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Clinical Application of One-Step Diagnosis for Ectopic Pregnancy by HCG Ratio: Hemoperitoneum Versus Venous Serum

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1. Introduction

Suspected ectopic pregnancy (SEP) means a woman whose hemoperitoneum and pregnancy test are positive but the gestational sac is uncertain, which is finally diagnosed as an ectopic pregnancy (EP) or a hemoperitoneum with intrauterine pregnancy (hiUP). For emergency physicians, it is mostly important to differentiate EPs rapidly from hiUPs of which the vast majority can be managed without surgery. The combination of transvaginal ultrasound and serum HCG determination seem to be reliable for the early diagnosis of EP (Kaplan et al., 1996; Mol et al., 1998.). However, in most of the emergency rooms (especially on the night shift) in the general hospital, transvaginal ultrasound is often unavailable or instead of transabdominal ultrasound operated by a nonprofessional gynecologist in developing countries, which limits the prompt and accurate diagnosis of EP. Besides, the serial transvaginal ultrasound and HCG quantity result in a lot of workload for the gynecologist and additional medical costs for the patients (Condous et al., 2005.).

A serum: cerebrospinal fluid (CSF) HCG ratio less than 40 is an accurate indication of the presence of brain metastases of gestational trophoblastic tumor, and may have considerable predictive value. However, false-negative serum: CSF HCG ratio (greater than 40) frequently occur in patients with proven brain deposits, and the cerebrospinal fluid puncture or lumbar puncture is difficult to perform for the gynecologist (Bakri et al., 2000.). Magnetic resonance imaging head scan, hence, is now preferred as the most sensitive and safe technology available for brain metastases of gestational trophoblastic tumor.

Culdocentesis is the transvaginal passage of a needle into the posterior cul-de-sac in order to determine whether free blood is present in the abdomen. It is a simple procedure to determine whether there is intraperitoneal hemorrhage. It has been used less frequently in recent years because many gynecologists think it useless for the diagnosis of EP. In the light of the idea that serum: CSF HCG ratio is indication of the presence of brain metastases, making use of the simple operation of culdocentesis, we have proved that HCG ratio of hemoperitoneum versus venous serum (Rp/v-HCG) of EPs is apparently different from that of hiUPs (Wang, et al., 2010.). Hence, in order to provide a single-visit method for predicting EP from SEP, we want to prospectively further assess the diagnostic value of the Rp/v-HCG for early EP. Furthermore, we want to discuss the availability of Rp/v-HCG for rare EP such as abdominal pregnancy et cetera.

2. Materials, methods and results

From March 2005 to Apr 2008, 103 SEPs were retrospectively analyzed for the cut-off value (Rp/v-HCG = 1.0) between EPs and hIUPs (Wang, et al., 2010.). From May 2008 to Nov 2010, we performed this prospective study to prove the diagnostic value of Rp/v-HCG for EPs. All of the 299 patients with stable vital signs were enrolled and evaluated at the out-patient department, in-patient department or emergency center of the Hospital affiliated to JiaoTong University, Shanghai, China.

The hemoperitoneum was collected by culdocentesis (n=255) before surgery or by aspiration during surgery (n=44, thirteen patients among of them rejected the culdocentesis before surgery). Once the hemoperitoneum was obtained, the venous serum was prepared within 1h. The HCG levels of venous serum and hemoperitoneum were quantified by chemiluminescence at the same batch with the same set and HCG kit (Strada per Crescentino, snc, 13040 Saluggia-Ital). Those SEPs with a Rp/v-HCG of ≥ 1.0 were presumed as EPs, those SEPs with a Rp/v-HCG of < 1.0 , however, were classified as hIUPs. The SEPs were finally performed by laparotomy (n=50), laparoscopy (n=141), D&C (n=59) or serial transvaginal ultrasound (n=49).

The final diagnoses of hIUPs were confirmed by sonography during follow up with the presence of an intrauterine fetal heartbeat, by D& C in the presence of chorionic villi or falling serum HCG levels (< 5 U/L) after D& C. A final diagnosis of EP was confirmed by surgical histological pathology, or by exclusion of an hIUP.

The following parameters were recorded in the medical history: gestational age, the existence of vaginal bleeding, venous and peritoneal serum HCG concentration (U/L), ectopic position of sac, with or without active bleeding, the times and the complications of the culdocentesis. A quantitative estimate of the hemoperitoneum was carried out during surgery by calculating the volume of aspirated and irrigated fluid.

As the routine method in the present medical treatments, both the culdocentesis (18 G long needle, 5 ml syringe and a disposable speculum are enough) and quantitative HCG used in the study were carried out simply and safely (no complications were recorded in this study) for the diagnosis of EP by the gynecological resident and laboratory technicians.

The study was performed in accordance with the 1975 Helsinki Declaration on Human Experimentation and approved by Institutional Review Board (IRB). The patient consent forms for culdocentesis, surgery and collecting private medical information were obtained.

2.1 Inclusive criteria

All the suspected ectopic pregnancy (SEP) patients whose peritoneal blood and urine HCG test are positive were enrolled.

2.2 Excluded criteria

All those whose vital sign is unstable or whose hemoperitoneum is absent were excluded.

2.3 Study design

This was a retrospective development of a protocol, followed by a prospective trial.

2.4 Statistical analysis

Analyses were carried out using a statistical package for social sciences (SPSS, Ver 13.0). Unless otherwise stated, values were expressed as means \pm SD or percentage. The

independent sample wilcoxon test or chi-squared test was used to compare variables between the two groups.

The diagnostic performance of Rp/v-HCG for active tubal hemorrhage was expressed using a scatter diagram. The one-step diagnostic value of the Rp/v-HCG for EP was evaluated in terms of the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (CI). The simple kappa coefficient of Rp/v-HCG test was also given for the 2x2 table to assess how the prediction of Rp/v-HCG agreed with the final diagnosis of the EPs.

Significance was defined as p-values less than 0.05 for all the tests and two sided P-values were reported.

2.5 Results

A total of 299 SEPs (average age, 33.1 years; range, 19-42 years) were enrolled and followed to the final diagnosis, which were finally divided into EP group (248 cases, 82.9 percent of SEPs) and hIUP group (51 cases, 17.1 percent of SEPs).

Table 1 shows a statistically significant difference ($P < 0.001$) between the EP group and the hIUP group in terms of the Rp/v-HCG (18.1 ± 40.75 and 0.72 ± 0.29 , respectively) and the conservative treatment (23.0 % and 90.2 %, respectively). The culdocentesis before surgery was performed successfully for 255 SEPs except thirteen patients who rejected the culdocentesis, the success rate of the culdocentesis was 89.2 % (255/ 286), the success rate of the “first-time-right” was 76.9 % (220/ 286), even though the peritoneal fluid depth by ultrasound was only 8-12 mm (Figure 1). No complications of culdocentesis were recorded in this study. Of all the hIUPs, 90.2 percent of patients (46/ 51) were cured relying on the hemostatic therapy (Reptilase) instead of the surgical intervention (laparoscopy). 77.8 percent of patients (14/ 18) who desire to fertility succeeded to continue pregnancy with miscarriage treatment (progesterone).

Group	EP (n=248)	hIUP (n=51)	<i>P value</i>
Rp/v-HCG	18.1±40.75	0.72±0.29	$P < 0.001$
Successful culdocentesis	89.2 % (215/241)	88.9 % (40/45)	$P > 0.05$
PFD (mm)	39±24	41±22	$P > 0.05$
Non-surgical treatment	23.0 % (57/248)	90.2 % (46/51)	$P < 0.001$

* $P < 0.001$ vs hIUP

EP: ectopic pregnancy; hIUP: hemoperitoneum or hematocolpos with intrauterine pregnancy; Rp/v-HCG: HCG ratio of peritoneal serum versus venous serum; PFD: peritoneal fluid depth by ultrasound.

Table 1. Comparison of managements between hIUP group and EP group.

We further confirmed the same cut-off value of the Rp/v-HCG (Rp/v-HCG = 1.0) as the previous results. At this point, the sensitivity and specificity was 98.5% and 100%, respectively (Figure 2).

The SEPs were predicted as EP group and hIUP group according to the Rp/v-HCG cut-off value. The final diagnosis versus the “predicted” diagnosis for suspected EPs were represented in Table 2. When the protocol was tested prospectively on the 299 SEPs, The overall sensitivity of Rp/v-HCG in the diagnosis of ectopic pregnancy was 98.4 % with a specificity of 100 %, a PPV of 100 % and an NPV of 93 %, whilst the likelihood ratio of a

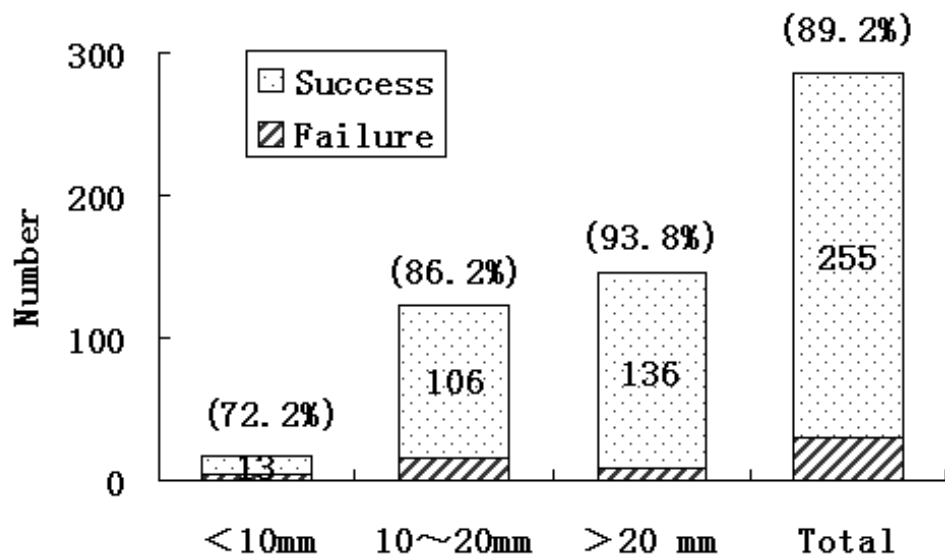


Fig. 1. The success rate of the culdocentesis. The culdocentesis was performed successfully for 255 SEPs in all of the 286 patients, the total success rate of the culdocentesis was 89.2 % (255/ 286). 84.4% (119 /141) percent of SEPs were successfully performed even when the peritoneal fluid depth by ultrasound was of < 20 mm.

negative test (LR-) decreased to 1.5 percent on the test set. The small kappa coefficient of 0.956 ($P = 0.022$) for the prospective test demonstrated that the predicted diagnosis according to the Rp/v-HCG agreed extremely with the final true diagnosis.

For active bleeding of EP, Figure 3 sees no suggested Rp/v-HCG cut-off value for predicting the active tubal hemorrhage.

Four cases of EPs whose Rp/v-HCG was of <1.0 were performed by laparoscopy, which saw no active bleeding but swollen fallopian, or pink peritoneal fluid from the ruptured ovarian luteinized cyst (surgery sees a tension-free cyst). Most of all the other hemoperitoneum of EPs were dark red fluid.

Two cases of abdominal pregnancy (one is splenic pregnancy) with hemoperitoneum were confirmed during surgery according to intact adnexa uteri (the absence of ectopic gestational sac or chorionic villi) and a Rp/v-HCG of > 1.0.

2.5.1 Retrospective analysis: cut-off value of Rp/v-HCG=1.0 between hIUP and EP

SEPs comprise of EPs (or heterotopic pregnancy, HP) and hIUPs (including hemorrhagic corpus luteum combined with pregnancy and hemorrhagic salpingitis, etc.). HP (coexistence of intrauterine and ectopic pregnancy) is a rare entity, the incidence of which has increased with the widespread use of artificial reproductive technology (ART) (Hsieh, et al., 2004.). While the frequency of spontaneous HP varies from 1 : 10,000 to 1 : 50,000 in normal population, the widespread use of ART may play a role in the increased incidence (according to some series nearly 1%) including ampullary and isthmic tubal EP as well as interstitial ectopic ones (Chang, et al., 2003.). Despite increased medical knowledge and use of improved reproductive technologies, an HP or EP still remains a diagnostic and therapeutic challenge to practitioners. Although signs and symptoms such as abdominal pain, adnexal mass, peritoneal irritation, and enlarged uterus have been reported to be predictive of an HP, they are nonspecific and may be confused with other normal or abnormal pregnancy manifestations.

An HP or EP is difficult to ascertain as pain and bleeding might be attributed to a hIUP, such as threatened abortion, hemorrhagic corpus luteum combined with pregnancy (HCLP) or hemorrhagic salpingitis with pregnancy (Barrenetxea, et al., 2007; Cheng, et al., 2004.). Although hemorrhagic corpus luteum cysts are frequently seen during sonography of the female pelvis, their diagnosis is often challenging as a result of variations in size, thickness of the cyst wall, and internal echo pattern depending on the formation and lysis of the clot (Swire, et al., 2004.). It is necessary for gynecological doctor to set up a new method for distinguishing hIUP from EPs.

In tubal EP, the gestational sac is implanted typically in the wall of the tube, in the connective tissue beneath the serosa, where may be little or no decidual reaction and minimal defense against the permeating trophoblast. The trophoblast invades blood vessels so as to cause local hemoperitoneum. A hematoma in the subserosal space enlarges as pregnancy progresses. Distention of the tube then predisposes to rupture or abortion from isthmus or ampullary. For EP, local hCG level of hemoperitoneum is much higher than that of venous serum. The reasons of this finding can be: 1) Blood filling the posterior pouch of Douglas or Morisson's space is from the implantation site of gestational sac, into where the hCG secreted by syntrophoblasts directly flows (hCG secreted into venous serum is relatively low). 2) The metabolism of hCG in the hemoperitoneum is slower than that in venous serum. In HCLP, blood in posterior pouch is from ovarian vessels in which the hCG level is near to that of venous serum (Wang, et al., 2010.). The hCG level of venous serum, however, gradually increases as the IUP proceeds. Then, the last Rp/v-HCG is less than or near to 1.0. Therefore, Rp/v-HCG may promptly distinguish EP from hIUP: as the Rp/v-HCG of EP is always greater than 1.0 while the Rp/v-HCG of hIUP is always less than or near to 1.0.

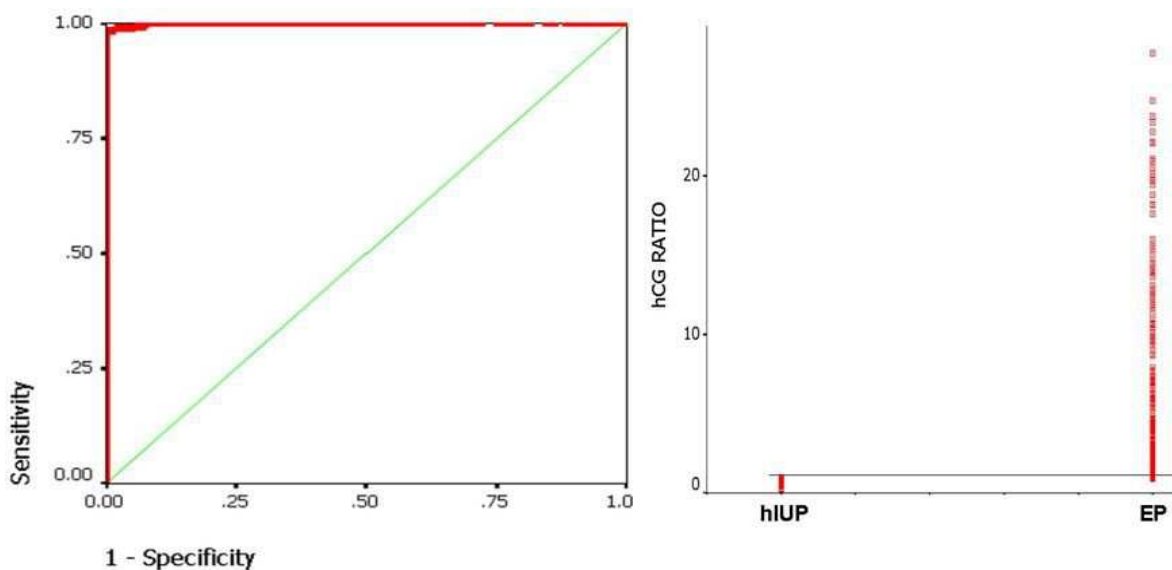


Fig. 2. Cut-off value of the Rp/v-HCG for discriminating EPs from SEPs. ROC analysis showed that the Rp/v-HCG could be used for the differential diagnosis of EP from hIUP, with the area under the curve being 1.0 ($P < 0.001$). The threshold for the diagnosis of EP was 1.0 (at this point sensitivity was 98.5%, and specificity was 100%). Scatter plots of the Rp/v-HCG levels for EPs and hIUPs showed that the Rp/v-HCG levels of EPs mostly located above the value of 1.0. However, the level of hIUPs was absolutely under the suggested cut-off value of 1.0.

In conclusion, in suspected ectopic pregnancy patients, the $Rp/v\text{-HCG} = 1.0$ could be a helpful and practical index for the early differential diagnosis of SEPs. If hemoperitoneum and culdocentesis are positive, the $Rp/v\text{-HCG}$ could help discriminate EPs (or HP) from hIUP, and accordingly avoid the unnecessary surgical interventions.

2.5.2 Prospective analysis: Rapid diagnostic value of $Rp/v\text{-HCG} \geq 1.0$ for EPs before surgery

EP can not be diagnosed solely on the basis of clinical symptoms, such as lower abdominal pain and vaginal bleeding. The ultrasound visualization of heart activity in either intrauterine or extrauterine gestations is important for diagnosis, but rare to accomplish (Oliveira, et al., 2001.). Moreover, during an ultrasound examination, an EP or HP is easily misdiagnosed as a luteal cyst, especially if the concurrent intrauterine pregnancy is reassuring (Habana, et al., 2000.). It is not accurate and rapid enough to meet the need of a clinical gynecologist though a total of 87~93.2% of ectopic pregnancies can be diagnosed using serial transvaginal sound alone (Shalev, et al., 1998; Rosello, et al., 2003.).

Though a single serum hCG value neither identifies an intrauterine or ectopic pregnancy nor predicts ruptured ectopic, it can be used to determine the level of “discriminatory hCG value” at which the sensitivity of ultrasonography for the detection of intrauterine pregnancy approaches 75% and at which the absence of an intrauterine pregnancy suggests abnormal or ectopic gestation. This reported “discriminatory hCG value”, however, ranges from 1500 to 3000 mIU per milliliter. The use of a value at the lower end of the range increases the sensitivity for the diagnosis of an ectopic pregnancy, but it also increases the false positive rate, with the attendant risk of interrupting a normal gestation by surgical or medical intervention. In one study, when the hCG value was below 1500 mIU per milliliter, the positive predictive value of ultrasonographic testing for the diagnosis of intrauterine pregnancy was only 80% and the positive predictive value for the diagnosis of ectopic pregnancy was 60% (Barnhart KT, et al., 1999; Romero R, et al., 1985).

When using an HCG ratio (HCG at 48 h/ HCG at 0 h) cut-off of 0.87, the sensitivity and specificity for the prediction of failing Pregnancy of unknown locations were 92.7 and 96.7%, respectively (Condous., 2006.). A rate of decline in serum HCG 21% could define spontaneous resolution of the pregnancy of unknown locations (Barnhart et al., 2004.). Serial quantitative HCG, however, could not meet the rapid diagnosis of EPs.

Laparoscopy is currently considered as the golden standard for the diagnosis of ectopic pregnancy (Ankum et al., 1993.). However, the application of diagnostic laparoscopy is limited to the expensive charge and apparent trauma.

Dilatation and curettage is recommended as a diagnostic method for use in conjunction with low progesterone or $\beta\text{-HCG}$ concentrations and in women in whom transvaginal ultrasound suggests a non-viable intrauterine pregnancy. (McCord et al., 1996; Stovall et al., 1992.) The absence of chorionic villi is associated with an ectopic pregnancy in 40% of women with an empty uterus on ultrasound. An ectopic pregnancy is suggested in women whose $\beta\text{-HCG}$ concentrations do not fall by at least 15 % in the 12 h after dilatation and curettage, or in whom the histological findings do not include chorionic villi. However, use of dilatation and curettage in the diagnostic workup of SEPs has not been widely adopted, in part because some women are reluctant to give up the desiration of fertility, and in part because many women who miscarry can be managed without the need for curettage (Mol, et al., 2002; Wieringa-de, et al., 2002; Dart, et al., 1999.).

Predicted Diagnosis	True diagnosis		Total	
	EP	hIUP		
Rp/v-HCG \geq 1.0:EP	244	0	244	Kappa=0.956 (P<0.001)
Rp/v-HCG<1.0:hIUP	4	51	55	
Total	248	51	299	

Sensitivity=98.4 %; Specificity=100 %;
 NPV =93.0 %; PPV =100%;
 LR(-)=1.5%; π =98.7 %; Youden index=98.4 %

EP: ectopic pregnancy; hIUP: hemoperitoneum or hematocolpos with intrauterine pregnancy; Rp/v-HCG: HCG ratio of peritoneal serum versus venous serum

Table 2. Evaluation of Rp/v-HCG: final diagnosis versus predicted diagnosis.

It is noted that four cases of SEPs with pink fluid and Rp/v-HCG of < 1.0 were all proved to be EPs, whose hemoperitoneum (pink or bloody-like fluid) were not from fallopian tube rupture or abortion but from the hemorrhagic corpus luteal cyst (3 cases) and hemorrhagic salpingitis (1 case). Therefore, the Rp/v-HCG of < 1.0 could not completely exclude the diagnosis of EP, especially when hemoperitoneum is pink or bloody-like fluid (Qiu, et al., 2010.). That is to say, for SEPs whose Rp/v-HCG of < 1.0, serial transvaginal sound may be followed to prove the intra-uterine pregnancy.

Table 2 shows that the success rate of the culdocentesis is 89.2 % (255 /286) without any complications. 90.2 percent of the hIUPs (46/51) are successfully managed with conservative treatment instead of the surgical intervention (P<0.001). The overall sensitivity of Rp/v-HCG > 1.0 in the diagnosis of ectopic pregnancy is 98.4 % (95% CI: 95.9-99.6) with a specificity of 100 % (95% CI: 93.0-100), a PPV of 100 % (95% CI: 98.5-100) and an NPV of 92.7 % (95% CI: 82.4-98.0). The kappa value of Rp/v-HCG test comparing to the final diagnosis is 0.956 (P < 0.0001). Hence, the Rp/v-HCG \geq 1.0 is practical and rapid for the diagnosis of EPs.

2.5.3 Rp/v-HCG for predicting the active tubal hemorrhage of EPs

No apparent Rp/v-HCG cut-off value for predicting the active tubal hemorrhage is shown when the HCG level of venous serum is more than 1500U/L. When the HCG level of venous serum is less than 1500U/L, however, few patients have the active tubal hemorrhage. It seems that the Rp/v-HCG is higher; the incidence rate of active tubal hemorrhage is lower. It is very important for gynecological emergency doctor to predict the presence of tubal hemorrhage in EPs. No ideal marker for tubal hemorrhage of EPs, however, has been founded in the present medical procedure till to now.

2.5.4 Rp/v-HCG > 1.0 for diagnosing the abdominal pregnancy during surgery

Abdominal pregnancy is an extremely rare form of ectopic pregnancy (EP) with potentially life-threatening complications both to mother and the fetus, which is historically defined as an implantation in the peritoneal cavity, exclusive of tubal, ovarian or intraligamentary pregnancy.

Due to infrequency of abdominal pregnancy, it is often unsuspected and remains a diagnostic challenge despite improvements in imaging techniques (Dassah, et al., 2009.). A retrospective analysis show there were 20 cases of abdominal pregnancy out of 58, 000

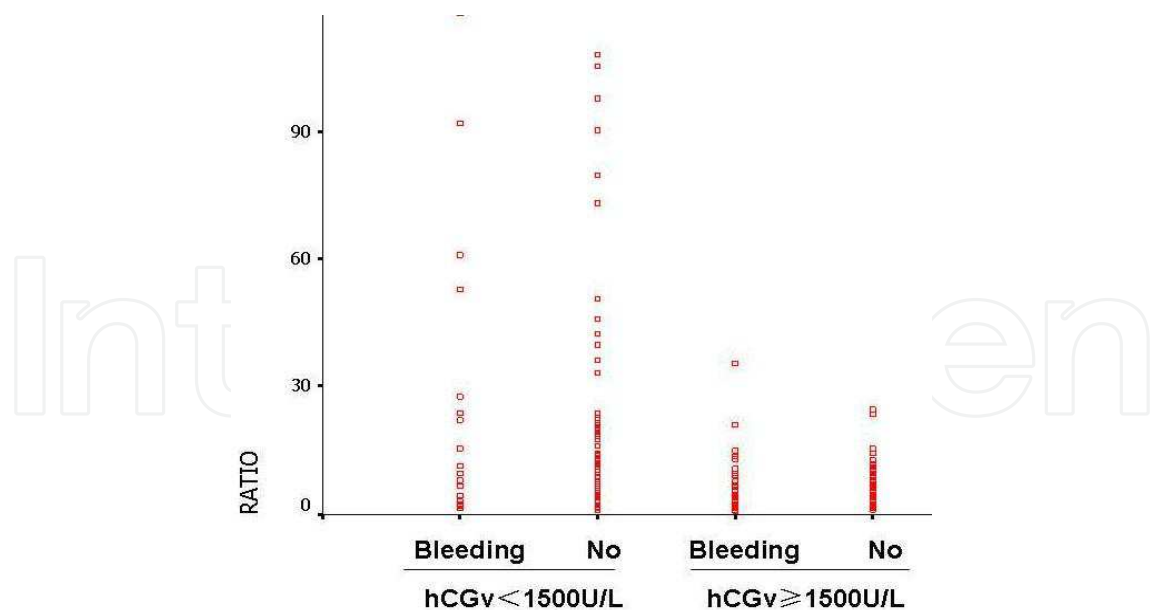


Fig. 3. Scatter diagram of the Rp/v-HCG levels for active bleeding group and without active bleeding (No) group when HCG of venous serum was more than 1500U/L or less than 1500U/L. No suggested Rp/v-HCG cut-off value for the distribution of the active tubal hemorrhage was shown when HCG of venous serum was more than 1500U/L.

deliveries, giving an incidence of 0.34 per 1,000 deliveries. The diagnoses were missed in 10 cases and there was one maternal death. The rate of 50% missed diagnosis in this analysis highlights the need for a high index of suspicion in the diagnosis of abdominal pregnancies as the clinical features are varied. The maternal and fetal outcomes relate to early diagnosis and skilled management, which calls for vigilance on the part of the obstetrician (Sunday-Adeoye, et al., 2011.).

In this study, two SEPs whose Rp/v-HCG was of > 1.0 showed normal fallopian tube and ovary but hemoperitoneum during the laparotomy. They were both diagnosed as abdominal pregnancy (one was splenic pregnancy) finally after thorough pelvic and abdominal exploration. One of the splenic pregnancy suffered second exploration and splenectomy because it is mistaken as hemorrhagic corpus luteum combined with pregnancy by the gynecologist who ignored of Rp/v-HCG was of > 1.0 . Hence, the criteria of diagnosis for abdominal pregnancy may be considered: 1) No evidence of gestational sac or chorionic villi in the adnexa is seen during the surgery, 2) Rp/v-HCG, however, is of > 1.0 .

Transvaginal ultrasound and serial β -hCG level are of little use for the differential diagnosis between hemoperitoneum with intrauterine pregnancy and ectopic pregnancy including abdominal pregnancy, however, the overall specificity of Rp/v-HCG > 1.0 in the diagnosis of ectopic pregnancy is 100% (95% CI: 93.0–100), a PPV of 100% (95% CI: 98.5–100). Therefore, we may consider the definitive diagnosis of ectopic pregnancy when preoperative Rp/v-HCG is of > 1.0 and consider the diagnosis of abdominal pregnancy when preoperative or intraoperative Rp/v-HCG is of > 1.0 , however, the adnexa sees no evidence of gestational sac. It is useful for gynecologists to reduce omission diagnostic rate of abdominal pregnancy, especially during the emergency surgery without enough preoperative preparation. Due to the rare case, further study with more data of abdominal pregnancy is needed.

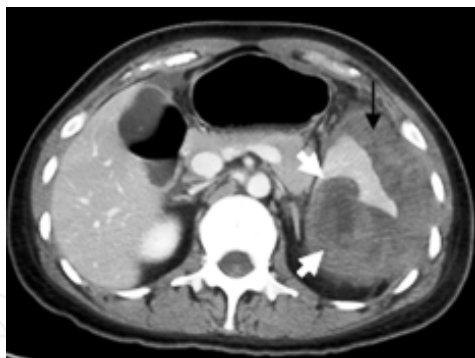


Fig. 4. Contrast enhancement scan of computerized tomography (CT) for splenic pregnancy. One SEP whose Rp/v-HCG = 2.2 (22286 IU/L /9974.9 IU/L) showed intact fallopian and ovary during laparoscopy and then was performed by D &C. Twelve days after operation, CT showed the embryo sac (white arrow) and hematoma under splenic capsule (black arrow).

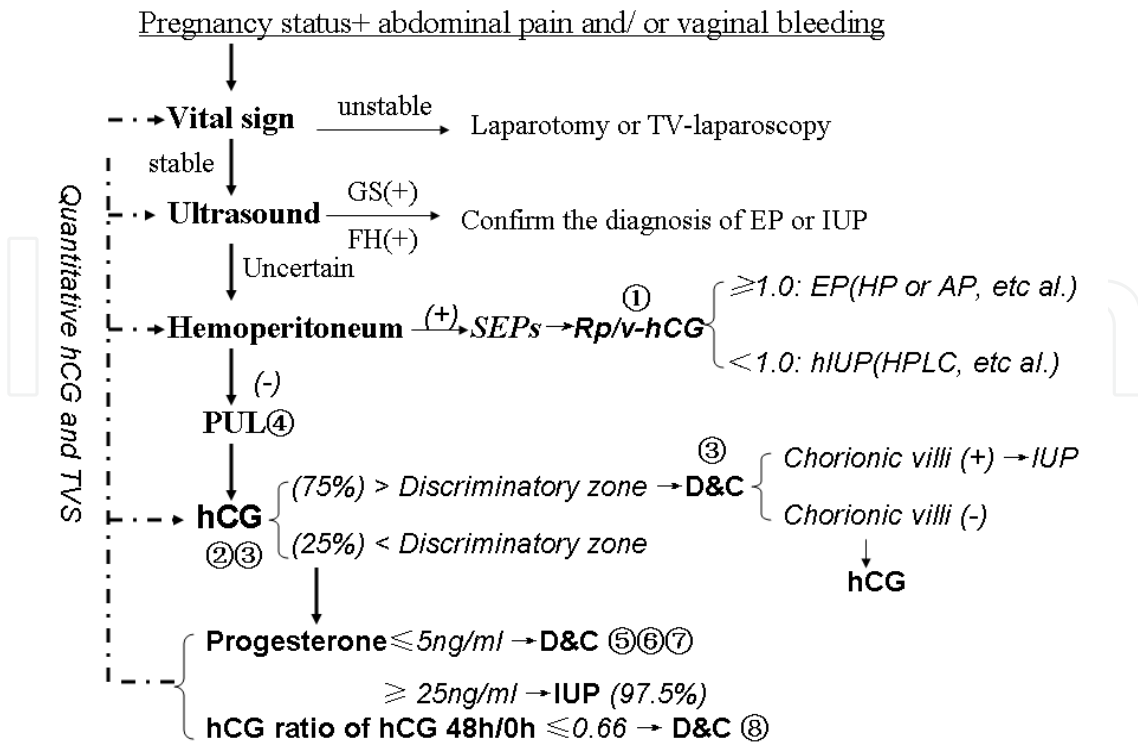
3. Conclusion

Early diagnosis of ectopic pregnancy is the key to optimal treatment, especially is essential in order to minimize the morbidity and to assess the need for urgent surgical intervention. Intervention prior to rupture prevents hemorrhage, potentially enhances fertility, and allows for nonsurgical methods (Segal, et al., 2010.). Observational studies indicate that among women treated with salpingostomy as compared with those treated with salpingectomy, rates of subsequent intrauterine pregnancy are higher (73% vs. 57%) though the rates of subsequent ectopic pregnancy are also higher (15% vs. 10%) (Seeber, et al., 2006; Mol, et al., 2008.).

Though the advent of β -HCG measurements and improved transvaginal ultrasound techniques has made laparoscopic diagnosis of ectopic pregnancy almost redundant and allowed for both expectant and medical management options, combining transvaginal ultrasonography with gonadotropin quantification could not give the most satisfactory results since it takes an average of 36 h to diagnose EP, not including the resources devoted to collecting blood samples (Garcia, et al., 2001.). Hence, additional new tests or diagnostic methods are necessary to be established for a rapid and accurate diagnosis of EP prior to initiation of either medical or surgical intervention.

Besides laparoscopy and transvaginal sound, serum biomarkers (including HCG) may be helpful for the early diagnosis of EPs. Over 20 serum biomarkers have been identified to date in an attempt to permit earlier diagnosis of ectopic pregnancy, the instigation of earlier management and reduce healthcare costs (Cartwright, et al., 2009; Pedersen, et al., 1991.). The ideal marker for the diagnosis of ectopic pregnancy would be specific for tubal damage or present only after endometrial implantation. Various markers have been assessed, including creatinine kinase (Lavie, et al., 1993.) and fetal fibronectin (Ness, et al., 1998.), but none is sufficiently sensitive or specific for the diagnosis of ectopic pregnancy.

Certain serum biomarkers have been shown initially to be of discriminatory value but then subsequent studies have found them to be of limited use (such as placental protein 14) (Daponte, et al., 2008; Mantzavinos, et al., 1991.). A number of biomarkers (such as estradiol, pregnancy associated plasma protein A, cancer antigen 125) can distinguish a tubal ectopic from a viable intrauterine pregnancy but are unable to distinguish the former from a non-viable intrauterine pregnancy (miscarriage) (Mueller, et al., 2004; Katsikis, et al., 2006).



Note: IUP: intrauterine pregnancy; PUL: pregnancies of unknown location; SEP: suspected ectopic pregnancy; GS: gestational sac; FH: fetal heart; Rp/v-hCG: hCG ration of peritoneum versus venous serum. Discriminatory zone or discriminatory concentration is depend on the standard utilized in any given laboratory, in general, 6500 IU/L for abdominal ultrasound and 1500 IU/L (or 2400U/L) for transvaginal ultrasound. Uterine curettage may be useful following endocrine documentation that suggests a nonviable pregnancy regardless of it's location.

①Wang et al., 2010; ②Barnhart et al., 1994; ③Barnhart et al., 2002; ④Kirk et al., 2007; ⑤Stovall et al., 1992; ⑥Anonymous., 1992; ⑦Dart et al., 2002; ⑧Kadar et al., 1988.

Fig. 5. Diagnostic flow chart of EP



Fig. 6. Pink fluid from not ruptured fallopian tube but hemorrhagic salpingitis of an EP (A); dark red fluid from fallopian tube abortion of an EP (B)

Other markers (such as vascular endothelial growth factor, creatinine kinase and progesterone) have been studied extensively in relation to ectopic pregnancy but the results have been so conflicting that none have been put into clinical use (Develioglu, et al., 2002.). The clinical utility of these biomarkers is limited because of variable results due, for the most part, to limitations in study design. In many studies, the cohort examined was very small and the prevalence of ectopic pregnancy within the study population was not constant. In some studies, patients were not accurately matched for gestation. This reflects the difficulty in determining the gestational age of an ectopic pregnancy. Some of the serum biomarkers also limited their own use, as they did not follow a steady pattern (increase or decrease) with a normal gestation. Moreover, changes in the serum assays and the reagents used to detect the biomarkers over the decades have led to conflicting results between studies.

It was once concluded that culdocentesis is not a useful tool in the diagnosis of suspected ectopic pregnancies because the false negative rate for culdocentesis was 14.8% or so. What is more important, it does not distinguish an ectopic pregnancy from hIUP (Elliot, et al., 1990; Glezerman, et al., 1992.). According to our data, culdocentesis could be routinely, safely and simply performed during clinical practice without any complications. The success rate of the culdocentesis was 89.2 %, even though the peritoneal fluid depth by ultrasound was only 8-12 mm. Moreover, positive culdocentesis could contribute to a quick and accurate differential diagnostic algorithm for SEPs. In this study, we proved that a patient whose Rp/v-HCG is more than 1.0 may be diagnosed and treated instantly as an EP to avoid tubal rupture. The overall sensitivity of $Rp/v-HCG \geq 1.0$ in the diagnosis of ectopic pregnancy is 98.5 % with a specificity of 100 %, whilst the small kappa coefficient of 0.956 for the prospective test demonstrates that the predicted outcome according to the Rp/v-HCG agreed extremely with the final true diagnosis. At least, Rp/v-HCG involving the culdocentesis provides a new method for rapid diagnosis of EP, which is helpful for fulfilling the diagnostic flow chart of EPs (see Fig 2), though the patients should be managed according to Garcia et al if culdocentesis is negative (Garcia, et al., 2001.).

The culdocentesis will reveal nonclotting blood if intra-abdominal bleeding has occurred. Although nonclotting blood is assumed to be from a ruptured ectopic, similar results can also be obtained under other circumstances (eg, a hemorrhagic corpus luteum), and thus a positive results is not diagnostic of a ruptured ectopic pregnancy. In other words, not all the positive hemoperitoneum on ultrasound examination or by culdocentesis be an absolute contraindication to conservative management of tubal ectopic pregnancy (Bignardi, et al., 2009.). Therefore, whether Rp/v-HCG could predict the existence of active bleeding is important for the prognosis of EPs. Though there was a statistically significant difference between the Rp/v-HCG of the patients with or without active bleeding when the venous hCG (hCGv) of EP was >1500 U/L (Wang, et al., 2010.), no diagnostic value was seen in this study, that is, it is of no use for predicting the prognosis of fallopian tube or EP patient.

In order to expand the application of the new one-step protocol for not only the SEPs whose hemoperitoneum and culdocentesis are positive but also those whose hematocolpos is positive, it is necessary to determine whether the HCG ratio of hematocolpos versus venous serum (RC/V-HCG) alone also could provide a rapid diagnosis of EP.

4. Acknowledgment

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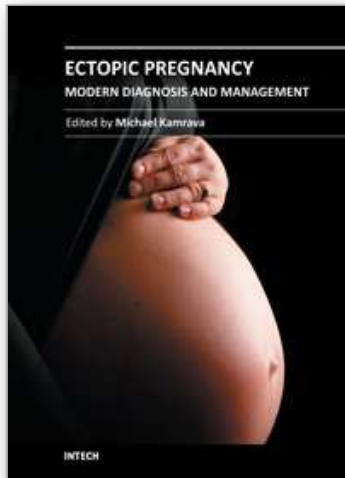
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