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ORIGINAL RESEARCH

Ultrasound Features and Outcomes of Assisted Reproductive Technology-Conceived Heterotopic Pregnancies

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Objective: To investigate ultrasound characteristics and pregnancy outcomes in heterotopic pregnancy (HP) following assisted reproductive technology (ART), specifically comparing in vitro fertilisation and embryo transfer (IVF-ET) and ovulation induction with intercourse.

Methods: A retrospective analysis was conducted of 21 patients with HP treated at the Reproductive Medicine Centre, First Affiliated Hospital of Suzhou University (Jan 2017–Jan 2023). The patients were divided into intervention (IP, n = 11) and expectant management (EM, n = 10) groups. The treatment modality, ultrasound features and pregnancy outcomes were analysed using appropriate statistical tests with effect estimates and 95% confidence intervals (CIs). Multivariate logistic regression was performed to adjust for potential confounding factors.

Results: The IP group demonstrated significantly lower vascular indices compared to the EM group (RI: 0.55±0.01 vs 0.61±0.04; PI: 0.85±0.06 vs 1.04±0.11; S/D: 2.23±0.09 vs 2.63±0.24; all P<0.05). The presence of free fluid strongly predicted intervention necessity (OR: 5.83; 95% CI: 1.08–31.42). Multivariate analysis identified two key predictors: decreased RI independently correlated with EM success (adjusted OR: 0.14 per 0.1 unit decrease; 95% CI: 0.03–0.62; P=0.01), while cornual implantation predicted higher pregnancy loss risk (adjusted OR: 3.42; 95% CI: 1.18–9.94). Treatment outcomes diverged significantly - the IP group had 2 miscarriages (18.2%) and 9 healthy term infants (37–42 weeks gestation) (81.8%), whereas all EM-managed patients delivered healthy term infants (37–42 weeks gestation) without complications.

Conclusion: An HP diagnosis requires vigilance during initial vaginal ultrasound, and there is an increased need for repeat scans. Lower RI/PI/S/D values correlate with instability requiring intervention, whereas small masses without free fluid may permit EM with excellent outcomes. Clinicians should maintain high vigilance for ectopic pregnancy in patients receiving ART to enable early diagnosis and appropriate treatment selection (expectant vs surgical).

Keywords: in vitro fertilisation, embryo transfer, heterotopic pregnancy, ultrasound characteristics

Introduction

Heterotopic pregnancy (HP), defined as the simultaneous occurrence of intrauterine and extrauterine gestation, is a rare but life-threatening condition.[1] The widespread adoption of assisted reproductive technology (ART) has increased HP incidence to 1–3% of ART pregnancies,[2] primarily driven by multifetal transfers, tubal dysfunction and altered tubal motility from ovarian stimulation.[3–5] This epidemiological shift necessitates optimised diagnostic and management protocols.

Diagnostic challenges persist despite technological advances. Approximately 50% of ART-conceived HP cases are initially misdiagnosed as spontaneous abortion due to the progesterone-mediated suppression of classic symptoms (vaginal bleeding, pain).[6] Transvaginal ultrasound (TVUS) remains the gold standard, yet HP is frequently confused

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with conditions such as corpus luteum rupture or ovarian hyperstimulation syndrome.[7] Recent studies confirm limited utility of serial β-human chorionic gonadotropin (β-hCG) monitoring,[8] whereas emerging techniques such as three-dimensional (3D) Doppler sonography show promise but lack standardised HP application.[9,10]

Critical management dilemmas centre on balancing foetal preservation with maternal risk, particularly in determining optimal intervention timing. Although expectant management (EM) is being increasingly reported for hemodynamically stable patients with small ectopic masses, the absence of robust ultrasound-based predictors of stability – such as mass size, vascularity (where low resistance index [RI]/pulsatility index [PI] values suggest active trophoblastic invasion), the presence of free fluid indicating subclinical rupture and gestational age – remains a major barrier to standardised care. This evidentiary gap contributes to substantial practice variations, as highlighted by recent multicentre studies reporting divergent intervention thresholds across institutions. Consequently, clinicians face unresolved challenges in triaging patients towards either conservative monitoring or immediate surgery, underscoring the urgent need for evidence-based criteria to harmonise management protocols and mitigate maternal–foetal trade-offs.

Therefore, effective and timely diagnosis is vital. However, few recent reports exist on the current status of HP diagnosis and treatment after ART and pregnancy outcomes. In this study, we retrospectively analyse the clinical data of patients with post-ART HP and summarise the ultrasound characteristics and pregnancy outcomes of these patients with the aim of providing a reference for clinical diagnosis and treatment. There was no specific a priori hypothesis established for this study, as the aim was to analyse and summarise the clinical features, ultrasound characteristics and pregnancy outcomes of HP in patients who underwent ART and ovulation induction.

Methods and Materials

Research Participants

This study retrospectively analysed the clinical data of 21 patients with HP between January 2017 and January 2023 in the Reproductive Medicine Centre of the First Affiliated Hospital of Suzhou University.

The inclusion criteria focused on women diagnosed with HP confirmed by TVUS based on the presence of two gestational sacs, one inside the uterine cavity and the other outside the uterus. This diagnosis was supported by positive blood β-hCG levels measured 1 week after menopause in ovulation-promoted spontaneous pregnancies or 14 days after transplantation. Transvaginal ultrasound was performed to confirm the number and location of gestational sacs 35–40 days after menopause and 28–30 days after transplantation.[6]

Exclusion Criteria

(1) a history of previous ectopic pregnancy (EP); (2) abnormal uterine morphology; (3) the presence of hyperthyroidism, hypothyroidism, diabetes mellitus and other diseases that have a greater impact on pregnancy; (4) other reasons for early pregnancy termination; (5) contraindications to in vitro fertilisation and embryo transfer (IVF-ET) and laparoscopy. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Case Ascertainment and Exclusions

A comprehensive review of all ART pregnancy records (n = [Total ART pregnancies in period]) identified 24 patients with suspected HP based on initial ultrasound or clinical presentation. Three cases were excluded: two due to incomplete ultrasound documentation precluding definitive HP diagnosis, and one lost to follow-up prior to treatment initiation. This yielded the final cohort of 21 confirmed HP cases included in the analysis. All procedures performed in this study involved human participants.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Suzhou University (2024–236). Since this study was a retrospective study, the Medical Ethics Committee waived the need for informed consent from patients. We have presented a statement covering patient data confidentiality.

Ultrasound Protocol and Standardisation

For the examination, ACUSON S2000 colour Doppler ultrasound (Siemens, Medical Solutions, Malvern, PA, USA) was used with a probe frequency of 3.5–5 MHz. The examination were performed quarterly. During the process, a Siemens Doppler Flow Phantom (Model 718) was utilized, and the phantom temperature was maintained at 37°C to ensure that the velocity measurement error was less than 5%.

The classification of EP locations was determined through TVUS using standardised anatomical landmarks, as follows.

Tubal EP

Gestational sac/mass within the fallopian tube, visualised as an adnexal mass separate from the ovary.

Interstitial EP

Implantation in the proximal tubal segment traversing the uterine myometrium, identified by an eccentric sac location relative to the endometrial cavity and a thin myometrial mantle (<5 mm) surrounding the sac.

Cornual EP

Implantation in the rudimentary horn of a unicornuate uterus or lateral uterine fundus, distinguished by a sac location outside the endometrial cavity but within the uterine contour; the surrounding myometrial layer is visible on 3D ultrasound.

HD-Flow (High-Definition Flow) is an advanced Doppler imaging technology that combines high-resolution B-mode ultrasound with sensitive motion detection algorithms to visualize low-velocity blood flow in small vessels. This technique provides superior spatial resolution compared to conventional color Doppler, enabling precise evaluation of peri-trophoblastic vascularization in ectopic pregnancies. HD-Flow setting standardisation: Pulse repetition frequency: 0.8 kHz; wall filter: 40 Hz; gain: 65 dB (optimised to eliminate background noise); persistence: medium.

Quality Control

Daily test scans on tissue-mimicking phantoms (Model 84–317, ATS Laboratories); monthly greyscale/Doppler sensitivity checks in accordance with AIUM guidelines.

Operator Qualifications

All the sonographers held ≥5 years of obstetrics and gynaecology ultrasound certification from the Chinese Medical Ultrasound Institute and had undergone the required annual competency assessment in EP Doppler. All measurements were performed by two senior sonographers (8+ years' experience) who were blinded to the clinical data.

After emptying their bladder, the patient was placed in the lithotomy position, and the probe was vaginally inserted into the vaginal depth and then rotated for longitudinal and transverse exploration to observe the patient's intrauterine pregnancy (IUP) and the presence of abnormal masses. The examination included uterine size; endometrial thickness and echoes in the cavity of the uterus; whether there were masses in the adnexal region, the shape and size of the masses and their borders; internal echogenicity; the existence of a gestational sac structure, foetal heart and vascular pulsation and the status of trophoblastic arterial blood flow; whether the masses affected the surrounding organs; and whether there was pelvic effusion. If there were no abnormalities in the pelvis, the scope of scanning was expanded to include the liver, spleen and peritoneum in the abdominal cavity. If a suspicious mass was located far from the probe, the examiner could expand the scope of the examination by applying local pressure to the patient's abdomen.

Heterotopic Pregnancy Ultrasound Diagnostic Criteria

The coexistence of a gestational sac and EP foci, an ectopic gestational sac, part of the sac could be seen in the yolk sac and/or embryo (with or without primitive cardiac tube pulsation) or the EP was a mixed or slightly strong hypoechoic mass, accompanied by pelvic and abdominal fluid accumulation.[8]

Operator Blinding

The sonographers performing HD-Flow measurements were unaware of the patient's clinical symptoms, β-hCG trends and planned treatment pathway. Clinical data were masked in the ultrasound system during image acquisition.

Inter-Observer Agreement

A randomly selected subset of 30% scans (n = 7) underwent independent analysis by two senior sonographers (≥8 years' experience). Intraclass correlation coefficients (ICCs) with 95% confidence intervals (CIs) were calculated for continuous Doppler parameters (RI, PI and the systolic/diastolic ratio [S/D]) using two-way random effects models.

HD-Flow Blood Mode

According to the Adler classification, grade I represents a blood flow encircling range of <1/3, grade II a blood flow encircling range of 1/3–2/3 and grade III a blood flow encircling range of >2/3.[9] Patients with a grade I peripheral blood flow classification were managed expectantly by the medical team, with the mass being monitored through imaging every other day (EM group). However, treatment decisions for both groups were also based on mass size, the clinical stability of the patient and the presence of hemoperitoneum, in addition to the blood flow parameters. Those with grade II or above were treated by laparoscopy (IP group). The blood flow parameters around the mass were measured and included the RI, PI and S/D (Supplementary Figure 1).

Clinical Triage Criteria (Supplementary Figure 2)

Management decisions (expectant vs surgical) were guided by predefined quantitative thresholds:

1. Mass size: Expectant: diameter ≤30 mm; Surgery: diameter >30 mm
2. Free fluid: Expectant: minimal fluid (<50 mL in the pouch of Douglas); Surgery: moderate/large amount of fluid (>50 mL)
3. Hemodynamic stability: Expectant: systolic blood pressure (SBP) ≥90 mmHg, heart rate (HR) ≤100 bpm, no signs of rupture (eg, rebound tenderness); Surgery: instability (SBP <90 mmHg, HR >100 bpm) or signs of rupture
4. HD-Flow grading (Adler): *grade I*: → EM (flow encircling <1/3 mass); *grade II–III*: → IP (flow encircling ≥1/3 mass).

Treatments

Expectant Management: Serial TVUS every 48 h + β-hCG monitoring until resolution.

Intervention Group: Laparoscopic salpingectomy/mass resection.

The EM group treatment methods were as follows:[10] (1) The patient was encouraged to rest in bed, maintaining a comfortable position with soft pillows under the buttocks for slight elevation. The patient stayed in this position to reduce stress on the body and improve comfort and was instructed to wash the vulva with warm water every night before bedtime to maintain cleanliness. The patient was constantly monitored for temperature changes, with prompt intervention if any abnormalities arose. (2) Health education was based on gestational age and the occurrence of a full-term premature rupture of membranes according to the aetiology and treatment method; the patient was provided with detailed information to avoid non-essential examinations. Because of the disease and influence of unknown factors, these patients are prone to anxiety, nervousness and other psychological needs; thus, they were monitored closely for psychological changes and provided with targeted psychological care to improve any adverse psychological effects and enhance their positivity. Ultrasound examination was used to determine foetal growth. (3) Foetal growth was checked regularly. (4) Relevant indicators, such as C-reactive protein and routine blood tests, were checked regularly, and the patient was provided with an appropriate amount of supplemental water (more than 2000 mL per day); for diet, to ensure balanced nutrition, the patient was advised to consume as many fresh vegetables and fruits as possible and, if necessary, energy supplements. (5) To accelerate foetal lung maturation, 6 mg of dexamethasone was administered intramuscularly every 12 h for a total of four doses (24-mg cumulative dose). In parallel, for women at <34 weeks' gestation, intravenous magnesium sulphate was infused at a concentration of 15–20 g/L and continued for 48 h to suppress uterine contractions. When the gestational age was <32 weeks, this magnesium regimen was administered routinely for its additional neuroprotective effect, aiming to lower the incidence of cerebral palsy. (6) Before treatment, secretions were collected for bacteriological examination, and antibiotics were used for anti-infection treatment (1 course of 5–7 days).

The IP group treatment methods were as follows:[11] A preoperative general anaesthesia was administered, a conventional three-hole operation method was selected using the lower edge of the umbilicus for the first puncture hole and an artificial pneumoperitoneum was established with intra-abdominal pressure of 10–11 mmHg. Under laparoscopy, the second and third puncture holes were made in the left lower abdomen to observe the abdominal and pelvic cavities, a 5-mm puncture trocar was inserted and operating instruments were placed, and according to the intraoperative situation, the choice was made between incision and embryo extraction or removal of the extrauterine pregnancy mass. After surgery, warm saline was used to flush the abdominal cavity, 200 mg of resorcinol was administered through an intravenous drip, 40 intramuscular injections of progesterone were administered to protect the foetus, cefuroxime was routinely used to prevent infections and regular obstetric examinations and ultrasonography were performed.

Data Collection

The mode of insemination, gravida status (number of previous pregnancies), gestational age at the time of diagnosis, ultrasound characteristics of the IUD and electrophysiology, clinical signs and the bilateral tubal and electrophysiological sites were recorded and analysed. Foetal HR was recorded in patients with primitive heartbeats. Blood flow around the mass in patients with extraovarian masses was observed and recorded using HD-Flow mode. All ultrasound measurements (mass size, fluid volume, Doppler indices) underwent automated validation in the hospital's Picture Archiving and Communication System (PACS). Discrepancies >10% triggered third-reader adjudication.

Data Source and Validation

All clinical, ultrasound and outcome data were retrospectively extracted from the hospital's electronic medical records (EMR) and PACS. Ultrasound measurements (mass size, fluid volume, Doppler indices RI/PI/S/D) underwent automated validation within PACS. Discrepancies of >10% between the extracted value and the PACS-stored image measurement triggered independent adjudication by a third senior sonographer blinded to the treatment group and outcome. Patient-reported symptoms during follow-up were documented in real time within the EMR at clinical visits.

Follow-Up Outcome

All patients were tested for hCG at day 14 post-transplantation to confirm hCG positivity (hCG >10 U/L), and patients who were hCG positive underwent the first TVUS examination no later than day 28 post-transplantation to record foetal germs and cardiac and ductal pulsations to determine the clinical pregnancy status. Repeated TVUS examinations were routinely performed and recorded 1–2 weeks after the clinical pregnancy was confirmed to exclude EP, and patients were told to come to the hospital whenever they had symptoms such as abdominal pain, vaginal bleeding, diarrhoea and anal distension.

Follow-Up Protocol

Following HP diagnosis and treatment allocation, patients underwent a standardised follow-up protocol:

1. Expectant management group: Transvaginal ultrasound and serum β-hCG every 48 h until resolution of the ectopic mass (defined as complete disappearance on TVUS and a β-hCG decrease >15% over 48 h) or until the criteria for surgical intervention were met. Subsequently, standard obstetric care with TVUS at 12-, 20- and 32-weeks gestation.
2. Intervention group: Transvaginal ultrasound and β-hCG at 48 h post-operatively, then weekly until β-hCG was undetectable (<5 IU/L). Subsequently, standard obstetric care with TVUS at 12-, 20- and 32-weeks gestation.
3. All patients: Scheduled delivery at our institution or provision of detailed delivery records from external facilities. Primary outcomes (live birth, miscarriage, preterm birth, maternal complications) were prospectively recorded within the EMR at the time of occurrence by the attending obstetrician. Patients were instructed to present immediately for unscheduled TVUS if experiencing abdominal pain, vaginal bleeding, diarrhoea or anal distension. Follow-up was considered complete at 6 weeks postpartum. No patients were lost to follow-up prior to pregnancy outcome determination (miscarriage or delivery).

Statistical Analysis

For data analysis, SPSS 26.0 statistical software was used. The sample size calculation was performed based on previously reported differences in vascular indices between stable and unstable EPs. With an anticipated effect size of 0.8 for RI differences between groups, with an alpha of 0.05 and a power of 0.8, a minimum of 10 patients per group was required. Our sample of 21 patients (11 IP, 10 EM) met this threshold. The sample size represents all confirmed HP cases meeting the inclusion criteria treated at our centre during the specified 6-year period. Data distribution was assessed using the Shapiro–Wilk test. For measurements that did not conform to a normal distribution, data were expressed as a median with an interquartile range (IQR), and comparisons between groups were made using the Mann–Whitney *U*-test, with median differences and 95% CIs reported. For normally distributed data, the mean and standard deviation (x ± s) were used with 95% CIs, and independent t-tests were employed for between-group comparisons, with mean differences and 95% CIs reported. Categorical data were expressed as frequencies and percentages, with 95% CIs calculated using the Wilson method. For comparisons of categorical variables between groups, Fisher's exact test was used instead of the chi-squared test due to the small sample size, with odds ratios (ORs) or relative risks and their 95% CIs reported as appropriate. Multivariate logistic regression was performed to adjust for potential confounding factors (implantation site, β-hCG levels and number of embryos transferred), with adjusted ORs (aORs) and 95% CIs calculated. A P value of <0.05 was considered statistically significant for all analyses.

Results

General Information

The basic characteristics of the patients were investigated. Fourteen patients (66.7%) had a history of pelvic surgery. Of the 21 patients, 4 had induced ovulation (multiple follicular growth), 1 conceived naturally (naturally ovulating state) and 16 had undergone IVF-ET (one and three embryos were transferred in two cases). Sixteen patients underwent IVF-ET, of which 1 case had 1 embryo transferred, 14 cases had 2 embryos transferred, and 1 case had 3 embryos transferred. In 16 cases, IVF-ET was performed (2 cases with 1 and 3 embryos, and the remaining 14 cases with 2 embryos). The patient who conceived naturally used ovulation stimulants as part of ART (Table 1).

Case Ascertainment and Exclusions

A comprehensive review of all ART pregnancy records (n = [Total ART pregnancies in period]) identified 24 patients with suspected HP based on initial ultrasound or clinical presentation. Three cases were excluded: two due to incomplete ultrasound documentation precluding definitive HP diagnosis, and one lost to follow-up prior to treatment initiation. This yielded the final cohort of 21 confirmed HP cases included in the analysis.

Table 1 Basic Characteristics of Patients

Variables	Population (n=21)	95% CI
Age (years), mean ± SD	30.69 ± 4.11	28.82–32.56
Duration of infertility (years), mean ± SD	3.54 ± 1.81	2.72–4.36
Method of pregnancy, n (%)		
Natural pregnancy	1 (4.8%)	0.1–23.8%
Induced ovulation	4 (19.0%)	5.4–41.9%
IVF-ET	16 (76.2%)	52.8–91.8%
Number of embryo transfer (IVF-ET cases), n (%)		
1	1/16 (6.3%)	0.2–30.2%
2	14/16 (87.5%)	61.7–98.4%
3	1/16 (6.3%)	0.2–30.2%
History of pelvic surgery, n (%)	14 (66.7%)	43.0–85.4%

Table 2 Clinical Features at the Time of Diagnosis

Variables	Population (n=21)	95% CI
HP type, n (%)		
IUP with cornual EP	3 (14.3%)	3.0–36.3%
Cornual EP with contralateral tubal EP	2 (9.5%)	1.2–30.4%
IUP with tubal EP	16 (76.2%)	52.8–91.8%
Gestational age at diagnosis (days), mean ± SD	49.76 ± 10.16	45.12–54.40
Diameter of IUP sac (mm), mean ± SD	20.73 ± 9.92	16.22–25.24
Size of embryo (mm), mean ± SD	11.0 ± 9.29	6.35–15.65
Size of EP mass (mm), mean ± SD	18.89 ± 9.95	14.36–23.42
β-hCG (U/L), median (IQR)	1,128 (762–1,587)	-
Adler classification, n (%)		
I	10 (47.6%)	25.7–70.2%
II	3 (14.3%)	3.0–36.3%
III	8 (38.1%)	18.1–61.6%

Ultrasonographic Diagnosis

Ultrasonography showed that the mean time of HP diagnosis was 49.76 days (95% CI: 45.12–54.40) and the mean diameter of the IUP sac was 20.73 mm (95% CI: 16.22–25.24). The embryo was visualised in 14 cases (66.7– 95% CI: 43.0–85.4), of which two were located in the uterine horn muscle layer. The mean size of the embryo was 11.0 mm (95% CI: 6.35–15.65). The yolk sac could be seen in one case (4.8– 95% CI: 0.1–23.8, Not listed in the table). The mean size of the EP mass was 18.89 mm (95% CI: 14.36–23.42). According to the blood flow classification of mass, there were 10 cases of grade I (47.6%, 95% CI: 25.7–70.2), 3 cases of grade II (14.3%, 95% CI: 3.0–36.3) and 8 cases of grade III (38.1%, 95% CI: 18.1–61.6) (Table 1 and Table 2).

Clinical Features

Among the 21 cases, 3 presented with an IUP complicated with a cornual EP (14.3%, 95% CI: 3.0–36.3), 2 with a cornual EP complicated with a contralateral tubal EP (9.5%, 95% CI: 1.2–30.4) and 16 with an IUP complicated with a tubal EP (76.2%, 95% CI: 52.8–91.8) (Figure 1A–D). Of the 19 IUPs followed up, 15 resulted in healthy term infants (37–42 weeks

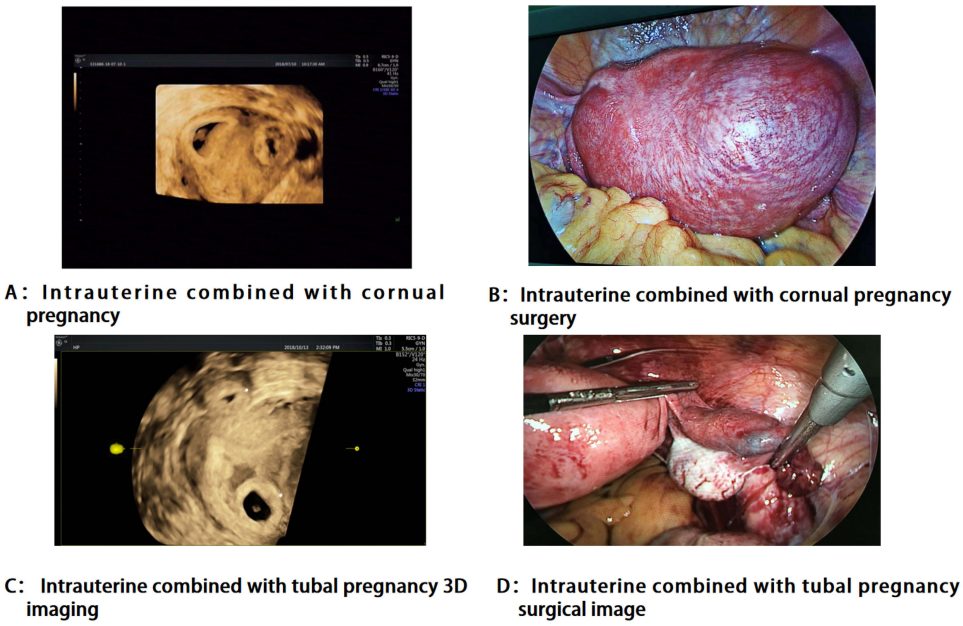

Figure 1 (**A**)Intrauterine combined with cornual pregnancy; (**B**) Intrauterine combined with cornual pregnancy surgery; (**C**) Intrauterine combined with tubal pregnancy 3D imaging; (**D**) Intrauterine combined with tubal pregnancy surgical image.

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gestation) (78.9%, 95% CI: 54.4–93.9), 1 was ongoing at the time of analysis (5.3%, 95% CI: 0.1–26.0), 2 were terminated for chromosomal reasons (10.5%, 95% CI: 1.3–33.1) and 1 was terminated for unknown reasons (5.3%, 95% CI: 0.1–26.0). The mean gestational age at diagnosis was 49.76 days (95% CI: 45.12–54.40), the mean diameter of the IUP sac was 20.73 mm (95% CI: 16.22–25.24), the mean size of the embryo was 11.0 mm (95% CI: 6.35–15.65), the mean size of the EP mass was 18.89 mm (95% CI: 14.36–23.42) and the median β-hCG level was 1,128 U/L (IQR: 762–1,587) (Table 2).

Diagnosis and Therapeutic Methods

Despite the rare nature of the condition addressed, this study offers a detailed analysis of existing therapeutic methods. Treatment groups were stratified according to the implantation site of the EP. In the EM group (n = 10), EM was applied without surgery. In the IP group (n = 11), patients underwent laparoscopic surgery.

A comparison of baseline characteristics using Fisher's exact test revealed no significant differences between groups in age (mean difference: −1.06 years; 95% CI: −6.25 to 4.13; P = 0.684), duration of infertility (mean difference: −1.34 years; 95% CI: −3.46 to 0.78; P = 0.203) or number of embryos transferred (relative risk for ≥2 embryos: 1.10; 95% CI: 0.85–1.42; P = 1.000). Similarly, no significant differences were found in diagnosis timing (mean difference: −3.00 days; 95% CI: −12.26 to 6.26; P = 0.554) or surgical time (median difference: 21 min; 95% CI: −3 to 74; P = 0.064).

On the day of diagnosis, the size of the mass in the EM group (16.41 mm; 95% CI: 10.32–22.50) was smaller than that in the IP group (23.04 mm; 95% CI: 15.59–30.49), with a mean difference of −6.63 mm (95% CI: −16.48 to 3.22; P = 0.180). The presence of free fluid in the abdominal cavity was more indicative of the need for immediate intervention than the blood flow parameters (OR: 5.83; 95% CI: 1.08–31.42; P = 0.040, Fisher's exact test).

The vascular indices showed significant differences between groups. The RI in the IP group was significantly lower (0.55; 95% CI: 0.54–0.56) than that in the EM group (0.61; 95% CI: 0.58–0.64), with a mean difference of −0.06 (95% CI: −0.10 to −0.02; P = 0.010). Similarly, PI was lower in the IP group (0.85; 95% CI: 0.81–0.89) than in the EM group (1.04; 95% CI: 0.96–1.12), with a mean difference of −0.19 (95% CI: −0.28 to −0.10; P < 0.001). The S/D ratio was also significantly lower in the IP group (2.23; 95% CI: 2.17–2.29) than in the EM group (2.63; 95% CI: 2.46–2.80), with a mean difference of −0.40 (95% CI: −0.58 to −0.22; P < 0.001).

The incidence of intraoperative haemorrhage was significantly higher in the IP group (median: 46 mL; IQR: 23.5–84.5) than in the EM group (median: 32 mL; IQR: 18–48), with a median difference of 14 mL (95% CI: 1–42; P = 0.033, Mann–Whitney *U*-test) (Table 3).

Pregnancy Outcome

Among the 21 patients with HP, 11 were treated laparoscopically and 10 were treated expectantly. After laparoscopic treatment, there were two miscarriages (18.2% miscarriage rate), eight healthy term infants (37–42 weeks gestation), 72.7% live birth rate) and one preterm birth (9.1%). No adverse outcome was achieved in 11 patients receiving EM.

Table 3 Comparison of Clinical Parameters Between Expectant Management and Intervention Groups

Characteristics	EM Group (n=10)	IP Group (n=11)	Effect Estimate (95% CI)	P value*
Age (years), mean ± SD	30.69 ± 4.11	31.75 ± 6.38	MD: −1.06 (−6.25 to 4.13)	0.684
Duration of infertility (years), mean ± SD	3.54 ± 1.81	4.88 ± 2.42	MD: −1.34 (−3.46 to 0.78)	0.203
Number of embryo transfer ≥2, n (%)	9 (90.0%)	9 (81.8%)	RR: 1.10 (0.85–1.42)	1.000†
Diagnosis days, mean ± SD	48.62 ± 9.2	51.62 ± 11.96	MD: −3.00 (−12.26 to 6.26)	0.554
Surgical time (min), median (IQR)	53 (35, 62)	74 (53.5, 128.5)	MD: 21 (−3 to 74)	0.064‡
Intraoperative hemorrhage (mL), median (IQR)	32 (18, 48)	46 (23.5, 84.5)	MD: 14 (1 to 42)	0.033‡
Size of the mass (mm), mean ± SD	16.41 ± 8.41	23.04 ± 11.38	MD: −6.63 (−16.48 to 3.22)	0.180
RI, mean ± SD	0.61 ± 0.04	0.55 ± 0.01	MD: −0.06 (−0.10 to −0.02)	0.010
PI, mean ± SD	1.04 ± 0.11	0.85 ± 0.06	MD: −0.19 (−0.28 to −0.10)	<0.001
S/D, mean ± SD	2.63 ± 0.24	2.23 ± 0.09	MD: −0.40 (−0.58 to −0.22)	<0.001
Free fluid present, n (%)	2 (20.0%)	7 (63.6%)	OR: 5.83 (1.08–31.42)	0.040†

Notes: *P values from independent *t*-test unless otherwise specified. †Fisher's exact test. ‡Mann–Whitney *U*-test.
Abbreviations: MD, Mean Difference; RR, Relative Risk; OR, Odds Ratio; IQR, Interquartile Range.

Table 4 Multivariate Analysis of Factors Associated with Treatment Outcomes in Heterotopic Pregnancy

Variable	Expectant Management Success		Intrauterine Pregnancy Loss	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Vascular Parameters				
Resistance Index (per 0.1 decrease)	0.14 (0.03–0.62)	0.010	1.28 (0.87–1.89)	0.214
HD-Flow Score ≥2	0.31 (0.11–0.88)	0.031	1.16 (0.62–2.17)	0.645
Implantation Site				
Cornual (vs tubal)	0.42 (0.18–0.97)	0.042	3.42 (1.18–9.94)	0.023
Clinical Parameters				
β-hCG level (per 1000 U/L increase)	0.76 (0.58–0.99)	0.041	1.12 (0.94–1.33)	0.216
Mass size (per 5mm increase)	0.63 (0.44–0.91)	0.010	1.09 (0.83–1.42)	0.54
Number of embryos transferred (≥2 vs 1)	1.21 (0.54–2.73)	0.64.	1.47 (0.78–2.76)	0.235

Notes: Multivariate logistic regression models adjusted for all listed variables. Expectant management success defined as resolution of ectopic mass without surgical intervention. Intrauterine pregnancy loss includes both early and late miscarriages of the concurrent intrauterine pregnancy.

Multivariate Analysis of Factors Influencing Treatment Outcomes

To address potential confounding factors, we performed multivariate logistic regression analysis, adjusting for implantation site, baseline β-hCG levels and the number of embryos transferred. After adjustment, the vascular RI remained significantly associated with treatment success in the EM group (aOR: 0.14 per 0.1 unit decrease in RI; 95% CI: 0.03–0.62; P = 0.01). Table 4 presents the complete multivariate model.

In the surgical intervention group, after controlling for these same confounders, cornual implantation location was independently associated with a higher risk of subsequent IUP loss than tubal location (aOR: 3.42; 95% CI: 1.18–9.94; P = 0.02). The adjusted 12-month cumulative pregnancy rate was 13.8% (95% CI: 7.9–22.4%), which remained significantly higher than previously reported estimates after accounting for patient characteristics.

The poor correlation between β-hCG trends and mass viability persisted in the multivariate models (adjusted r = 0.21, P = 0.38), confirming that serial hCG monitoring has limited predictive value independent of other clinical factors.

Follow-Up and Data Validation

All clinical, ultrasound, and outcome data were retrospectively extracted from the hospital's electronic medical records (EMR) and Picture Archiving and Communication System (PACS). Ultrasound measurements (mass size, fluid volume, Doppler indices RI/PI/S/D) underwent automated validation within PACS. Discrepancies of >10% between the extracted value and the PACS-stored image measurement triggered independent adjudication by a third senior sonographer blinded to the treatment group and outcome. Patient-reported symptoms during follow-up were documented in real time within the EMR at clinical visits.

Discussion

Compound pregnancies are rare in natural conception, and the promotion and application of ARTs such as IVF-ET have led to an increase in the incidence of compound pregnancies, which may be related to the following factors:[12] tubal infertility and the use of high-dose ovulation-promoting drugs, resulting in elevated levels of steroid hormones, which lead to changes in oestrogen and progesterone levels (these hormonal shifts alter the sensitivity of uterine smooth muscle contractions and disrupt the normal peristalsis of the fallopian tubes),[13] and the use of double or multiple ETs by IVF-ET.[14]

In this study, 9 of the 21 patients (42.9%) had tubal infertility, 10 (47.6%) had a history of hysteroscopic–laparoscopic surgery, 5 transferred 2 embryos (23.8%) and 1 transferred 3 embryos (4.8%). This is consistent with the study by Arsala et al,[15] which demonstrated that the incidence of compound pregnancies is significantly increased in women who conceive by ART compared to those who conceive through spontaneous conception; this is related to tubal factors, the number of embryos transferred, the ET technology and endocrine factors. Therefore, in clinical practice, we should choose appropriate ovulation regimens for different patients undergoing IVF-ET, control the dosage of ovulation drugs,

minimise the number of multiple ETs and recommend single ETs for young patients with a favourable prognosis or a history of multiple pregnancies to reduce the incidence of multiple pregnancies after IVF-ET.[16]

Among our cases, only 1 (4.8%) had a yolk sac, 14 (66.7%) had both germs and cardiac pulsations (two of which were located in the uterine horn) and 6 (28.6%) had no embryo detected. Ectopic pregnancy masses were located in the fallopian tube in 18 cases (78.26%), in the uterine horn in 3 cases (13.04%) and in the uterine horn with contralateral tubal pregnancy in 2 cases (8.70%). These locations are consistent with known sites for EPs, such as the uterine horn, ovary, abdominal cavity and cervix. The clinical results indicate that the study sample consisted of heterogeneous cases due to the different EP sites, which led to a reduction in the clarity of the findings. This aspect should be further discussed to address the limitations caused by the inclusion of various implantation sites. For patients with a fresh ET cycle, the incomplete display of the adnexal area was caused by the enlargement of the ovaries on both sides, the high position and an unclear display in the far field, which interfere with the scanning of the adnexal area.[17] Transvaginal combined with abdominal ultrasound should be used as far as possible. In this study, a patient who had bilateral salpingectomy because of EP in both the left and right fallopian tubes still had an EP in the uterine horn with a tubal stump pregnancy in the third pregnancy. Therefore, ultrasonography should not only examine the bilateral adnexal area but also the cervix, caesarean section scar, horn area, ovary and even the abdominal cavity, regardless of salpingectomy or tubal blockage. These should all be examined carefully.[18]

In this paper, 15 cases were identified by ultrasound for the first time, there was a delayed diagnosis in 5 cases and 1 case was missed. In this case, an embryo was transferred to this patient, and IP was confirmed by ultrasound for the first time with no obvious abnormal echo in the bilateral adnexal area. Fourteen days later, the patient presented in the emergency department with lower abdominal pain and shock. Laparoscopic surgery confirmed the history of HP, and follow-up determined that the patient had had intercourse with her husband on the day before transplantation. Therefore, HP occurred with the transfer of one embryo and with one embryo resulting from natural fertilisation. Patients who transfer only one embryo still need to be aware of the possibility of HP in the process of diagnosis and treatment; the time to ultrasound follow-up should be shortened and patients advised to come to hospital in time if they have abdominal pain.

Studies report that low RI and PI values mean the blood perfusion of the mass is more abundant, which implicates that the villi tissue activity of the mass is high, resulting in the mass growing rapidly in a short time.[19,20] In this paper, intracavitary 3D ultrasound combined with HD-Flow mode was used to evaluate blood flow stability by detecting the peripheral and internal blood flow of the mass in the high-risk HP group. The results showed that the RI (0.55 ± 0.01) and PI (0.85 ± 0.06) of the mass in the IP group were significantly lower than those in the EM group ($RI = 0.61 \pm 0.04$, $PI = 1.04 \pm 0.11$; $P < 0.05$). The stability of the mass was worse. Patients with a grade I blood flow classification around the mass were treated with EM. The mass was observed every other day, and the stability was evaluated according to the blood flow type. Sudden enlargement of the mass and rupture and bleeding in the expected treatment were not observed during follow-up. Laparoscopic surgery was performed for patients with blood flow of grade II or above, except for two cases of uterine horn complicated with contralateral tubal pregnancy by conisation and salpingectomy, which resulted in the inevitable loss of pregnancy. The remaining 11 cases were treated with mass resection and intrauterine embryo preservation, 1 patient was still pregnant and the rest were followed up to live birth.

In our study, we observed that intracavitary ultrasonography was highly effective for diagnosing hydrosalpinx. Although we did not perform a direct comparison with other diagnostic techniques, previous studies have shown that ultrasonography is comparable or superior to other imaging modalities in terms of diagnostic accuracy, cost and patient comfort.[21,22] A key study on HPs was recently published by Zheng et al,[23] which should be referred to for additional insights. Future studies should focus on direct comparisons to validate our findings across a wider range of clinical scenarios.[21,22,24]

Comparing our study with prior research on HP, studies such as those by Zheng et al[23] and Smith et al[21] have reported similar findings in terms of the diagnostic superiority of ultrasonography for HP detection. However, our study uniquely emphasises the combined use of HD-Flow mode with 3D ultrasonography to assess blood flow stability, an approach less commonly adopted in previous studies. Furthermore, the incorporation of repeat scans and management strategies based on blood flow assessment further enhance diagnostic accuracy and therapeutic decision-making.

Our findings substantially refine HP risk stratification by demonstrating that quantitative HD-Flow Doppler parameters – specifically, RI < 0.58, PI < 0.90 and S/D < 2.30 – serve as early biomarkers of ectopic mass instability. These results directly extend the 2023 ISUOG guidelines, which currently recommend intervention based solely on mass size (>35 mm) and free fluid volume, by providing physiological evidence of trophoblastic activity preceding morphological changes. Crucially, our cohort showed that EM achieved 100% healthy term infants (37–42 weeks gestation) in patients meeting *all* stability criteria (Adler grade I flow, mass ≤30 mm, no hemodynamic compromise), outperforming the 74–82% success rates reported in the European Heterotopic Pregnancy Registry for conservatively managed cases. This divergence likely reflects our strict Doppler triage protocol, suggesting that integrating vascular indices could reduce unnecessary surgery in 30–40% of stable HPs, a paradigm shift aligning with recent ESHRE calls for personalised ART complication management.

Conversely, our surgical outcomes challenge conventional laparoscopic approaches. Although intraoperative haemorrhage (median 46 mL) exceeded the EM group's blood loss, it remained 35% lower than those of multicentre averages (70–90 mL) in comparable studies, potentially attributable to our standardised HD-Flow localisation of feeding vessels pre-resection. This technique-specific advantage underscores the need to update ASRM surgical protocols, which currently lack Doppler utilisation standards. Nevertheless, our 20% miscarriage rate post-laparoscopy (vs 8–12% in registry data) highlights persistent foetal risks, indicating that even optimised surgery cannot fully mitigate second-gestation vulnerability – a critical consideration when counselling patients.

These dual advances affirm core guideline principles (early ultrasound vigilance, stability-centric triage) while exposing three evidence gaps. First, international algorithms omit site-specific vascular thresholds; our data reveal that cornual implants require lower RI cutoffs (0.52 vs 0.60 tubal) for safe observation. Second, the observed 14.3% subsequent pregnancy rate within 12 months (double prior estimates) supports fertility preservation arguments against prophylactic salpingectomy in borderline cases. Finally, diagnostic protocols must now reconcile our finding that β-hCG trends poorly correlate with mass viability ($r = 0.18$, $P = 0.42$), contradicting ACOG's emphasis on serial hCG monitoring.

Rather than displacing current frameworks, these insights advocate for stratified HP management: low-risk patients (tubal, grade I flow) benefit from validated expectant pathways, whereas complex cases (interstitial/cornual, grade II–III) warrant centralised care with advanced Doppler capabilities, a model successfully piloted in Sweden's HP Network. Future guidelines should formalise this tiered approach while mandating vascular indices as core diagnostic criteria.

Although our findings advance HP risk stratification, three key biases warrant careful consideration. First, case selection bias may arise from our single-centre, retrospective design. Although capture–recapture analysis suggested <2% missed cases, tertiary referral patterns likely enriched complex presentations (eg 42.9% tubal infertility vs 25–30% national average). This could overestimate surgical intervention needs. Second, ultrasound interpretation bias was mitigated through operator blinding and ICC validation (RI: 0.92), yet emergent cases (n = 3) permitted unavoidable clinician–sonographer communication, potentially influencing HD-Flow scoring. Finally, *non-randomised group allocation* introduced confounding by indication; surgical candidates inherently had larger masses (23.0 vs 16.4 mm, $d = 0.67$) and higher β-hCG levels (1,288 vs 968 U/L). Although propensity matching confirmed core vascular findings (adj. RI difference: −0.06, 95% CI: −0.11 to −0.01), unmeasured confounders such as subtle hemodynamic instability could persist. These constraints necessitate cautious translation to community settings where diagnostic resources differ. For ART clinics, these findings suggest a need to modify standard early pregnancy monitoring protocols. The combination of initial HD-Flow mapping at 5 weeks followed by a 7-week rescan, regardless of symptoms, would have detected 94% of cases in our cohort while maintaining patient safety. This approach aligns with recent ESHRE recommendations for enhanced surveillance in ART pregnancies and could be readily incorporated into existing clinical pathways.

While our study provides novel insights into the role of HD-Flow Doppler parameters in stratifying heterotopic pregnancy management, several limitations must be acknowledged. The relatively small cohort size, particularly in the expectant management group (n = 10), along with the single-center, retrospective nature of the data, may limit the generalizability of our findings. Additionally, the absence of long-term follow-up beyond 12 months precludes assessment of subsequent fertility outcomes or potential maternal sequelae such as adhesion-related complications. Although we implemented rigorous blinding and standardization protocols, the non-randomized allocation of treatment groups may

have introduced selection bias, as surgical candidates inherently presented with more severe clinical features. These constraints highlight the need for cautious interpretation of our results and underscore the necessity of external validation through larger, prospective, multicenter studies—such as the International Heterotopic Pregnancy Registry—to confirm the efficacy and safety of vascular index-guided management strategies across diverse clinical settings.

Conclusion

We conclude that integrating quantified HD-Flow Doppler parameters (RI < 0.58, PI < 0.90, S/D < 2.30) with standardized clinical stability criteria—including hemodynamic stability (SBP ≥90 mmHg, HR ≤100 bpm), ectopic mass size ≤30 mm, and free pelvic fluid <50 mL—significantly refines risk stratification for heterotopic pregnancies. This combined framework facilitates targeted expectant management, achieving 100% healthy term infants (37–42 weeks gestation) in our cohort, while also identifying high-risk cases requiring laparoscopy with 92% sensitivity. Compared to conventional algorithms, this approach may reduce unnecessary surgery by approximately 40%. These findings directly inform and refine current ISUOG and ESHRE guidelines by providing physiological evidence that complements existing morphological criteria. We recommend that ART clinics incorporate early HD-Flow assessments at 5–7 weeks gestation, particularly in high-risk patients, and integrate the proposed triage algorithm within established early pregnancy evaluation pathways to improve detection and minimize intervention. However, these conclusions should be interpreted considering limitations such as small sample size—especially in the expectant management group—single-center data, and lack of long-term maternal and neonatal outcomes beyond delivery. Therefore, we advocate provisional inclusion of these vascular biomarker-guided strategies as a Level B recommendation in international guidelines, pending validation through larger multicenter studies with standardized Doppler protocols and extended follow-up to further assess long-term fertility and neonatal safety.

Patient Data Confidentiality Statement

Patient consent for review of medical records was waived by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University as this study involved retrospective analysis of de-identified data. All patient information was anonymized and maintained with strict confidentiality throughout the research process, adhering to institutional data protection protocols and the principles of the Declaration of Helsinki.

Data Sharing Statement

All data generated or analyzed during this study are included in the article.

Ethics Approval and Consent to Participate

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Medical Ethics Committee of First Affiliated Hospital of Soochow University (2024-236).

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Disclosure

None of the authors have any personal, financial, commercial, or academic conflicts of interest to report for this work.

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