Ectopic Pregnancy and the Dilemma of Pregnancy of Unknown Location

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INTRODUCTION

Ectopic pregnancy (EP), the implantation of a fertilized ovum outside the endometrial cavity, is a life threatening condition which occurs in approximately 1.5 to 2.0% of pregnancies [1]. The associated mortality has decreased markedly to 0.5 deaths per 1000 pregnancies, primarily because of early diagnosis and treatment before rupture [2]. Nevertheless, ruptured EPs continue to occur, often because the clinician or the patient did not recognize the early signs and symptoms of the condition [3].

The advent of diagnostic ultrasound and use of serum hCG [4,5] and later β-hCG [6] has revolutionized the diagnosis of EP. Although the expertise of the ultrasonographer is important, it is known that transvaginal ultrasonographic (TVUS) examination can identify an intrauterine pregnancy (IUP) with almost 100% accuracy after 5.5 weeks gestation with a sensitivity of 73-93% [7-9]. Concurrent with the introduction of these modalities was a transition from laparotomy, to laparoscopic procedures, with a trend towards medical management with methotrexate or even expectant management [10]. Although recent data over a 5 year period between 2003 -2007 from the US suggest that the mortality rate from EP has declined significantly, an average of 21 deaths still occur from EP annually [11]. Thus, EP remains a leading cause of maternal morbidity and mortality, accounting for up to 6% of pregnancy related deaths [11-13].

Despite improvement in our understanding of the modalities available for diagnosis of EP, misdiagnosis and errors in management still occur. Such misdiagnosis occurs especially when an ultrasound is performed too early before an intrauterine pregnancy has had time to develop, or an ectopic is not identified by an adnexal mass separate from the ovary, or is misdiagnosed for bowel, a paratubal cyst, an endometrioma, or the corpus luteum. Misdiagnosis can also result from misinterpretation of β-hCG levels vis-à-vis its use to determine the discriminatory zone (serum β-hCG levels [2000mIU/L] at which the sac of an IUP becomes visible on US). Doubit and Benson [4] in their study found no significant relationship between initial β-hCG levels and either first-trimester or final pregnancy outcome, and 9 of 202 (4.5%) patients in their series with eventual viable IUP had no IUP on US even though their β-hCG were above 2000 mIU/mL [14]. The highest β-hCG in this study was 6567 mIU/mL, and the highest value that preceded a live born term baby was 4336 mIU/mL. Another point that is also often forgotten is that the concept of a discriminatory zone is based on a singleton pregnancy, and multiple gestations have a higher hCG at a given gestational age [15], which suggests that the best "discriminatory zone" should be based upon the gestation age and not solely the β-hCG level [16,17]. A patient found to have a negative TVUS with serum β-hCG above the "discriminatory zone", or a gestational age by last menstrual period of greater than 5 weeks, is described as having a "pregnancy of unknown location" (PUL). It is estimated that the rate of PUL can vary between 8-31% [18,19]. When managed expectantly as advocated by respected authorities, the diagnosis often become clear with time [16]; approximately 30% of patients with PUL will eventually be shown to have ongoing IUP [20].

When in doubt, and the pregnancy is deemed non-viable by inappropriate β-hCG rise of less than 53% or a fall of less than 12-32% (depending on initial β-hCG) in 2 days [21], the use of endometrial sampling has been advocated to help diagnose an IUP. The presence of villi on endometrial sampling or a subsequent decline in β-hCG of ≥ 15% are consistent with a failed IUP, and following such sampling, usually no further treatment is indicated [22,23]. Unlike with a formal D&C, general anesthesia is not required for outpatient endometrial suction with Pipelles or the Karmans cannula; such alternative treatments are also associated decreased cost. For the diagnosis of PUL, endometrial suction Pipelles have been shown to lack sensitivity and specificity [24,25]. However, it is debatable whether a formal D&C advocated by some [26-28] is required. Even when specimens are obtained from a D&C, evaluation by frozen section to look for chorionic villi and rule out EP before proceeding to laparoscopy can produce false negative diagnoses, a fact that should be considered in the operative planning of women with suspected EP [29].

Associated with errors in diagnosis are issues of inappropriate treatment, especially when the location of a pregnancy has not been confirmed and management is based on the discriminatory zone criteria, single rather than serial β-hCG values, or its inappropriate rise [16]. The improper administration of methotrexate (an abortifacient and a teratogen) when a viable IUP has not been ruled out as in cases of PUL can have serious
consequences in patient who eventually develop an IUP. Such use of methotrexate is more common than is reported and may result in the birth of severely malformed babies or fetal demise [30]. Nevertheless, it is still a subject of debate whether methotrexate should be used when the diagnosis of EP is presumed and not confirmed as in cases of PUL [16].

Another contentious issue is surgical management of patients with PUL who are asymptomatic, in whom the β-hCG is above the discriminatory zone. Such patients may be taken to the operating room because of fear that they may not follow up with serial hCG surveillance and repeat US, and the unwillingness to admit such patients for monitoring because of cost. Treatment at laparoscopy for EP involves either salpingostomy to remove the pregnancy or salpingectomy to remove both the pregnancy and the uterine tube. Too early intervention by laparoscopy in cases of PUL can result in negative findings and may not exclude the eventual diagnosis of EP, and may even end in tubal rupture. In contrast, a few of these patients have had their uterine tubes removed with no subsequent diagnosis of an EP [31].

It is the opinion of the author that it is time for definitive studies to be undertaken to formulate guidelines for the management of PUL. This will have the potential of educating the wider gynecology community, and help promote institution of evidence based management, while minimizing unnecessary intervention such as use of methotrexate or surgical intervention.

REFERENCES


