



## Original Article

## The indicator of clinical outcomes for patients with heterotopic pregnancy following in-vitro fertilization with embryo transfer

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## ABSTRACT

**Objective:** To explore the early predictors for pregnancy outcomes in patients with heterotopic pregnancy (HP) following in-vitro fertilization with embryo transfer (IVF-ET).

**Material and methods:** This retrospective study reviewed 81 patients with HP following IVF-ET in our institution between January 2003 and September 2017. The relationships between clinical outcomes and general characteristics, sonographic features and different management options were analyzed by logistic regression analysis.

**Results:** The gestational age at the time of diagnosis was  $50.9 \pm 12.3$  days. Among these cases, 76 were accurately diagnosed by TVS, 1 was misdiagnosed as adnexal torsion by TVS, and 4 were confirmed to have IUPs after the surgical treatment. Hence, the sensitivity of TVS for detecting HP was 93.8% (76/81). However, forty-seven patients (58.0%) had suspected HP when they underwent the initial TVS. Among these patients, live births occurred for 60 patients, 11 of whom delivered preterm. The miscarriage rate was 58.3% (14/24) for patients without IUP cardiac activity at HP diagnosis, and 12.3% (7/57) for patients with IUP cardiac activity; a significant correlation was identified ( $\chi^2 = 18.651$ ,  $P < 0.001$ ). Additionally, the abortion rate of patients following fresh non-donor embryo was higher than patients after frozen-thawed embryo ( $\chi^2 = 10.437$ ,  $P = 0.001$ ). Further by logistic regression analysis, patients following frozen-thawed embryo and an IUP with cardiac activity at HP diagnosis were identified as two independent factors of pregnancy outcome. (OR = 0.060, 95%CI = 0.008–0.471,  $P = 0.007$ ; OR = 0.010, 95%CI = 0.001–0.124,  $P < 0.001$ ).

**Conclusions:** Patients following frozen-thawed embryo and an IUP with cardiac activity at HP diagnosis could be the independent predictors for a favorable prognosis.

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## Introduction

Heterotopic pregnancy (HP) is defined as the simultaneous presence of the intrauterine and ectopic pregnancies (EP) in an individual [1]. HP is a rare but potentially life-threatening condition, its incidence is known to be 1 in 30,000 in spontaneous conceptions increasing to a rate of 0.15%–1% in gestations after assisted reproductive technology (ART) [2–5]. An early diagnosis and a prompt gynecologic intervention implemented at the correct time can reduce adverse complications, such as tubal rupture, hypovolemic shock and the requirement for blood transfusions,

which also jeopardize the intrauterine pregnancy (IUP) [6–8]. Unfortunately, this fatal condition can be easily misdiagnosed due to the co-existence of an IUP and atypical clinical symptoms [9–11].

Transvaginal sonography (TVS) is critical for the diagnosis of HP, which presents as an IUP co-existing with a separated adnexal mass, gestational sac, or ring sign [12]. However, TVS continues to have low sensitivity, and an EP may also be missed or misdiagnosed as adnexal torsion, a hemorrhagic corpus luteum cyst, a tubo-ovarian abscess or appendicitis [9–11]. The primary goal of HP management is to ensure maternal safety and minimize the threat to the IUP. Generally, HP treatments include expectant management, surgical management, and sonography-guided embryo aspiration with or without embryo-killing drugs [6,7]. Despite the widespread use of laparoscopy and TVS, HP remains a diagnostic and therapeutic challenge.

The purpose of this study was to assess the early diagnostic value of TVS and explore the risk factors for pregnancy outcomes

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for patients with HP following in-vitro fertilization with embryo transfer (IVF-ET).

## Materials and methods

### Participants

This retrospective chart enrolled 81 patients diagnosed with HP following IVF-ET in our hospital between January 2003 and September 2017. The women providing incomplete information, without undergoing the first TVS examination in our institution, or the fetus with chromosomal and anatomical abnormalities were excluded. Prior written consent was obtained from the patients for the use of their clinical materials for research purposes. The study was approved by the Institutional Review Board of the First Affiliated Hospital, Sun Yat-sen University.

### Ultrasound assessments and data collection

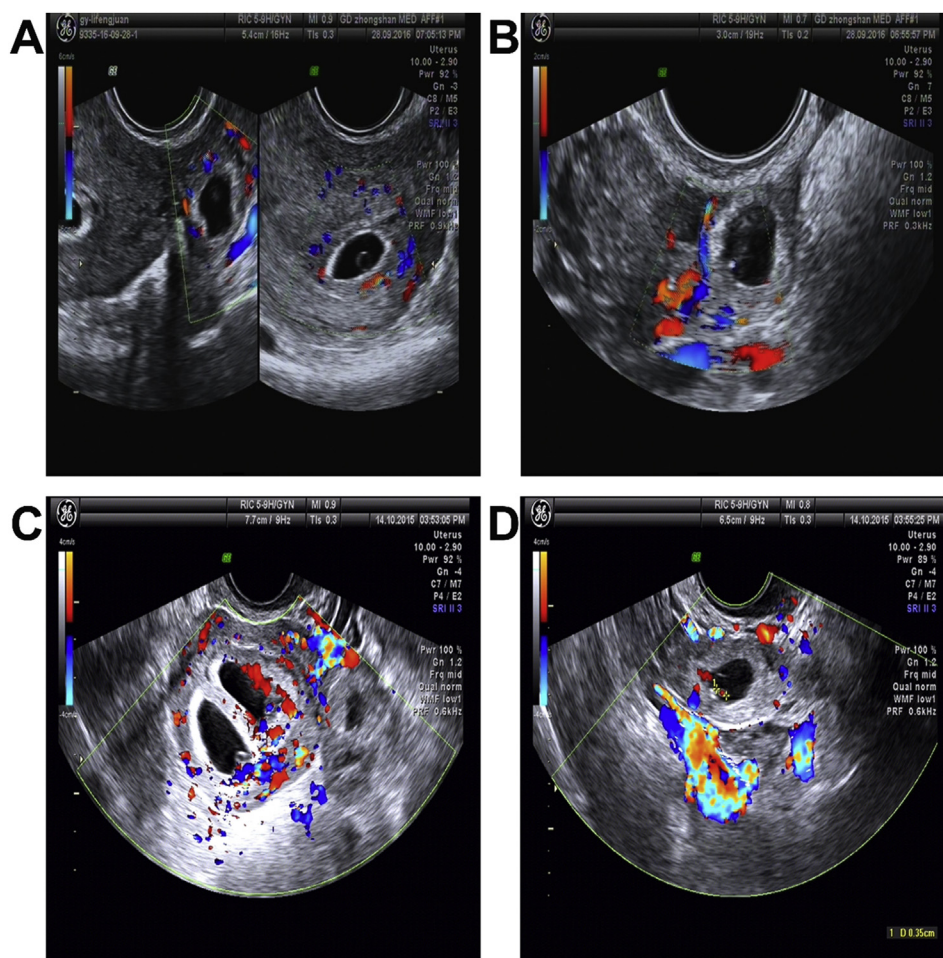
TVS was conducted by experienced sonographers using a 5-9-MHz (Voluson 730, E6, E8; GE Medical Systems, Zipf, Austria) vaginal probe. The diagnostic criteria of HP mentioned in the literature included a visible intrauterine gestational sac that was noted with (1) an inhomogeneous adnexal mass or a 'blob' adjacent to the ovary that moved separately from the ovary; (2) an empty

extrauterine gestational sac observed as a hyperechoic ring; or (3) a yolk sac and/or fetal pole with or without cardiac activity in an extrauterine sac [12] (Fig. 1). The diagnosis of an IUP was confirmed by repeating TVS at 12 weeks' gestation or by histopathology in the case of a miscarriage.

When an HP was detected, patient characteristics, cycle characteristics, sonographic features, different treatment modalities, clinical pregnancy details as well as pregnancy outcomes were collected and summarized in Tables 1 and 2. Each patient received a telephone follow-up interview to inquire about her clinical outcomes, which included maternal and pregnancy outcomes. The endpoint of the follow-up was the completion or termination of the respective pregnancy. Maternal outcome included a transfer to another treatment modality, blood transfusion, and complications.

### Statistical analysis

SPSS 20.0 software was used for statistical analysis. Measurement data that followed normal distributions were expressed as the mean  $\pm$  standard deviation. Enumeration data are shown as the percentage (%). Measurement data was compared using Student's t-test, count data was compared using chi-square test and Fisher's exact test. Logistic regression analysis was conducted to identify the independent impact factors of clinical outcomes in patients with HP. A value of  $P < 0.05$  was considered statistically significant.



**Fig. 1.** Transvaginal color Doppler ultrasound images of patients with HP. TVS showing a gestational sac with a viable fetal heartbeat in both the uterus (A) and the left adnexa (B) in a patient following a single embryo transfer. In the other patient following a two-embryo transfer, TVS revealed intrauterine gestation with dichorionic diamniotic twins (C) and a gestational sac with cardiac activity in the left adnexa (D).

**Table 1**General characteristics and clinical outcomes of patients with HP following in-vitro fertilization with embryo transfer ( $n = 81$ ).

Variables	No. (%) of patients
Age, mean $\pm$ SD (range), yr	31.5 $\pm$ 4.5 (23–44)
History of abortion, $n$ (%)	
0	42 (51.9)
1–2	37 (45.6)
3	2 (2.5)
History of pelvic surgery, $n$ (%)	
Tubal surgery	52 (64.2)
Non-tubal surgery	9 (11.1)
No surgery	20 (24.7)
Type of infertility, $n$ (%)	
Primary	38 (46.9)
Secondary	43 (53.1)
Causes of infertility, $n$ (%)	
Tubal factors	51 (63.0)
Male factors	11 (13.6)
Unknown factors	19 (23.4)
Method of IVF-ET, $n$ (%)	
Fresh non-donor embryo	41 (50.6)
Frozen-thawed embryo	40 (49.4)
Days of transferred embryos, $n$ (%)	
D2/3	60 (74.1)
D5/6	21 (25.9)
Number of transferred embryos, $n$ (%)	
1	1 (1.2)
2	48 (59.3)
3	32 (39.5)
Clinical manifestations, $n$ (%)	
Asymptomatic	22 (27.2)
Abdominal pain or/and vaginal bleeding	56 (69.1)
Hypovolemic shock	3 (3.7)
Gestational age at diagnosis, mean $\pm$ SD (range), d	50.9 $\pm$ 12.3 (22–92)
Diameters of gestational mass, mean $\pm$ SD (range), mm	37.7 $\pm$ 16.6 (10–87)
Site of ectopic pregnancy, $n$ (%)	
Tubal (right or left)	61 (75.3)
Interstitial (right or left)	15 (18.5)
Corner	4 (5.0)
Cesarean scar	1 (1.2)
Management of HP, $n$ (%)	
Expectant management	25 (30.9)
Surgical management	52 (64.2)
Embryo aspiration management	4 (4.9)
Blood transfusion, $n$ (%)	
Yes	5 (6.2)
No	76 (93.8)
Clinical outcomes, $n$ (%)	
Term delivery	49 (60.5)
Preterm delivery	11 (13.6)
Abortion	21 (25.9)
Mode of delivery, $n$ (%)	
Vaginal delivery	12 (20.0)
Cesarean section	48 (80.0)

IVF-ET: in-vitro fertilization with embryo transfer.

## Results

### General characteristics

Overall, 81 pregnancies following IVF-ET and 2 cases of spontaneous conceptions were diagnosed as HP with complete clinical data in our hospital between January 2003 and September 2017. Among the 81 cases, 52 patients had experienced tubal surgery, 9 patients had undergone non-tubal surgery, another 20 patients had no history of pelvic surgery. Of these women, 60 conceptions were from day-2/3 transfers and 21 were from day-5/6 transfers; 41 patients had pregnancies via fresh non-donor embryo transfer cycles, 19 of which resulted in the ovarian hyperstimulation syndrome (OHSS), and 40 patients conceived after frozen-thawed embryo transfer. On average, 2.27 embryos were transferred to each patient during the ET cycles. Among the 81 patients, 60 (74.1%)

had already delivered, and 11 of these deliveries were preterm (Table 2). No congenital abnormalities were observed. Surprisingly, we experienced two cases of HP after a single embryo transfer (SET). These two cases share two common characteristics: they both underwent day-5 frozen-thawed embryo transfers and had histories of intercourse during IVF-ET treatment.

### Ultrasound assessments

The cases comprised 61 tubal pregnancies, 15 interstitial pregnancies, 4 corner pregnancies, and 1 cesarean scar pregnancy. The gestational age at the time of diagnosis was 50.9  $\pm$  12.3 (range, 22–92) days, 93.8% of the HPs were diagnosed between 5 and 8 weeks' gestation, 6.2% were diagnosed between 9 and 10 weeks. The mean gestational mass diameter of the EPs was 37.7  $\pm$  16.6 (range, 10–87) mm. Moreover, abnormal EPs were present as inhomogeneous masses in 27 patients, empty gestational sacs in 18 patients, and extrauterine gestational sacs with yolk sacs or fetal poles (with or without cardiac activity) in 36 patients. Among these cases, 76 were accurately diagnosed by TVS, one was misdiagnosed as adnexal torsion by TVS, and four were confirmed to have IUPs after the surgical treatment. Hence, the sensitivity of TVS for detecting HP was 93.8% (76/81). However, forty-seven patients (58.0%) had suspected HP when they underwent the initial TVS.

### Different treatment modality

Among the 81 patients, 52 underwent laparotomy or laparoscopy under general anesthesia without anesthetic complications, 25 received expectant management, and the remaining 4 underwent sonography-guided embryo aspiration. In the group receiving expectant management, 2 patients suffered rupture of ectopic pregnancy and 3 patients transferred to surgical management during the period of strict observation. The total miscarriage rate was 40.0% (10/25) during observation. In this study, only 4 patients underwent sonography-guided embryo aspiration. The TVS re-examinations 1 week after management showed that one patient's ectopic gestational sac grew rapidly, and therefore, another sonography-guided embryo aspiration with anhydrous alcohol was performed to avoid EP rupture. The pregnancies of these 4 patients were all eventful, and no miscarriages occurred.

In the surgical group, 5 patients suffered tubal ruptures, and 3 patients had interstitial ruptures. Among these eight patients, 3 required blood transfusions, and 3 patients suffered miscarriages during follow-up. Eight patients with stable hemodynamics suffered miscarriages during the postoperative period. One patient suffered uterine rupture 2 months after corner resection, and the dead fetuses were found during the subsequent surgery. The total miscarriage rate in the surgical group was 21.2% (11/52). Furthermore, there was no significant difference between obstetric outcome in the surgical vs. other management groups ( $P = 0.189$ , Table 3).

### Comparisons of general and sonographic variables with obstetric outcomes

Next, the association between the miscarriage rate and the general, sonographic features of the HP patients were analyzed. TVS at HP diagnosis revealed that a gestational sac of an IUP with fetal cardiac activity was found in 57 patients, while without fetal cardiac activity was found in 24 patients. Moreover, all of the six pregnancies with empty gestational sac for the IUP ended in early miscarriage in our study. The miscarriage rate was 58.3% (14/24) for patients without IUP cardiac activity at HP diagnosis, and 12.3% (7/57) for patients with IUP cardiac activity; a significant correlation

**Table 2**The clinical outcomes of patients with HP following in-vitro fertilization with embryo transfer ( $n = 81$ ).

Variables	N	Abortion	Premature birth	Full-term birth	$\chi^2$	P value
IUP without cardiac activity					18.651 <sup>a</sup>	<0.0001 <sup>a</sup>
Empty gestational sac	6	6	0	0		
Yolk sac	10	5	0	5		
Yolk sac and fetal pole	8	3	1	4		
IUP with cardiac activity	57	7	10	40		

<sup>a</sup> 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 ( $\chi^2 = 18.651$ ,  $P < 0.001$ ). IUP: intrauterine pregnancy.

was identified ( $\chi^2 = 18.651$ ,  $P < 0.001$ ) (Table 2). Additionally, The abortion rate of patients following fresh non-donor embryo was higher than patients after frozen-thawed embryo, and the difference was significant ( $\chi^2 = 10.437$ ,  $P = 0.001$ ).

Further by logistic regression analysis, patients following frozen-thawed embryo and an IUP with cardiac activity at HP diagnosis were identified as two independent factors of pregnancy outcome. (OR = 0.060, 95%CI = 0.008–0.471,  $P = 0.007$ ; OR = 0.010,

**Table 3**

Comparisons of general characteristics, sonographic features and different management options with clinical outcomes of patients with HP following IVF-ET.

Variable	N	Obstetric outcomes		Chi-square value	P value
		Live birth	Miscarriage		
Age (years)					
$\geq 34$	27	21	6	0.289	0.591
$< 34$	54	39	15		
Method of IVF-ET, n (%)					
Fresh non-donor embryo	41	24	17	10.437	0.001
Frozen-thawed embryo	40	36	4		
Days of transferred embryos, n (%)					
D2/3	60	43	17	0.698	0.403
D5/6	21	17	4		
Number of transferred embryos, n (%)					
1 or 2	49	38	11	0.781	0.377
3	32	22	10		
Gestational age at diagnosis, d					
$\geq 52$	29	20	9	0.614	0.433
$< 52$	52	40	12		
Suspected HP at the initial TVS, n					
Yes	47	35	12	0.009	0.924
No	34	25	9		
Gestational mass diameter (mm)					
$< 30$	32	24	8	0.024	0.878
$\geq 30$	49	36	13		
EP fetal heartbeat					
Yes	21	18	3	2.000	0.157
No	60	42	18		
IUP fetal heartbeat					
Yes	57	50	7	18.651	<0.001
No	24	10	14		
HP positions					
Adnexal regions	61	44	17	0.486	0.486
Other regions	20	16	4		
Ectopic mass					
Inhomogeneous mass	45	32	13	0.463	0.496
Empty gestational sac					
Gestational sac with a yolk sac or fetal pole	36	28	8		
Pelvic hemorrhage volume, n					
$\leq 400$ ml	66	50	16	0.159	0.690
$> 400$ ml	15	10	5		
Ruptured EP, n					
Yes	10	6	4	0.489	0.484
No	71	54	17		
Ovarian hyperstimulation syndrome, n					
Yes	19	13	6	0.118	0.731
No	62	47	15		
Hydrosalpinx fluid, n					
Yes	19	14	5	0.000	1.000
No	62	46	16		
Uterine fluid, n					
Yes	16	12	4	0.000	1.000
No	65	48	17		
Treatment modality, n					
Surgical managements	52	41	11	1.722	0.189
Other managements	29	19	10		

IVF-ET: in-vitro fertilization with embryo transfer; HP: heterotopic pregnancy; IUP: intrauterine pregnancy; EP: ectopic pregnancies.



95%CI = 0.001–0.124,  $P < 0.001$ ). However, the miscarriage rate exhibited no significant association with other variables, such as age, gestational age at diagnosis, first TVS-suspected HP, gestational mass diameter, EP fetal heartbeat, HP positions, ectopic mass, pelvic hemorrhage volume, OHSS, hydrosalpinx fluid or uterine fluid (Table 4).

## Discussion

History of an EP is an acknowledged risk factor for subsequent HP in the setting of IVF-ET [13,14]. In the present study, 64.2% of the patients with HPs had a history of tubal surgery. In addition to EP history, a dramatically increased incidence of HP is associated with the widespread aid of ART [15,16]. Therefore, gynecologist should be aware of HP in these patients. To the best of our knowledge, twin pregnancies after SET are commonly considered to be monozygotic, and only 1 in 10 twin births following SET are dizygotic [17]. In 2015, Gergolet et al. introduced the first case of a HP after an ET, which was transferred on day 5 after oocyte retrieval [5]. Shortly after, Lee et al. [18] reported a second case, but this embryo had been cryopreserved for 3 years. We experienced two interesting cases of HP after a SET, who both underwent day-5 frozen-thawed embryo transfers and had histories of intercourse during IVF-ET treatment. According to these studies, HP following SET is

extremely rare and occurs more often in frozen SET cycles, which have a greater chance of concurrent spontaneous ovulations than fresh cycles.

Some studies have strongly suggested that the relatively high levels of serum estrogen and progesterone in fresh cycles impair endometrial receptivity, which apparently accounted for most implantation failures [19–21]. Interestingly, we also found that the abortion rate of patients following fresh non-donor embryo was higher than patients after frozen-thawed embryo. Therefore, frozen-thawed embryo appears to be a better choice for a favorable prognosis than fresh embryo transfer. Guan et al. [7] suggested that fresh transfer cycles were associated with a significantly higher incidence of HP compared to frozen embryo cycles, and speculated that high levels of serum estrogen and progesterone increase uterine contractility on stimulated cycles and are responsible for pushing the embryo into the tube [22,23]. However, our results showed that approximately one-half of patients with HPs had undergone frozen cycles. Therefore, whether frozen embryo transfer cycles are associated with a significantly lower incidence of HP remains controversial.

Although TVS performed by an experienced sonographer has a high sensitivity for correctly diagnosing HP, only a half of patients were suspected of HP when they underwent their initial TVS scans. Therefore, an early diagnosis of HP remains challenging. A series of

**Table 4**

Uni- and Multi-variable logistic regression of predictive factors associated with clinical outcomes in HP patients following IVF-ET.

Variable	Univariate analyses			Multivariate analyses	
	N	P	Regression coefficient (SE)	P	HR (95%CI)
Age (years)					
≥34	27				
<34	54	0.591	1.342 (0.554)	0.189	0.305 (0.052–1.795)
Method of IVF-ET, n (%)					
Fresh non-donor embryo	41				
Frozen-thawed embryo	40	<0.001	0.350 (0.254)	0.007	0.060 (0.008–0.471)
Days of transferred embryos, n (%)					
D2/3	60				
D5/6	21	0.407	1.680 (0.625)	0.841	1.253 (0.139–11.309)
Number of transferred embryos, n (%)					
1 or 2	49				
3	32	0.379	0.637 (0.513)	0.027	8.625 (1.274–58.381)
Gestational age at diagnosis, d					
≥52	29				
<52	52	0.435	0.667 (0.519)	0.434	1.996 (0.354–11.260)
Suspected HP at the initial TVS, n					
Yes	47				
No	34	0.924	0.952 (0.513)	0.838	1.223 (0.177–8.439)
Gestational mass diameter (mm)					
<30	32				
≥30	49	0.878	0.923 (0.521)	0.642	1.539 (0.250–9.459)
EP fetal heartbeat					
Yes	21				
No	60	0.168	2.571 (0.684)	0.258	4.143 (0.354–48.544)
IUP fetal heartbeat					
Yes	57				
No	24	<0.001	10.000 (0.578)	<0.001	0.010 (0.001–0.124)
HP positions					
Adnexal regions	61				
Other regions	20	0.488	1.545 (0.628)	0.419	2.518 (0.268–23.666)
Ectopic mass					
Inhomogeneous mass	45				
Empty gestational sac	36	0.497	1.422 (0.519)	0.208	0.273 (0.036–2.062)
Pelvic hemorrhage volume, n					
≤400 ml	66				
>400 ml	15	0.471	0.640 (0.618)	0.133	0.064 (0.002–2.308)
Ruptured EP, n					
Yes	10				
No	71	0.286	0.472 (0.703)	0.085	31.758 (0.618–1633.258)
Treatment modality, n					
Surgical managements	52				
Other managements	29	0.193	1.962 (0.518)	0.879	1.148 (0.194–6.810)

routine TVS scans is necessary, especially in asymptomatic patients. Due to the rarity of HP, there are few studies report the prognosis of HP. Therefore, our study incorporated various parameters and explored the predictive factors of pregnancy outcomes. In the present study, the total live birth rate was 74.1%, which was comparable to the results of previous reports [24–26]. Moreover, our result suggested that the miscarriage rate was higher in the group of patients with absent cardiac activity in the IUP at HP diagnosis than in the group with cardiac activity. In our study, the mean gestational age at the time of diagnosis was 50.9 days. According to the normal embryo development process, the embryo of IUP should have heart beat during this period. The empty gestational sac or fetal pole without cardiac activity of IUP at this time indicated that the quality of the embryo may be poor, and may cause early abortion. Moreover, the miscarriage rate exhibited no significant association with any other clinical and ultrasonic variables. Therefore, an IUP with fetal cardiac activity at HP diagnosis is an important indicator of a favorable prognosis for patients with HP, and routine TVS examinations at 6–8 weeks' gestation should be performed.

The women were managed expectantly or surgically depending on their clinical symptoms, hemodynamic parameters, findings from repeat TVS examinations and preferences. The primary objectives of HP management are to ensure maternal safety and to preserve the IUP. In recent years, an increasing amount of evidence has suggested that surgery is effective and safe during the first trimester of pregnancy with the application of laparoscopy, which has the advantages of better operative field exposure, less post-operative pain, a shorter length of hospitalization, and minimal manipulation [27]. In our study, 50 out of 77 patients underwent laparotomies or laparoscopies under general anesthesia without any anesthetic complications or congenital abnormalities. However, there was no significant difference between outcome in the surgical vs. other management groups. So far, the choice of treatments for HP remains controversial. Hence, more randomized controlled trials are needed to be performed in the future.

In summary, patients following frozen-thawed embryo and an IUP with cardiac activity at HP diagnosis could be taken as the independent predictors for a favorable prognosis.

## Conflicts of interest

The authors have no conflicts of interest to disclose related to this work.

## Declaration of interest

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