

Diagnostic Criteria in Extrauterine Pregnancy

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Abstract

Ectopic pregnancy is characterized by implantation of an embryo outside the uterine cavity and usually is located in the distal portion of the fallopian tube. The common triade of symptoms includes: abdominal pain, vaginal bleeding and amenorrhea. The ectopic pregnancy is still considered an important cause of death in the first trimester of pregnancy, for this reason a rapid and accurate diagnosis is considered the most important factor for reducing maternal morbidity and mortality and preserving the fertility. We reviewed published works that analyzed the common diagnostic methods classifying in four categories: clinical, biochemical, ultrasound and radiological and surgical diagnose. Actually, according to American College of Obstetricians and Gynecologists (ACOG) guidelines the most efficacious strategy to diagnose an ectopic pregnancy appears to be the combination of ultrasound, physical examination and biochemical tests.

Keywords: Diagnostic methods; Ectopic pregnancy; B-Hcg levels; Intrauterine pregnancy; Tubal gestation; Ultrasound

Introduction

Ectopic pregnancy (EP) is characterized by the implantation of an embryo outside the uterine cavity with an incidence of about 1-2% of all pregnancies and causes about 4-6% of all pregnancy related deaths [1-3]. Early diagnosis and management improve the survival from 31.2 to 16.9/1000 maternities indeed the incidence remains the same [4]. In fact the rapid identification and accurate diagnosis of EP is considered an important factor to reduce maternal morbidity and mortality and preserving the future fertility.

Regarding the site, in the 93-97% of cases of EP the site of implantation is the distal portion of the fallopian tube, less commonly the isthmic, infundibular and interstitial portions. Other extratubal sites include ovary, cervix, cornua, prior cesarean scar, interstitial and abdomen [5]. Most common factors for the pathogenesis of EP are the tubal damage, such as salpingitis, progressive loss of myoelectrical activity, deciliation of the tube, which cause an impairment of embryo transport in the tube. Other reasons include atrophy of endometrium with an increase in the level of progesterone and problems related to embryo development [6].

Several risk factors for EP have been identified and classified into three categories: high, moderate and low risk factors [7-9]. Previous tubal pregnancy, surgery, sterilization and pathology, and use of intrauterine device (IUD) are classified as high risk factors. Moderate risk includes infertility, pelvic inflammatory disease (PID), sexually transmitted diseases, in particular chlamydia related disease and gonorrhea, multiple sexual partners and smoking. History of pelvic or abdominal surgery, vaginal douching and an age < 18 represent low risk factors [7-10]. The common symptoms of EP are abdominal pain, vaginal bleeding and amenorrhea [11]. Thus, the aim of our review is to analyze a list of common diagnostic methods to identify earlier and more accurately EP.

Materials and Methods

We searched on PubMed using a combination of MeSH and text words to generate two subsets of quotes combined with “AND”, one indexing “ectopic pregnancy” and the other “diagnosis and management”. Publication language restriction was applied and we have considered only articles published in English, Italian or French. All potential papers were screened for eligibility by review of the title and abstract, to identify those focused on diagnosis of any type of EP. Reference lists of all primary and review articles were examined for any relevant citation to include studies missing in the original key word search.

Results

We screened several abstracts and full text from the literature. We have chosen that studies whose met inclusion criteria and we analyze only studies regarding the diagnosis methods for EP. Therefore, we decided to classificate these methods into four categories:

- Clinical diagnosis
- Biochemical diagnosis
- Ultrasound and radiological diagnosis
- Surgical diagnosis

Clinical diagnosis

The patient history, including risk factors, and physical examination were frequently used as the first approach in women with possible EP. EP should be suspected in all women in reproductive age with vaginal bleeding, amenorrhea from six to eight weeks and abdominal pain [10-12]. Moreover, normal or slightly enlarged uterus, pelvic pain with manipulation of the cervix, and a palpable adnexal mass significantly increase the likelihood to have an ectopic pregnancy. Significant abdominal tenderness associated with hypotension, tachycardia and fever suggest a possible EP ruptured and hemoperitoneum [10-13]. The EP symptoms are often not specific, in particular in women with early EP. In fact, in the 30% of patients no vaginal bleeding occurred and 10% have a normal physical examination [14]. An important issue remains the differentiation of EP from other gynecological, gastrointestinal and urological symptoms [15].

Biochemical diagnosis

In a Intra Uterine Pregnancy (IUP), the β -hCG level doubles every 2 day until 6 weeks. In the EP and miscarriage the performance of β -hCG level is different. A decrease or shutdown of this level is commonly associated with miscarriage. The slower increase is also predictive for abnormal pregnancy and requires an assessment over time. In 1981 a study has proposed an increase of β -hCG level after 48 hours less than 66% could predict a diagnosis of EP [16]. However the 13% of EP was undiagnosed and 15% of IUP was considered abnormal. In the same study was emphasized the importance of ultrasound combined with β -hCG concentration and was proposed a discriminatory β -hCG zone (6500IU/l), defined as the minimal β -hCG concentration above which the sac of an IUP always can be identified by sonography [16].

In patient with low serum β -hCG concentration and inconclusive ultrasound performing every 2 days and using a cutoff value of for the β -hCG concentration 1.000 IU/L; it was reached a sensitivity of 90% and a specificity of 98% in the diagnosis of EP [17-19]. The progesterone level is not very helpful in the diagnosis of EP and lower levels are correlated with miscarriage. A meta-analysis of 26 studies stated that a single progesterone measurement was useful to identify women at risk for EP thus needing an accurate monitoring [20].

Ultrasound and radiological diagnosis

In 1969 Kobayashi et al described for the first time the use of ultrasonography for the diagnosis of EP [21]. Transvaginal ultrasound (TVS) is today considered the gold standard to diagnose the location of the gestational sac. Usually, at 4 weeks of gestational age with human chorionic gonadotropin (β -hCG) levels between 1500 and 2000 IU/L it is possible by TVS to visualize an intrauterine gestational sac [22] and at 5 weeks it's possible to identify an embryonic pole, while for transabdominal ultrasound (TAS) is necessary to wait at least another week [23]. It has been shown that the TVS has a higher sensitivity for the diagnosis of EP if compared with TAS (88-90% versus 77-80%) [24-25]. In a recent review it was reported that TVS has a greater sensitivity than in previous years reaching 99% with a specificity around 94-99% [12]. The visualization of IUP does not exclude a EP, specially in pregnancy obtained with assisted reproductive

techniques (ART). The simultaneous findings of a IUP and EP, heterotopic pregnancy, is rare with an incidence of 1:30000 pregnancies, but increase to 1-3:100 in pregnancies obtained with ART [26-27]. There are no specific features regarding the thickness of the endometrium for the diagnosis of EP. In about 20% of cases there is a small amount of liquid in the cavity which is considered a "pseudosac" [28]. The finding of an hypoechoic area must always be re-evaluated, combining with laboratory data, to exclude an early intrauterine pregnancy (IUP) [29]. The presence of echogenic fluid in Douglas was reported in 28-56% of EP cases correlated with hemoperitoneum at the time of surgery, but we need to consider that a small amount is also found in IUP [30-31]. Another sign of hemoperitoneum is the presence of fluid in Morrison's Pouch between the liver and the kidney [32]. In a percentage varying from 8 to 31% it is not possible, in early pregnancy, detect with TVS between intrauterine or ectopic, determining a clinical presentation defined as pregnancy of unknown location (PUL) [33-34]. Recent studies have demonstrated that the incidence of PUL decreased between 8 and 10% when ultrasound examinations are performed by referral centers [35-36]. It's important to discriminate PUL from early IUP, EP or miscarriage by ultrasound and biochemical follow-up. Regarding tubal EP, in 1969 Kobayashi *et al.* attempted to establish the ultrasound diagnostic criteria [21], but diagnostic accuracy is greatly improved in recent years with the introduction of TVS [25-30-37].

In a study conducted by Cacciatore *et al.* reported that the finding of an adnexal mass on ultrasound was highly predictive in cases of tubal EP [38]. In a meta-analysis it was shown that the presence of an adnexal mass, even in the absence of a visible embryo, had a sensibility of 84.4% and a specificity of 98.9% for the diagnosis of tubal EP [39]. In the same meta analysis and in more recent has been proposed, to apply a pressure on the abdomen that may demonstrate the sliding sign among the ovary and the adnexal mass in order to differentiate between corpus uterine and tubal EP [39-40]. More recent studies showed an increase of sensibility in detection of tubal EP well above 90% due to the advances in ultrasound technology [41-42]. In the literature, there are few data regarding the sonographic criteria for the diagnosis of non tubal EP. In a retrospective study conducted on 12 interstitial EP, Ackerman and colleagues reported that visualization of an echogenic line extending into the midportion of the gestational sac is predictive for interstitial pregnancy [43]. According to the study of Timor-Tritsch an empty uterine cavity, a gestational sac >1 cm from the most lateral point of the endometrial cavity and a gestational sac surrounded by a thin myometrial layer was predictive for interstitial EP [44].

In 1999, Hafner *et al.* found that the interstitial segment of the tube often measured <1 cm in length [45]. Jurkovic *et al.* in an editorial of 2007, proposed the visualization of the interstitial line adjoining the gestational sac and the lateral aspect of the uterine cavity and the continuation of myometrial mantle around the ectopic sac as diagnostic criteria for interstitial EP [46].

In 2007 Mavrelou *et al.* proposed as predictive factor for diagnosis of cornual EP, the presence of a single interstitial portion of Fallopian tube in the main uterine body, a gestational sac, mobile and separate from the uterus, surrounded by myometrium and a vascular pedicle contiguous to the gestational sac [47]. Intramural pregnancy can be difficult to differentiate from intrauterine pregnancy and some authors say that it cannot be diagnosed with ultrasound alone [48]. However an other study reported that it is possible to see the gestational sac get striking into the myometrium with no visible communication to the uterine cavity [49-51].

Kobayashi *et al.* in 1969 first described the criteria for the diagnosis of cervical EP with transabdominal ultrasound (TAS) [21], and then revised by Hofmann *et al.* in 1987 due to the use of TVS. The authors established that no evidence of IUP, hourglass uterine shape with ballooned cervical canal, presence of a gestational sac in cervical canal and internal uterine orifice closed were diagnostic for cervical EP [52].

Vial *et al.* described two different type of cesarean scar EP, one due to the implantation of gestational sac on the scar with progression of the pregnancy in the uterine cavity through cervico-isthmic space and the second deeply implanted in the cesarean scar defect with progression toward disruption demonstrating that trophoblast was mainly located between bladder and uterus [53].

Recently diagnostic criteria for cesarean scar EP were clarified as follows: the presence of gestational sac located below the level of the internal uterine orifice or within a visible myometrial defect in the site of previous Cesarean section scar, the evidence of functional trophoblastic/placental circulation with color Doppler examination, characterized by high-velocity (peak velocity >20 cm/s) and low

impedance (pulsatility index <1) blood flow and a negative 'sliding organs sign', characterized by the inability to displace, applying pressure by probe, the gestational sac from its position at the level of the internal uterine orifice [46].

Concerning ovarian EP, it is necessary to differentiate between early unruptured and ruptured ovarian EP. In the first case the gestational sac is enclosed by ovarian cortex with the corpus luteum adjacent and this allows to make a differential diagnosis from tubal EP. Furthermore, if it's possible to demonstrate the absence of sliding with ipsilateral ovary, even it is not a specific sign [54-55]. In case of ruptured ovarian pregnancy, it's hard to distinguish from ruptured tubal ectopic pregnancy and from ruptured hemorrhagic ovarian cyst. The 3D ultrasound may be helpful in these cases [55].

Allibone *et al.* in 1981, described a series of four abdominal pregnancies diagnosed in the second trimester by demonstration of the presence of an extrauterine fetus in a gestational sac, the failure to visualize the uterine wall between fetus and bladder, the closeness between fetus and anterior abdominal wall and the localization of placenta outside the uterine cavity [56]. The use of TVS allowed the diagnosis in the first trimester [57-58].

In 2004 Gerli *et al.* Proposed for the diagnosis in the first trimester the sign of absence of an intrauterine gestational sac and the exclusion of tubal dilatation or a complex adnexal mass; the demonstration, also, of a gestational sac surrounded by bowel and separated from the uterus and the mobility of the gestational sac [58]. Occasionally EP could be incidentally detected by Magnetic Resonance Imaging (MRI) or computed tomography (CT) during evaluation of pelvic pain of unknown cause or in the setting of trauma. Moreover it may be helpful combining TVS with MRI or CT to have more information or when complications are suspected [59].

Surgical diagnosis

The role of surgical diagnosis for ectopic pregnancy is therefore rapidly diminishing and it should be used strictly for treatment, thanks to advancing ultrasound technology and sensitivity of serum β -hCG [46]. Surgical procedures may be reserved for women with sign of shock and acute abdomen or in that patient with PUL who became symptomatic [15]. In 1991, Li *et al.* showed that 4,5% of negative laparoscopies were followed by a diagnosis of EP. Similar results were reported by Atri *et al.* in which a 4% of false negative rate and 5% of false positive rate were associated with laparoscopy [60-61]. Uterine curettage was rarely used to diagnose an EP from nonviable IUP, caused by the high risk to disrupt an early IUP [62-64]. According to the American College of Obstetricians and Gynecologists (ACOG) guidelines published in 2008, with doubtful ultrasound or a low serum progesterone level related to a failed pregnancy, serial hCG levels must be used to evaluate an ongoing pregnancy. An increasing of hCG less than 53% in 48 hours confirms, of an abnormal pregnancy in 99% of cases [65-66]. In these cases, to distinguish between a failed IUP and EP, it's useful to make an endometrial sampling to confirm or deny the presence of IU chorionic villi. Whereas, in clinically stable patients with non diagnostic ultrasound and normal or doubtful biochemical data, it's recommended to perform another TVS after hCG reaching the discriminatory zone [65].

Conclusion

Ectopic pregnancy is still considered an important cause of death in the first trimester of pregnancy. This review of the literature shows that patient history and clinical examination alone are insufficient to diagnose a EP. Although, surgery in the past decades has represented the gold standard for the diagnosis, it's actually reserved for the treatment, except in rare cases. Actually, TVS is the first diagnostic approach in the suspect of EP, but it's operator dependent and requires appropriate training and a significant experience. In conclusion the most efficacy strategy to diagnose an EP appears to be the combination of ultrasound, physical examination and biochemical tests according to guidelines. Moreover, a rapid identification and accurate diagnosis of ectopic pregnancy reduce maternal morbidity and mortality and preserve the future fertility.

Conflict of interest

The authors declare that no potential conflict of interest exists.

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