Pregnancies of unknown location: update on nomenclature and final outcomes

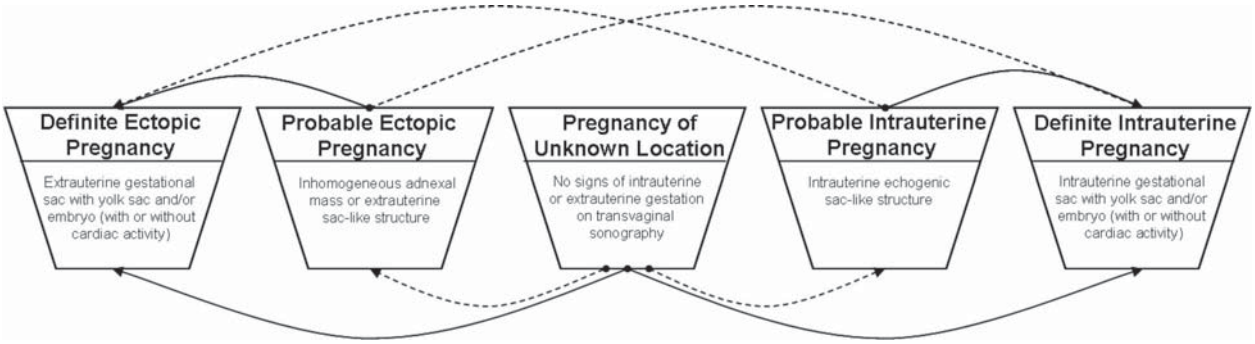

Figure 1: Categorisation for ultrasound diagnosis of a woman with a positive pregnancy test (with permission from Barnhart, *et al. Fertil Steril* 2011 1; 95 (3): 857–66).

Ectopic pregnancy occurs in 1–2% of pregnancies and is the leading cause of maternal mortality in the first trimester; accounting for up to 15% first trimester deaths. There is a worldwide consensus regarding the use of transvaginal ultrasound (TVS) and (serial) quantitative serum human chorionic gonadotrophin (hCG) levels in the diagnosis of ectopic pregnancy. Diagnosis can be straightforward when TVS definitively identifies an intra-uterine pregnancy (IUP) or an ectopic pregnancy. Both TVS diagnoses are made based upon either the positive visualisation of either an intra-uterine gestational sac or an adnexal mass separate to the ovary. However, in a substantial number of women, the location of a gestation after TVS can be inconclusive. This situation is termed a pregnancy of unknown location (PUL), necessitating further diagnostic tests and follow-up to achieve a final diagnosis.

Approximately 10% of women who present to an Early Pregnancy Unit (EPU) for a first trimester TVS will be classified with a PUL. This is not a pathological entity but rather an ultrasound classification defined on TVS when there is no intra- or extra-uterine pregnancy visualised and the absence of retained products of conception. According to many published data, on follow up, ectopic pregnancies account for 8–14% of women classified with a PUL. Therefore it is of great importance that clinicians follow up women with a PUL until either the pregnancy is located or found to have failed spontaneously. There are four final pregnancy outcomes in women initially classified with a PUL and these include: failed PUL, intra-uterine pregnancy (IUP), ectopic pregnancy, or persisting PUL.

In a recent consensus statement in Fertility Sterility, by Barnhart, *et al*. 2011, on PUL nomenclature, definitions and outcome, the expert panel agreed that "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 PUL final outcomes of a woman in the current literature were not clearly and consistently used. It was therefore decided that careful definition of populations and classification of final outcomes were essential so that both past and future research could be interpreted correctly.

The panel proposed the following categorisation for first trimester ultrasound diagnosis (see Figure 1):

1 *Definite ectopic pregnancy*: extra-uterine gestational sac with yolk sac and/or embryo (with or without cardiac activity) on TVS.
2 *Probable ectopic pregnancy*: inhomogeneous adnexal mass ("bagel" sign) or extra-uterine sac-like structure on TVS.
3 *PUL*: no signs of either ectopic pregnancy or IUP on TVS.
4 *Probable IUP*: intra-uterine echogenic sac-like structure eccentrically placed within the endometrial cavity on TVS.
5 *Definite IUP*: intra-uterine gestational sac with yolk sac and/or embryo (with or without cardiac activity) eccentrically placed within the endometrial cavity on TVS.

Therefore at presentation, women who present to an EPU for an early pregnancy ultrasound, can be classified with one of the five aforementioned categories based upon their TVS findings.

There was also consensus that final PUL outcomes reported in the literature should be as definitive as possible. Active or present tense terms such as "failing" or "resolving" PULs should also be avoided in presented manuscripts. It was also the panel's opinion that the audience be able to understand the criteria used to diagnose ectopic pregnancy or IUP as well as have an appreciation of the certainty of the diagnosis. In other words, the ultrasound criteria used to diagnose an EP or IUP should be clearly documented as too should the criteria used to classify the various categories of a non-viable IUP.

The panel also proposed the following categorisation of PUL final outcome based upon pregnancy location (see Figure 2):

1 Ectopic pregnancy

- Visualised ectopic pregnancy; this is a confirmed ectopic pregnancy 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.
- Non-visualised ectopic pregnancy is defined as a rising hCG level after uterine evacuation.

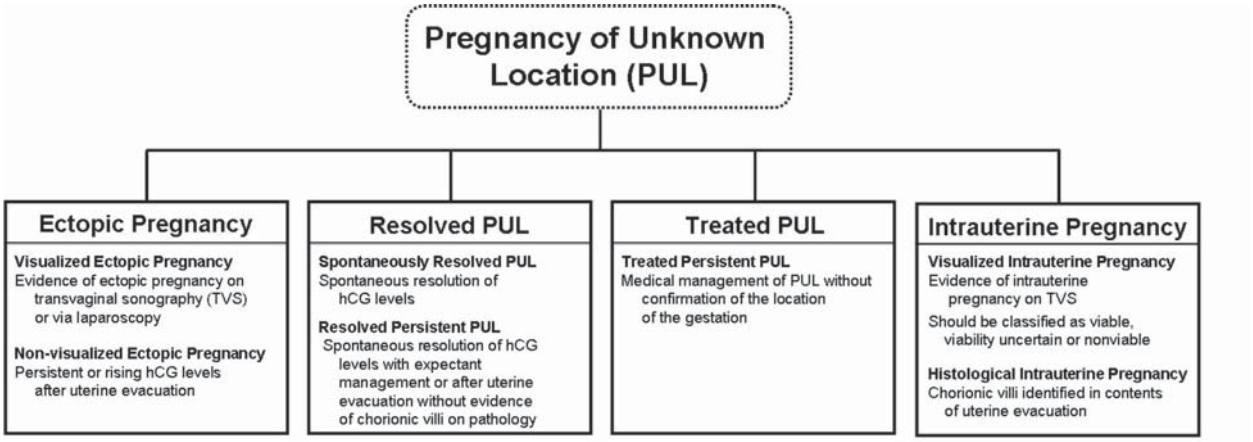

Figure 2: Classification of pregnancy of unknown location outcome based on final location (with permission from Barnhart, *et al. Fertil Steril* 2011 1; 95 (3): 857–66).

2 IUP

- Visualised 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
  - Non-viable intra-uterine gestation (definitive ultrasonic evidence of empty sac, embryonic demise, or retained trophoblastic tissue).
- Histological IUP is defined as identification of chorionic villi in the contents of the uterine evacuation.

3 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 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.

4 Treated persistent PUL

- Defined as those who are treated medically without confirmation of the location of the gestation by TVS, laparoscopy or uterine evacuation.

This proposed classification system means that the final PUL categories are ectopic pregnancy, IUP, treated PUL or failed PUL (see Figure 2).

I would encourage ALL EPUs and ultrasound-based gynaecological services to adopt this consensus classification for final PUL outcomes. This in turn will result in more consistent and precise terminology when discussing and reporting the ultrasound findings in women who present for first trimester ultrasound. According to Barnhart, "ultimately, consensus should aid in the generalisability of study results and potentially lead to improved clinical care".

Assoc Prof George Condous
Editor

References

1 Barnhart K, van Mello NM, Bourne T, Kirk E, Van Calster B, Bottomley C, Chung K, Condous G, Goldstein S, Hajenius PJ, Mol BW, Molinaro T, O'Flynn O'Brien KL, Husicka R, Sammel M, Timmerman D. Pregnancy of unknown location: a consensus statement of nomenclature, definitions, and outcome. *Fertil Steril* 2011 1; 95 (3): 857–66.