SPECIAL CONTRIBUTION

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

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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.

Design: 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.

Result(s): 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 nonvisualized EP, treated persistent PUL, resolved persistent PUL, or histologic IUP. These specific categories can be used to characterize the natural history or location (intrauterine vs. extrauterine) of any early gestation where the initial location is unknown.

Conclusion(s): 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. (Fertil Steril® 2011;95:857–66. ©2011 by American Society for Reproductive Medicine.)

Key Words: Nomenclature, pregnancy of unknown location, international consensus, ectopic pregnancy

Ectopic pregnancy (EP) occurs in 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

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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 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.

MATERIALS AND 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 in the following paragraphs (7, 8, 26–32).

Global Differences in Diagnostic Strategy

There are differences in the diagnostic strategy based on geography. In the United Kingdom 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 United States is to follow serial serum hCG concentrations until these levels deviate from what is expected for a potential viable gestation or miscarriage (33–35). Other investigators have advocated the use of serum P as an adjuvant in the diagnostic process (17, 26, 36, 37). Condous et al. (38) 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. In contrast in the United States, Barnhart et al. (39, 40) have demonstrated very good prediction of final outcome of women at risk for EP solely from presenting clinical signs and symptoms. 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 United Kingdom 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). 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 articles 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 articles originating from the United States 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 articles from the United Kingdom 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 articles published and this affects both the population evaluated (as described previously) as well as the classification of final outcome.

Pregnancy of unknown location Pregnancy of unknown location 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. Pregnancy of unknown location 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 United States have been categorized into three groups: IUP, EP, and miscarriage or spontaneous abortion (SAB). The literature from the United Kingdom and European countries has stratified final outcomes into four categories: IUP, EP, failed PUL, and persisting PUL.

Intrauterine pregnancy In studies originating from the United States, 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 (an embryonic 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 the United Kingdom 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.

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