

Study On Diagnosis And Management Strategies On Heterotopic Pregnancy

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Abstract

Objective The aims of this study were to analysis the clinical characteristics of women with heterotopic pregnancy (HP) following embryo transfer (ET) and explore the early predictors for pregnancy outcomes.

Methods This retrospective study reviewed patients with HP following assisted reproductive technology (ART) in our institution between January 2013 and December 2020. The relationships between pregnancy outcomes and general features, ultrasonic characteristics and different treatment modality were analyzed by logistic regression analysis.

Results Fourty patients were identified, including 27 with tubal HP, 7 interstitial HP and 6 cornual HP. The most frequent manifestations before diagnosis was vaginal bleeding (30.0%), while 7 patients (17.5%) had no symptoms before diagnosis. The mean gestational age at symptom onset was 44.8 ± 8.6 days (range 27–68). Gestational age at diagnosis was 49.4 ± 7.6 days (range 29–68). Among these cases, twenty-nine patients of HP were accurately diagnosed by transvaginal ultrasonography (TVS). Hence, the sensitivity of TVS for detecting HP was 72.5% (29/40). Eleven patients received expectant management, while 29 patients underwent laparotomy (13/29) or laparoscopy (16/29) surgery. Gestational age at surgery day was 51.0 ± 8.6 days (range 33–67). Live births occurred for 18 patients in the surgery group, 3 of whom delivered preterm. Additionally, the miscarriage rate was lower for patients with IUP cardiac activity (16.7% vs. 90.0%) than patients without IUP cardiac activity at HP diagnosis ($P < 0.001$). Further by logistic regression analysis, an IUP with cardiac activity at HP diagnosis was identified as an independent factors of pregnancy outcome ($P < 0.001$).

Conclusions Symptoms combined with routine TVS scans could reduce misdiagnosis and facilitate the diagnosis of HP. An IUP with cardiac activity at HP diagnosis as predictors for a favorable prognosis of HP. Prompt surgical intervention after diagnosis may minimize the incidence of abortion of IUP.

Plain English Summary

Heterotopic pregnancy (HP) refers to the simultaneous presence of the intrauterine pregnancy (IUP) and ectopic pregnancy (EP) in an individual. HP is a rare but potentially life-threatening event with a high risk of tubal rupture, hemorrhage shock, and maternal death, which also jeopardize IUP, thus an early accurate diagnosis and a positive treatment modality can decrease adverse complications. The aims of this study were to analysis the clinical characteristics of women with heterotopic pregnancy (HP) following embryo transfer (ET) and explore the early predictors for pregnancy outcomes.

In this retrospective study, we reviewed patients with HP following assisted reproductive technology (ART) in our institution between January 2013 and December 2020. The relationships between pregnancy outcomes and general features, ultrasonic characteristics and different treatment modality were analyzed by logistic regression analysis. We found that the most frequent manifestations before diagnosis was vaginal bleeding (30.0%), while 7 patients (17.5%) had no symptoms before diagnosis. Twenty-nine patients of HP were accurately diagnosed by transvaginal ultrasonography (TVS).

Hence, the sensitivity of TVS for detecting HP was 72.5% (29/40). Eleven patients received expectant management, while 29 patients underwent laparotomy (13/29) or laparoscopy (16/29) surgery. Live births occurred for 18 patients in the surgery group, 3 of whom delivered preterm. Additionally, the miscarriage rate was lower for patients with IUP cardiac activity (16.7% vs. 90.0%) than patients without IUP cardiac activity at HP diagnosis ($P < 0.001$). Further by logistic regression analysis, an IUP with cardiac activity at HP diagnosis was identified as an independent factors of pregnancy outcome ($P < 0.001$).

In conclusion, symptoms combined with routine TVS scans could reduce misdiagnosis and facilitate the diagnosis of HP. We supported an IUP with cardiac activity at HP diagnosis as predictors for a favorable prognosis of HP, and prompt surgical intervention after diagnosis may minimize the incidence of abortion of IUP.

Key Message

Gestational age at intervention may as the main independent risk factor for miscarriage rate, the early diagnosis and treatment of HP are extremely important to prevent maternal life-threatening conditions.

Introduction

Heterotopic pregnancy (HP) refers to the simultaneous presence of the intrauterine pregnancy (IUP) and ectopic pregnancy (EP) in an individual [1]. The incidence of HP is known to be less than 1 in 30,000 in spontaneous conceptions and has been reported to raise to a rate of 0.09%-1% in gestations after ovarian induction or assisted reproductive technology (ART) [2, 3]. HP is a rare but potentially life-threatening event with a high risk of tubal rupture, intraperitoneal hemorrhage, and maternal death, which also jeopardize IUP, thus an early accurate diagnosis and a positive gynecologic treatment implemented at the correct time can decrease adverse complications [4].

The early diagnosis of HP is challenging due to the co-existence of a viable IUP and the absence of atypical clinical symptoms [5]. Serial β -human chorionic gonadotropin (β -hCG) level and β -hCG rise are helpful to discriminate between EP and one normal IUP, but it is useless to predict HP. Transvaginal ultrasonography (TVS) is critical for the diagnosis of HP with high sensitivity (87–99%) and specificity (94–99.9%) [6]. However, if EP lesion is too small to identify or failing to inspect the pelvic fully, may lead to increase the difficulties in early-stage HP diagnosis. It is worthy to be familiar with risk factors of HP and clinical characteristics after ART.

The aim treatment of HP is to remove EP mass while maintaining normal IUP as much as possible, so as to decrease risk of adverse pregnancy outcomes. Treatment strategies include surgical management, expectant management, and ultrasound-guided gestational sac aspiration with or without embryo-killing drugs [7]. However, HP remains a diagnostic and therapeutic challenge due to the treatment experiences remain limited and without sufficient evidence-based medicine data of good perinatal outcome of IUP.

The objective of this study was to summarize the clinical characteristics of HP, analyze the influence of different treatment strategies on IUP and evaluate the potential risk factors that predict HP, and thus to explore the standard therapeutic schedule for such a rare event and ensure better perinatal outcome of IUP.

Materials And Methods

Participants

We retrospectively included 40 patients diagnosed with HP in Fujian Maternity and Child Health Hospital between January 2013 and December 2020. Data including patient characteristics, clinical pregnancy details, treatment strategies of EP, as well as perinatal pregnancy outcomes of IUP were prospectively collected into a database for analyzed. The women without undergoing the first TVS examination in our institution, providing incomplete information, or the fetus with anatomical and chromosomal abnormalities were excluded. Approval was not requested from the human institutional review board, since the study was a summary of information of diagnosis and treatment was considered routine management at our hospital.

HP was diagnosed mainly based on TVS examination (first TVS), the serum β -HCG level and the history clinical manifestations used as a reference. Biochemical pregnancy was defined as a β -HCG level above 10 MIU/ml, measured at 13 days after embryo transfer (ET), and continuing to rise. IUP was defined as a yolk sac and/or fetal pole in an intrauterine sac, regardless of cardiac activity detecting by TVS. The diagnosis of tubal HP (excluded interstitial) was suspected when an IUP was accompanied with a gestational sac with or without cardiac activity, an empty extrauterine sac with a hyperechoic ring or a heterogeneous adnexal mass in an extrauterine sac[8]. The differential diagnosis of cornual pregnancy and tubal interstitial pregnancy was based on as follows: the gestational sac location, inner/lateral side of the uterine horn, complete muscular layer around, connecting with the endometrial line, and inside/outside the ligament during the operation.

When a suspiciously HP was diagnosed, patients were managed different treatment modalities depending on repeated TVS and clinical symptoms. Patients with interstitial/cornual HP received cornual resection by experienced senior surgeons to remove the ectopic mass and those with tubal HP received laparotomic or laparoscopic salpingectomy. After the patient discharged, patient clinical manifestations, treatment protocol of HP, related complications after surgical treatment as well as clinical pregnancy details were summarized. Each patient received a telephone follow-up interview to inquire about her clinical outcomes, which included miscarriage rate, rate of live birth, unviable premature delivery, term delivery rate and fetal development, etc. The endpoint of the follow-up was the completion or termination of the respective pregnancy.

Statistical analysis

The statistical analyses were carried out in SPSS software(ver.21.0). Continuous variables that followed normal distributions were expressed as the mean \pm standard deviation and categorical variables were shown as percentage or raw numbers. Measurement data was compared using Student's t-test, if homogeneity test of variances was not significant, otherwise, Mann–Whitney U-test was chosen. Count data was compared using chi-square test and Fisher's exact test. Multiple linear regression analysis was performed to explore independent predictors for gestational age at diagnosis and to identify the independent impact factors of clinical outcomes in patients with HP. A value of $P \leq 0.05$ was considered statistically significant.

Results

The clinical characteristics of HP were listed in Table 1. The mean age of the 40 patients was 30.4 ± 4.9 (range 21–45) years, the mean body mass index (BMI) was 21.7 ± 2.7 (range 17.3–29.6) kg/m². About the surgical history, 12 (30.0%) patients had undergone uni/bilateral tuboplasty to treat fallopian tube obstruction, and seven (17.5%) patients bilateral salpingectomy/tubal ligation because of severe hydrosalpinx. Five (12.5%) patients had received unilateral salpingectomy due to tubal ectopic pregnancy, and sixteen patients had no history of tubal surgery. Fifteen (37.5%) patients had a history of primary infertility, and twenty-five patients reported a history of pregnancy. All patients have two embryos transferred. Of these women, 15 patients had pregnancies via fresh non-donor embryo transfer cycles, and 25 patients conceived after frozen-thawed embryo transfer.

Table 1
General characteristics

Variables	No. (%) of patients
Age, mean \pm SD (range), yr	30.4 \pm 4.9(21-45)
BMI, mean \pm SD (range), kg/m ²	21.7 \pm 2.7 (17.3–29.6)
History of abortion, n (%)	
0	15 (37.5)
1-2	12 (30.0)
\geq 3	13 (32.5)
History of tubal surgery, n (%)	
Salpingotomy	0
Uni/bilateral tuboplasty	12 (30.0)
Unilateral salpingectomy	5 (12.5)
Bilateral salpingectomy/tubal ligation	7 (17.5)
No	16 (40.0)
Type of infertility, n (%)	
Primary	15 (37.5)
Secondary	25 (62.5)
Method of pregnancy, n (%)	
Frozen-thawed embryo	15(37.5)
Fresh non-donor embryo	25(62.5)
SD Standard deviation, BMI body mass index	

The symptoms of HP were reported as abdominal pain, irregular vaginal bleeding, rectal tenesmus and sometimes nausea or dizzy in cases (listed on Table 2). The most frequent manifestations before diagnosis were vaginal bleeding (30.0%), 9 patients (22.5%) had abdominal pain, but 7 patients (17.5%) had no symptoms and were found by routine ultrasound examination. We reviewed previous abortion, previous ectopic pregnancy, and pelvic surgery history in HP, 37.5% (15/40) of HP had no abortion before; and 12.5% (5/40) of HP had ectopic pregnancy before. HP could constantly occur at fallopian tubes, and occasionally happen at ovary or at tubal stump (the distribution of EP location was shown in Table 2). Most of ectopic lesion in HP occurred at fallopian tubes, taking up 67.5% (27/40); and 17.5% (7/40) of ectopic lesion occurred at interstitial fallopian. States of ectopic embryos was confirmed by surgery, nine

patients were diagnosed with rupture of EP, two of them had suffered hypovolemic shock, fortunately with no maternal death.

Table 2
Diagnostic information

Variables	No. (%) of patients
Clinical manifestations, n (%)	
Asymptomatic	7(17.5)
Abdominal pain	9(22.5)
Vaginal bleeding	12(30.0)
Abdominal pain and vaginal bleeding	9(22.5)
Rectal tenesmus	3(7.5)
Location of EP, n	
Tubal (right vs. left)	27 (13 vs. 14)
Interstitial (right vs. left)	7 (5 vs. 2)
Cornual (right vs. left)	6 (3 vs. 3)
Gestational age at symptom onset, mean \pm SD (range), d	44.8 \pm 8.6 (27–68)
Gestational age on first TVS, mean \pm SD (range), d	46.3 \pm 7.6 (29–68)
Gestational age at diagnosis, mean \pm SD (range), d	49.4 \pm 7.6 (29–68)
First TVS suspected HP, n (%)	
Yes	29(72.5)
No	11(27.5)
Diameters of gestational mass, mean \pm SD (range), mm	24.1 \pm 11.5 (11.3–56.3)
EP Ectopic pregnancy, TVS transvaginal sonography, HP heterotopic pregnancy, IUP Intrauterine pregnancy	

Thirty-five patients (83.3%) had symptoms appearing before first TVS, and the other 5 patients after TVS, the mean gestational age at symptom onset was 44.8 \pm 8.6 (range, 27-68) days. The gestational age at the time of diagnosis was 49.4 \pm 7.6 (range, 29-68) days. The time of diagnosis by TVS ranged from 15 and 54 days after ET, and the mean gestational age on first TVS was 46.3 \pm 7.6 (range, 29–68) days. The mean gestational mass diameter of the EP was 24.1 \pm 11.5 (range, 11.3-56.3) mm. Twenty-nine (85.5%) patients had suspected HP when they received first TVS. Among these cases, 23 patients were present as inhomogeneous masses, 3 patients were extrauterine empty gestational sacs, 3 patients were gestational sacs with yolk, and 11 patients were feta poles with cardiac activity. Moreover, patients who found no

sign of ectopic embryos on first TVS had received repeated TVS before they were admitted to inpatient department. Hence, the sensitivity of TVS for detecting HP was 72.5% (29/40).

In order to monitor the changing situation of HP, patients were admitted to receive repeated TVS. The last TVS before surgery showed that 30 patients (75.0%) were detected the fetal cardiac activity in intrauterine conception (Table 3). Eleven patients received expectant management, 29 patients underwent laparotomy (13/29) or laparoscopy (16/29) without anesthetic complications, and no patients received ultrasound-guided embryo aspiration. The mean gestational age at surgery day was 51.0 ± 8.6 (range 33–67) days. In the expectant group, no patients suffered rupture of ectopic pregnancy and 3 miscarriages occurred during the period of strict observation. In the surgical group, 9 patients had EP ruptures, 3 of whom required blood transfusions. The total miscarriage rate in the surgical group was 37.9% (11/29). Furthermore, there was no significant difference between perinatal outcome in the expectant management vs. surgical groups ($P=0.169$).

Table 3
Surgical information and clinical outcomes

Variables	No. (%) of patients
Management of HP, n (%)	
Expectant management	11(27.5)
Surgical management	29(72.5)
Embryo aspiration management	0
TVS before surgery	
IUP, n (%)	
Gestational sac	10(25.0)
Fetal cardiac activity	30(75.0)
HP, n (%)	
Inhomogeneous/hyperechoic mass	23(57.5)
Gestational sac	6(15.0)
Fetal cardiac activity	11(27.5)
Gestational age at surgery day, mean \pm SD (range), d	51.0 \pm 8.6 (33–67)
Clinical outcomes, n (%)	
Term delivery	22(55.0)
Preterm delivery	4(10.0)
Abortion	14(35.0)
Mode of delivery, n (%)	
Vaginal delivery	5(19.2)
Cesarean section	21(80.8)
IUP Intrauterine pregnancy	

TVS at HP diagnosis revealed that a gestational sac of an IUP without fetal cardiac activity was found in 10 patients, while with fetal cardiac activity was found in 30 patients. Moreover, both 3 patients with empty gestational sac and 4 patients with yolk sac for the IUP were ended in early miscarriage. The miscarriage rate was 16.7% (5/30) for patients with IUP cardiac activity at HP diagnosis, and 90.0% (9/10) for patients without IUP cardiac activity; a significant correlation was identified ($\chi^2 = 18.857$, $P < 0.001$) (Table 4). Additionally, the abortion rate of patients after frozen-thawed embryo was lower than patients following fresh non-donor embryo ($P < 0.05$). Further logistic regression models indicated that

patients following an IUP with fetal cardiac activity at HP diagnosis were identified as an independent factor of perinatal outcome ($P < 0.001$) (Table 5). However, the rate of miscarriage exhibited no significant association with other factors, such as patients' age, first TVS-suspected HP, gestational age at diagnosis, HP positions, ectopic gestational mass diameter, EP fetal heartbeat, pelvic hemorrhage volume (Table 5).

Table 4
The clinical outcomes of patients with HP

Variables	No. of patients	Abortion	Premature birth	Full-term birth	χ^2	P value
IUP without cardiac activity					18.857	<0.0001 ¹
Empty gestational sac	3	3	0	0		
Yolk sac	4	4	0	0		
Yolk sac and fetal pole	3	2	0	1		
IUP with cardiac activity	30	5	4	21		
1 The abortion rate of patients without IUP cardiac activity group was higher than patients with IUP cardiac activity group at HP diagnosis, and the difference was significant ($\chi^2 = 18.857$, $P < 0.001$).						

Table 5

Uni- and Multi-variable logistic regression of predictive factors associated with pregnancy outcomes in HP patients

Variables	Univariate analyses			Multivariate analyses	
	N	P	Regression coefficient (SE)	P	95%CI
Age (years)					
<34	29	0.406	0.144(0.172)	0.846	-0.286~0.347
≥34	11				
Method of IVF-ET, n (%)					
Frozen-thawed embryo	15	0.130	0.240(0.155)	0.412	-0.175~0.416
Fresh non-donor embryo	25				
Gestational age at diagnosis, d					
<52	24	0.694	-0.062(0.158)	0.870	-0.288~0.338
≥52	16				
Suspected HP at the initial TVS, n					
Yes	29	0.406	0.144(0.172)	0.805	-0.470~0.368
No	11				
Gestational mass diameter (mm)					
<30	30	0.262	0.200(0.176)	0.151	-0.084~0.520
≥30	10				
EP fetal heartbeat					
Yes	11	0.914	-0.019(0.173)	0.267	-0.600~0.173
No	29				
IUP fetal heartbeat					
Yes	30	<0.001	0.733(0.133)	<0.001	0.474-1.119
No	10				
HP positions					
Adnexal regions	27	0.758	0.051(0.165)	0.655	-0.390~0.249

Variables	Univariate analyses			Multivariate analyses	
	N	P	Regression coefficient (SE)	P	95%CI
Other regions	13				
Pelvic hemorrhage volume, n					
<400ml	32	0.540	-0.107(0.172)	0.669	-0.504~0.328
≥400ml	8				
Ruptured EP, n					
Yes	9	0.333	0.188(0.191)	0.499	-0.645~1.294
No	31				
Treatment modality, n					
Surgical managements	29	0.512	-0.122(0.184)	0.634	-0.646~1.043
Other managements	11				

Discussion

Despite use of improved ART and increased medical knowledge, the early diagnosis of HP remains challenging and elusive to practitioners due to the coexistence of a viable IUP and the absence of clinical symptoms [1]. The typical symptoms of HP are supposed as abdominal pain, irregular vaginal bleeding, and adnexal mass; however, these symptoms are nonspecific. Moreover, most of HP are asymptomatic (50%) [9] and diagnosed by routine TVS after ART procedures. We found that patients without symptoms were diagnosed later than those with symptoms before diagnosis (7.1 vs. 6.9 weeks), and the gestational age at diagnosis was (49.4 ± 7.6) days, which was comparable to the results of previous reports[10, 11]; this evidence suggest that patients afflicted with HP could be found earlier if they had symptoms before diagnosis, and improvement of ultrasonic diagnosis level and clinicians' vigilance to those with high-risk factors are particularly important for the early diagnosis of HP.

Many studies demonstrated that pelvic adhesion and tubal infertility factors increase the risk of HP after ART [12–14] and more HP had a history of hydrosalpinx and previous surgery [15]. Fallopian tube lesion was demonstrated as the most well-defined risk factor predisposing to the occurrence of HP [16], and the level of risk depends on the extent of anatomic alteration and the degree of damage [17]. Moreover, tubal pregnancy history is an acknowledged risk factor for subsequent HP [18], we found 60.0% of the patients with HP had a history of tubal surgery. In addition, the widespread aid of ART is associated with a dramatically increased incidence of HP [19]. HP rarely occurs in women without high-risk factors or spontaneous conceptions, other possible risk factors include age ≤35 years, smoking history and use of

intrauterine device [20, 21]. Thus, we can conclude that the vast majority of patients with HP are women with a history of pelvic surgery or tubal inflammation after ART.

TVS plays an important role in the diagnosis of HP due to its assessment capability of the whole pelvis, however, weather atypical symptoms can lead to a low sensitivity. It has been reported that 6 patients were diagnosed as HP after 3 weeks of missed abortion [18]. Therefore, patients are accepted repeated routine TVS scans, especially in asymptomatic women with an suspiciously diagnosis of HP. For the purposes of the prognosis of HP, we incorporated analysis various potentially elements and explored the predictive factors of perinatal outcomes. Our result suggested that the total live birth rate was 65%, the miscarriage rate was lower in patients with cardiac activity in the IUP at HP diagnosis than those with absent cardiac activity ($P < 0.05$). In the present study, gestational age at diagnosis was 49.4 days, the abnormal embryo without cardiac activity of IUP during this period indicated that the poor quality of the embryo which may cause early abortion. Therefore, routine TVS scans at gestational age 6-8 weeks should be performed, and a normal embryo with fetal cardiac activity in IUP at diagnosis gestational age may have a favorable prognosis for patients with HP.

The individualized treatment plan of HP should be formulated according to clinical symptoms, the location of EP, mass size, hemodynamic situation and the development of IUP. Aim of HP treatment is to eliminate EP effectively, maintain IUP with minimal manipulation of the uterus and ensure maternal safety to obtain good perinatal outcome. Expectant management is suitable for asymptomatic patients with a stable hemodynamic situation. In our study, 3 patients received surgery due to EP rupture in expectant group; thus, surgical may as a priority for the management of HP. Studies have demonstrated that laparoscopy is effective and safe during the first trimester of pregnancy [22], which has the advantages of less postoperative pain, better operative field exposure, and minimal manipulation [23]. In the present study, 29 (72.5%) patients underwent surgery without any congenital abnormalities or deleterious anesthetic complications. However, there was no significant difference between pregnancy outcome in the expectant vs. surgical groups. So far, the preferred treatment modality for HP women remains unpredictable and lack of data confirmation, more prospective studies are required to be performed in the future. Hence, positive individualized interventions should be taken to avoid the need for emergency surgery after the diagnosis of HP.

The strength of our study is that we analyzed the clinical features of HP patients to identify detail risk factors for early abortion to ensure better perinatal outcomes. An IUP with cardiac activity at HP diagnosis made a significant difference ($P < 0.05$), which might be taken as predictors for a favorable prognosis of HP. Our study also has several limitations. First, the data were collected from our hospital, it may lead to false-negative results because of inevitable selection bias and the limited sample size. Multi-center studies with larger samples are needed to further investigation. Furthermore, for general population of female, our findings may not applicable to this group because they may have diverse risk factors than patients undergoing ART.

Conclusions

In summary, we supported an IUP with cardiac activity at HP diagnosis as predictors for a favorable prognosis of HP. Symptoms combined with routine TVS scans could reduce misdiagnosis of HP. Prompt surgical intervention after diagnosis may minimize the incidence of abortion of IUP and improve the prognosis of HP. We hope to raise awareness and improve the management process for such a rare event to reduce the risk of miscarriage and ensure a favorable indeed live birth rate.

Abbreviations

HP:Heterotopic pregnancy, IUP:intrauterine pregnancy, EP:ectopic pregnancy, ART:assisted reproductive technology, TVS:Transvaginal ultrasonography, ET:embryo transfer, β -hCG: β -human chorionic gonadotropin

Declarations

Ethical approval

Approval was not requested from the human institutional review board, since the study was a summary of information of diagnosis and treatment what was considered routine management at our hospital.

Informed consent

Informed consent was obtained from all individual participants included in the study, when they admitted to inpatient department.

Author contributions

YZ: Project development, Data Collection, Manuscript writing. XC: Project development, Manuscript editing. YL: Data collection. CL: Data collection. XX: Data collection. All authors contributed to the article and approved the submitted version.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article. Informed consent was obtained from all individual participants included in the

study, when they admitted to inpatient department.

Data availability statement

The patients' clinical data that support the findings of this study are not publicly available due to privacy or ethical restrictions.

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