The term "pregnancy of unknown location" is here to stay

George Condous, Simon Winder and Shannon Reid

Acute Gynaecology, Early Pregnancy and Advanced Endosurgery Unit, Sydney Medical School Nepean, University of Sydney. Nepean Hospital, Penrith, Sydney, New South Wales 2750, Australia.
Correspondence to author via ASUM. Email authors@asum.com.au

Abstract The term "pregnancy of unknown location" is an ultrasound classification and not a final diagnosis. The use of this terminology is here to stay and should continue as long as there is an appreciation for what it really means. It is the responsibility of the clinician, who follows up these women with a PUL, to ensure that a final diagnosis is achieved while preserving the well-being of these women.

Introduction

We recently read with great interest the most recent triennial report into maternal deaths in the United Kingdom, *Saving Mothers' Lives 2006–2008*[1]. In chapter six, *Deaths in early pregnancy*, one of the recommendations by the report is that the term "pregnancy of unknown location" (PUL) be abandoned (see excerpt below).

The term "pregnancy of unknown location" based on early pregnancy ultrasound examination should be abandoned. An early pregnancy ultrasound which fails to identify an intrauterine sac should stimulate active exclusion of tubal pregnancy, and even in the presence of a small uterine sac, ectopic pregnancy cannot be excluded.

This recommendation is made following one of the early pregnancy maternal deaths which occurred in a woman who was initially classified as a PUL. According to the limited synopsis of the case, serial serum human chorionic gonadotrophin (hCG) were arranged. She then was readmitted to another hospital a few weeks later with diarrhoea, dizziness, abdominal pain and vaginal bleeding. A repeat ultrasound a few hours later demonstrated the presence of a possible intra-uterine gestational sac (9 mm) and haemoperitoneum. It was decided to perform a uterine evacuation and consider laparoscopy if products of conception were not obtained. Uterine evacuation was performed by a junior doctor not familiar with the case and on return to the ward, the woman collapsed and died several hours later. Post mortem revealed a ruptured ectopic pregnancy and massive intra-peritoneal haemorrhage.

The recommendation to abandon the use of the term "PUL" would be a retrograde step indeed, a backwards step to the 1980s, when the diagnosis of ectopic pregnancy was often based on the transabdominal ultrasound exclusion of an intra-uterine gestational sac. In modern 21st century management, the diagnosis of an ectopic pregnancy should be based upon the positive visualisation of an adnexal mass using transvaginal ultrasonography (TVS)[2]. A woman should only be classified as having a PUL if there are no signs of intra- or extra-uterine pregnancy on TVS as well as nil retained products of conception on scan[3]. PUL is a descriptive term, like the description "thickened endometrium" is used in the postmenopausal population, and not a final diagnosis. In the same way that the vast majority of women with a "thickened endometrium" will not have an underlying endometrial cancer, the same can be said for early pregnancy women classified with a PUL at the first TVS; i.e. the vast majority will not have an ectopic pregnancy on subsequent follow up. In the subsequent management of these early pregnancy women with a PUL, the onus of responsibility is on the clinician to meticulously follow up these women until a final diagnosis is established. In the example of the "thickened endometrium", follow up in the postmenopausal group will confirm an endometrial polyp, endometrial hyperplasia or an endometrial carcinoma. In an early pregnancy woman with the ultrasound classification of a PUL, the final diagnosis will be a failed PUL, an intra-uterine pregnancy (viable or non-viable) or an ectopic pregnancy. In experienced sonology hands, the prevalence of ectopic pregnancy in the PUL population is as low as 8%[3]. This means that expectant management of these PULs on an outpatient basis is safe. Expectant management reduces the need for unnecessary interventions and is not associated with serious adverse outcomes[3]. The development of an understanding of ultrasonographic appearances of both early intra- and extra-uterine pregnancies has resulted in greater clarity for the remaining non-diagnostic ultrasound scans, i.e. the PULs.

At Nepean Hospital, the most important fact is that women with an ultrasound classification of a PUL will have undergone a thorough real-time dynamic pelvic ultrasound and systematic approach to all possible pregnancy locations. The clinician who takes the history is the same person who performs the ultrasound and makes the subsequent management plan. This is a critical point of difference to other early pregnancy units in Australia. Once the absence of an intra-uterine gestational sac is confirmed on TVS, then both adnexal regions are carefully visualised to exclude the presence of a tubal ectopic pregnancy. Once the adnexal regions are deemed to be clear of trophoblastic tissue, then all other potential non-tubal pregnancy sites need to also be carefully inspected. These include the cervix, left and right interstitial regions of the uterus, left and right ovaries and the previous lower segment caesarean section scar in women who have had a previous caesarean section. This systematic ultrasonographic approach requires an experienced sonographer or sonologist to perform the TVS. How do we define "experienced"? If we use the International Ovarian Tumour Analysis' (IOTA) definition of "experience", then one needs to have performed more than 15,000 scans! I think this arbitrary number may not be achievable by all sonographers or

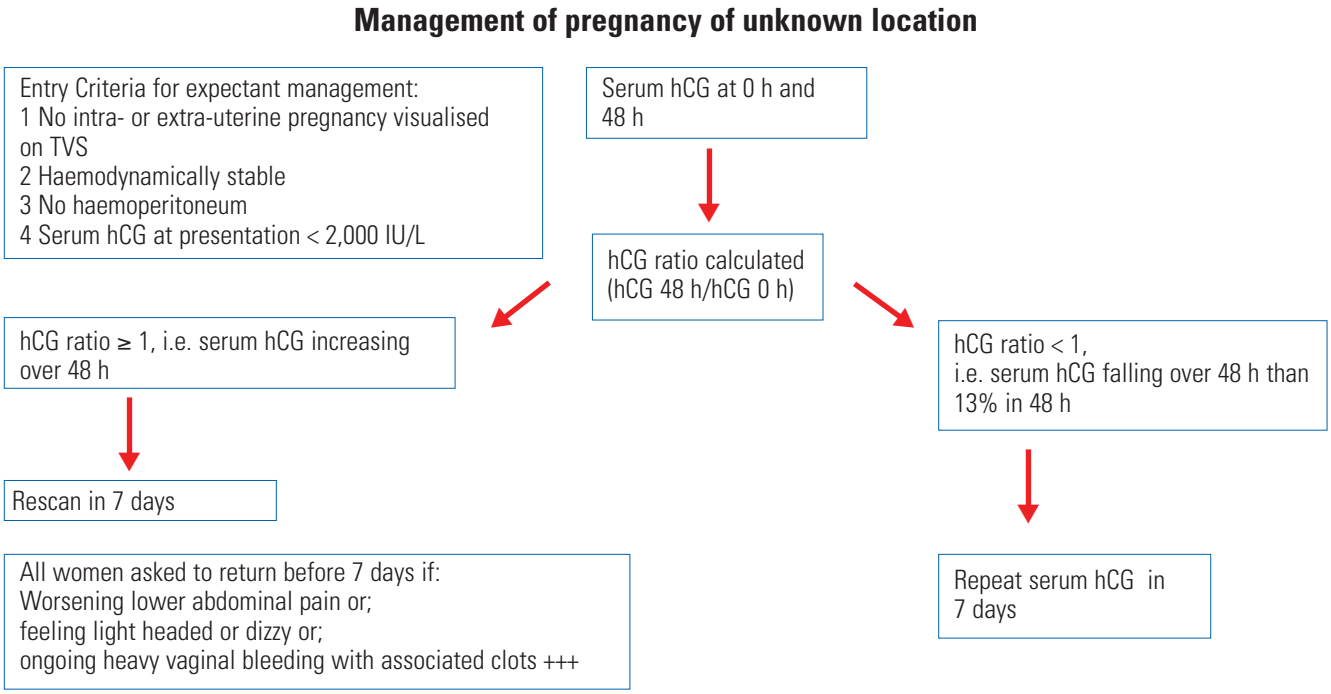

Fig. 1: Flow diagram for the management of women with PULs.

sonologists, however, this is a goal to strive for. Once we have excluded both intra- and extra-uterine pregnancy, then we can safely classify the woman as having a PUL. The subsequent outpatient management of women with a PUL is then based upon the hCG ratio which is defined as: Serum hCG at 48 hours/Serum hCG at 0 hours (Fig. 1).

At Nepean Hospital's Early Pregnancy Unit, if the hCG ratio is < 1 at 48 hours, i.e. the serum hCG levels are falling, then the trophoblast is likely to be dying spontaneously. We then recheck the serum hCG levels at seven days to confirm the diagnosis. If the hCG ratio is > 1 at 48 hours, i.e. the serum hCG levels are increasing, then the trophoblast is likely to be still active. We then re-scan these women at seven days to confirm pregnancy location. This simple algorithm reduces the need for unnecessary repeat serum hCG levels/ultrasound scans without compromising safety. All women classified with a PUL are told to return to the Early Pregnancy Unit or the Emergency Department if they experience any worsening vaginal bleeding and/or lower abdominal pain during the seven day window period.

The proportion of ectopic pregnancies in a PUL population is dependent on the quality of ultrasound[4]. In other words, as the sonographer or sonologist becomes more experienced in the skill of TVS, then the rate of ectopic pregnancy in the PUL population will be low[4]. In fact, in experienced hands, in women with ectopic pregnancies who are initially classified as PULs, failure of visualisation of the ectopic pregnancy on the initial TVS is likely to be due to the fact that they are too small and probably too early in the disease process[5].

The case described in the most recent confidential enquiry into maternal deaths is a most unfortunate case where the outcome could have been very different[1]. The use of the term PUL in this case was not the primary reason why this woman died but rather her death was a consequence of catastrophic systems failure involving multiple clinicians and two hospitals.[6] Holes or deficiencies in any woman's management arise from two reasons: active failures and latent conditions[6].

On multiple levels, the system failed in this woman's care:

1 What procedures and protocols were in place at the primary hospital and why was the woman not followed up after her first ultrasound scan classified her as having a PUL?
2 Serial serum hCG levels were arranged but what was the response of the first unit?
3 Why was the diagnosis of ruptured ectopic pregnancy not entertained even before the second ultrasound scan was arranged at the second hospital as the woman presented with the textbook clinical triad of amenorrhoea (positive pregnancy test), lower abdominal pain and vaginal bleeding?
4 Why was the diagnosis of ruptured ectopic pregnancy not considered when she presented with dizziness and diarrhoea? According to every triennial report since 2000–2002, women with ectopic pregnancies may have atypical symptoms suggesting gastrointestinal dysfunction[1,7,8].
5 What did the second ultrasound really demonstrate? Was there a true intra-uterine gestational sac (visualised eccentrically in the endometrial cavity) or was this cystic structure just intra-cavitary fluid[9,10]? If the latter, this should have alerted the sonologist to a potential extra-uterine pregnancy as the cause for the haemoperitoneum noted on scan. Most extra-uterine pregnancies (87–99%) in the presence of haemoperitoneum can and should be seen on transvaginal ultrasound[11–15].
6 Why was there no transabdominal evaluation of Morison's pouch (hepato-renal space) by the sonologist to exclude significant haemoperitoneum[16]? There is no doubt that Morison's pouch would have been positive for blood in this case and this equates to a minimum of 670 mL of blood in the intra-peritoneal cavity when the transabdominal scan is performed in the supine position[17].

The initial use of the term PUL in this case was appropriate, however this terminology did not trigger the appropriate

follow up in management. All early pregnancy units should have their own evidence-based guidelines for managing such women with a PUL. This should include serum hCG follow up and repeat TVS when appropriate.

The use of the term PUL is not new by any means. In 2005, when the European Society for Human Reproduction and Embryology (ESHRE) Special Interest Group published its revised nomenclature for use in early pregnancy events, the term PUL was recommended. They suggested that when there is no identifiable pregnancy on ultrasound scan in a woman with a positive serum hCG, these women should be classified as having a PUL[18]. In 2006, the Royal College of Obstetricians and Gynaecologists (RCOG) also embraced the term PUL and the definition published by the ESHRE Special Interest Group for Early Pregnancy (SIGEP)[18,19]. The RCOG agreed with the ESHRE SIGEP that it was important to align terminology used in early pregnancy literature[19]. These two authoritative bodies came to such a consensus following more than a decade of peer reviewed published evidence on women with a PUL[20–47]. There has not been a single maternal mortality in any of these published studies[20–47].

The term "pregnancy of unknown location" is an ultrasound classification and not a final diagnosis. The use of this terminology is here to stay and should continue as long as there is an appreciation for what it really means. The subsequent outpatient management and safety of these women with a PUL is dependent on the experience of the person who performs the primary scan. This sonographer or sonologist must be experienced in gynaecological ultrasound and have a clear understanding of the ultrasonographic markers in first trimester ultrasound. Most importantly, the operator needs to have a thorough imaging knowledge of the varying ultrasound appearances of both early intra-gestational sacs as well as the different ultrasonographic morphological appearances of ectopic pregnancy. Safety is paramount in women with a PUL. It is the responsibility of the clinician, who follows up these women with a PUL, to ensure that a final diagnosis is achieved while preserving the well-being of these women. Remember that as clinicians we manage patients, not serum hCG levels and not ultrasound scans.

References

1 Lewis, G (ed). Saving Mothers' lives: Reviewing maternal deaths to make motherhood safer – 2006–2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011; 118 Supp 1: 1–205.

2 Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, *et al*. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. *Hum Reprod* 2005; 20: 1404–9.

3 Condous G, Timmerman D, Goldstein S, Valentin L, Jurkovic D, Bourne T. Pregnancies of unknown location: a consensus statement. *Ultrasound Obstet Gynecol* 2006; 28: 121–2.

4 Condous G, Kirk E, Lu C, Van Huffel S, Gevaert O, De Moor B, *et al*. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2005; 26: 770–5.

5 Kirk E, Daemen A, Papageorghiou AT, Bottomley C, Condous G, Moor BD, Timmerman D, Bourne T. Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination? *Acta Obstet Gynecol Scand* 2008; 87: 1150–4.

6 Reason J. Human error: models and management. *BMJ* 2000; 320: 768.

7 Lewis G, Drife J, (editors). Why Mothers Die, Triennial Report 2000–2002. The Sixth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. RCOG Press, 2004 (November).

8 Lewis, G (ed). The Confidential Enquiry into Maternal and Child Health (CEMACH). saving mothers' lives: reviewing maternal deaths to make motherhood safer – 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: 2007 CEMACH.

9 Condous G, Okaro E, Bourne T. The conservative management of early pregnancy complications: a review of the literature. *Ultrasound Obstet Gynecol* 2003; 22: 420–30.

10 Condous G. The management of early pregnancy complications. *Best Pract Res Clin Obstet Gynaecol* 2004; 18: 37–57.

11 Braffman BH, Coleman BG, Ramchandani P, Arger PH, Nodine CF, Dinsmore BJ, *et al*. Emergency department screening for ectopic pregnancy: a prospective US study. *Radiology* 1994; 190 (3): 797–802.

12 Shalev E, Yarom I, Bustan M, Weiner E, Ben-Shlomo I. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experience with 840 cases. *Fertil Steril* 1998; 69 (1): 62–5.

13 Atri M, Valenti DA, Bret PM, Gillett P. Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy. *J Clin Ultrasound* 2003; 31 (1): 1–8.

14 Kirk E, Papegeorghiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. *Hum Reprod* 2007; 22: 2824–8.

15 Bignardi T, Condous G. Does tubal ectopic pregnancy with hemoperitoneum always require surgery? *Ultrasound Obstet Gynecol* 2009; 33: 711–5.

16 Abrams BJ, Sukumvanich P, Seibel R, Moscati R, Jehle D. Ultrasound for the detection of intraperitoneal fluid: the role of Trendelenburg positioning. *Am J Emerg Med* 1999; 17: 117–20.

17 Farquharson RG, Jauniaux E, Exalto N. ESHRE Special Interest Group for Early Pregnancy (SIGEP). Updated and revised nomenclature for description of early pregnancy events. *Hum Reprod* 2005; 20: 3008–11.

18 Guidelines and Audit Committee of the Royal College of Obstetricians and Gynaecologists. The management of early pregnancy loss: clinical green top guidelines No. 25. London: RCOG: 2006.

19 Banerjee S, Aslam N, Zosmer N, Woelfer B, Jurkovic D. The expectant management of women with early pregnancy of unknown location. *Ultrasound Obstet Gynecol* 1999; 14: 231–6.

20 Banerjee S, Aslam N, Woelfer B, Lawrence A, Elson J, Jurkovic D. Expectant management of early pregnancies of unknown location: a prospective evaluation of methods to predict spontaneous resolution of pregnancy. *BJOG* 2001; 108 (2): 158–63.

21 Gracia CR, Barnhart KT. Diagnosing ectopic pregnancy: decision analysis comparing six strategies. *Obstet Gynecol* 2001; 97: 464–70.

22 Barnhart KT, Katz I, Hummel A, Gracia CR. Presumed diagnosis of ectopic pregnancy. *Obstet Gynecol* 2002; 100: 505–10.

23 Condous G, Lu C, Van Huffel SV, Timmerman D, Bourne T. Human chorionic gonadotrophin and progesterone levels in pregnancies of unknown location. *Int J Gynaecol Obstet* 2004; 86: 351–7.

24 Condous G, Okaro E, Khalid A, Timmerman D, Lu C, Zhou Y, *et al*. The use of a new logistic regression model for predicting the outcome of pregnancies of unknown location. *Hum Reprod* 2004; 19: 1900–10.

25 Barnhart K, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: defining the normal curve. *Obstet Gynecol* 2004; 104: 975–81.

26 Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, Bourne T. A prospective evaluation of a single-visit strategy to manage pregnancies of unknown location. *Hum Reprod* 2005; 20: 1398–403.

27 Condous G, Okaro E, Khalid A, Bourne T. Do we need to follow up complete miscarriages with serum human chorionic gonadotrophin levels? *Br J Obstet Gynaecol* 2005; 112: 827–9.

28 Condous G, Kirk E, Syed A, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Do levels of serum cancer antigen 125 and

creatine kinase predict the outcome in pregnancies of unknown location? *Hum Reprod* 2005; 20: 3348–54.

29 Kirk E, Condous G, Haider Z, Lu C, Van Huffel S, Timmerman D, Bourne T. The practical application of a mathematical model to predict the outcome of pregnancies of unknown location. *Ultrasound Obstet Gynecol* 2006; 27: 311–5.

30 Gevaert O, De Smet F, Kirk E, Van Calster B, Bourne T, Van Huffel S, Moreau Y, Timmerman D, De Moor B, Condous G. Predicting the outcome of pregnancies of unknown location: Bayesian networks with expert prior information compared to logistic regression. *Hum Reprod* 2006; 21: 1824–31.

31 Condous G, Kirk E, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Failing pregnancies of unknown location: A prospective evaluation of the human chorionic gonadotrophin ratio. *Br J Obstet Gynaecol* 2006; 113: 521–7.

32 Condous G, Kirk E, Lu C, Van Calster B, Van Huffel S, Timmerman D, Bourne T. There is no room for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location. *Hum Reprod* 2006; 21: 2706–10.

33 Seeber BE, Barnhart KT. Suspected ectopic pregnancy. *Obstet Gynecol* 2006; 107: 399–413.

34 Seeber BE, Sammel MD, Guo W, Zhou L, Hummel A, Barnhart KT. Application of redefined human chorionic gonadotropin curves for the diagnosis of women at risk for ectopic pregnancy. *Fertil Steril* 2006; 86: 454–9.

35 Condous G, Van Calster B, Kirk E, Timmerman D, Van Huffel S, Bourne T. Prospective cross-validation of three methods of predicting failing pregnancies of unknown location. *Hum Reprod* 2007; 22: 1156–60.

36 Kirk E, Condous G, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Rationalizing the follow-up of pregnancies of unknown location. *Hum Reprod* 2007; 22: 1744–50.

37 Condous G, Van Calster B, Kirk E, Haider Z, Timmerman D, Van Huffel S, Bourne T. Prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2007; 29: 680–7.

38 Condous G, Van Calster B, Kirk E, Haider Z, Timmerman D, Van Huffel S, Bourne T. Clinical information does not improve the performance of mathematical models in predicting the outcome of pregnancies of unknown location. *Fertil Steril* 2007; 88: 572–80.

39 Barnhart KT, Casanova B, Sammel MD, Timbers K, Chung K, Kulp JL. Prediction of location of a symptomatic early gestation based solely on clinical presentation. *Obstet Gynecol* 2008; 112: 1319–26.

40 Bignardi T, Condous G, Alhamdan D, Kirk E, Van Calster B, Van Huffel S, Timmerman D, Bourne T. The hCG ratio can predict the ultimate viability of the intrauterine pregnancies of uncertain viability in the pregnancy of unknown location population. *Hum Reprod* 2008; 23: 1964–7.

41 Kirk E, Papageorghiou A, Van Calster B, Condous G, Cowans N, Van Huffel S, Timmerman D, Spencer K, Bourne T. The use of serum inhibin A and activin A levels in predicting the outcome of 'pregnancies of unknown location'. *Hum Reprod* 2009; 24: 2451–6.

42 Day A, Sawyer E, Mavrelos D, Tailor A, Helmy S, Jurkovic D. Use of serum progesterone measurements to reduce need for follow-up in women with pregnancies of unknown location. *Ultrasound Obstet Gynecol* 2009; 33 (6): 704–10.

43 Casanova BC, Sammel MD, Chittams J, Timbers K, Kulp JL, Barnhart KT. Prediction of outcome in women with symptomatic first trimester pregnancy: focus on intrauterine rather than ectopic gestation. *J Women's Health* 2009; 18: 195–200.

44 Bignardi T, Condous G, Kirk E, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Viability of intrauterine pregnancy in women with pregnancy of unknown location: prediction using human chorionic gonadotropin ratio vs. progesterone. *Ultrasound Obstet Gynecol* 2010; 35: 656–61.

45 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; 95: 857–66.

46 Cordina M, Schramm-Gajraj K, Ross J, Lautman K, Jurkovic D. Introduction of a single visit protocol in the management of selected patients with pregnancy of unknown location: a prospective study. *BJOG* 2011 Feb 18. doi: 10.1111/j.1471-0528.2011.02893.x. [Epub ahead of print].