	IUP	EP	Miscarriage	Failed PUL	Persistent PUL
El bishry (26)	2008	UK	-	-	-	-	-
Kirk (27)	2007	UK	TVS intra uterine gestational sac ± fetal pole ± cardiac activity, or heterogeneous tissue within endometrial cavity suggestive of retained products of conception	TVS blob sign, bagel sign, ectopic gestational sac with/without cardiac activity	-	hCG ratio < 0.87 day 0/7	Analyzed as EPs
Florio (28)	2007	Italy	TVS intra uterine gestational sac	TVS adnexal mass, final diagnosis at laparoscopy and histology	Histology after evacuation of uterine contents	Spontaneous decrease of hCG to < 5 IU/L, with disappearance of symptoms	-
Condous (29)	2007	UK	TVS intra uterine gestational sac	TVS blob sign, bagel sign, ectopic gestational sac with/without cardiac activity and/or laparoscopy with histology of chorionic villi	-	P < 20nmol/L at presentation + fall in serum hCG < 5IU/L	Treated with MTX, location remains unknown, excluded in analysis
Hahlin (7)	1995	Sweden	-	Laparoscopic diagnosis	Histology after evacuation of uterine contents	Spontaneous resolution	-
Hajenius (8)	1995	NL	-	Strong suspicion EP thus indication for laparoscopy: Repeatedly negative TVS and hCG > 1000 IU/L. Plateauing hCG during follow-up.	-	Trophoblast in regression, declining hCG during follow-up in a patient with a harmless clinical picture. Analyzed as no EP	-
Rivera (30)	2009	USA	Not applicable	hCG decrease < 50% after D&C and no chorionic villi at pathology	Abnormal IUP: hCG decrease ≥ 50% with chorionic villi Complete SAB: hCG decrease ≥ 50% without chorionic villi	-	-
Dart (31)	2002	USA	Delivery or fetal heartbeat at TVS	EP visualized at laparoscopy, EP at follow-up TVS examination, hCG levels increase or plateau after D&Cand without villi at pathology	TVS abnormal sac, echogenic material, hCG > 3000 without intra uterine sac or decreasing hCG levels before curettage and evidence of chorionic villi at pathology No villi after curettage but hCG levels decreasing to zero without intervention No curettage and hCG levels that decrease to zero without intervention	-	-

First author		Country	IUP	EP	Miscarriage	Failed PUL	Persistent PUL
Barnhart (32)	2002	USA	Not applicable	Absence of chorionic villi or an increase in hCG after D&C, presence of chorionic villi in tube after laparoscopy	Presence of chorionic villi at pathology or consistent decline with complete resolution of hCG post operatively	-	-

PUL pregnancy of unknown location; IUP intrauterine pregnancy; EP ectopic pregnancy; D&C dilation and curettage