

Clinical outcomes of patients with heterotopic pregnancy after laparoscopic surgery

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ABSTRACT

Objective: This retrospective study aims to analyze laparoscopic surgical management and clinical consequences of patients with heterotopic pregnancy (HP) who underwent in vitro fertilization and embryo transfer (IVF-ET) and laparoscopic surgical management.

Material and methods: We conducted a retrospective analysis of clinical characteristics and pregnancy results of patients with HP who underwent IVF-ET at the Affiliated Maternity and Child Health Care Hospital of Nantong University between January 2013 and December 2022.

Results: 21 patients were diagnosed with HP, with an average diagnostic period of 49.1 ± 11.1 days. 11 cases (52.4 %) exhibited clinical manifestations such as abdominal pain and vaginal hemorrhage before the surgery, while 10 cases (47.6 %) were asymptomatic prior to diagnosis. All patients underwent laparoscopic surgery, resulting in 8 cases of miscarriage postoperatively (6.15 %), and all 13 neonates showed no anomalies at birth.

Conclusion: Laparoscopic surgery is a safe and effective treatment, and most patients can achieve satisfactory pregnancy outcomes after surgery.

1. Introduction

HP defines a pathological gestation characterized by the simultaneous establishment of two or more implantation sites. The preponderance of documented ectopic gestational sacs in heterotopic pregnancies resides within the fallopian tube, while a minority inhabit the cornua, and rare instances occur at cesarean section scar sites, the ovary, abdominal cavity, and cervix [1]. HP proves exceedingly rare in spontaneous conception, boasting an incidence rate of approximately 1 in 30,000. However, with the expansive evolution of assisted reproductive technologies, its frequency has markedly escalated to around 1 % [2].

Patients with HP face a heightened risk of uterine rupture, profound hemorrhaging, and hypovolemic shock, which can pose life-threatening consequences. Timely identification and prompt intervention in this scenario are crucial for safeguarding the integrity of the intrauterine pregnancy (IUP) [3]. The presence of an intrauterine gestational sac renders serum HCG levels an inadequate reference point. Ultrasound confirmation of an IUP precludes the possibility of an ectopic pregnancy (EP), as ascertained by the imaging specialist or obstetrician-gynecologist. HP manifests without distinctive symptoms or

indicators, making it prone to diagnostic errors. An examination encompassing 82 cases of HP unveiled that nearly 34 % of cases received diagnosis during the initial pregnancy ultrasound assessment [4].

The crux of surgical management for complex pregnancies lies in the simultaneous removal of ectopic pregnancies while minimizing the impact on intrauterine gestations and uterine physiological structures. Laparoscopic surgery is gradually superseding laparotomies, emerging as the primary modality for treating HP [5,6]. This study undertakes a retrospective analysis of general characteristics, diagnostic features, safety profile of laparoscopic surgery, and outcomes of 21 patients who underwent in vitro fertilization and embryo transfer (IVF-ET) and laparoscopic surgical treatment at the ART Center of Affiliated Maternity and Child Health Care Hospital of Nantong University. The objective is to provide valuable perspectives for the utilization of laparoscopic surgery in the management of HP.

List of Abbreviations.

Abbreviation	Meaning
HP	Heterotopic pregnancy
EP	Ectopic pregnancy
IUP	Intrauterine pregnancy
IVF-ET	In vitro fertilization and embryo transfer
ART	Assisted reproductive technology

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The list describes the significance of various abbreviations used throughout the article.

2. Materials and methods

Twenty-one patients were diagnosed as HP using TVS or surgical pathology in Affiliated Maternity and Child Health Care Hospital of Nantong University between January 2013 and December 2022. A retrospective analysis was undertaken on the clinical data of patients, including demographic information, characteristics of IVF-ET, details of surgical treatment, and reproductive outcomes. HP diagnostic criteria: the simultaneous presence of intrauterine gestational sacs and ectopic pregnancy lesions. Ultrasonic manifestations of ectopic pregnancy: mixed echogenic mass; annular high echogenic gestational sac; visible yolk sac and (or) germ (with or without primitive cardiac pulsations); accompanied by pelvic and abdominal fluid accumulation. Exclusion criteria: old ectopic pregnancies; termination of pregnancy required due to certain conditions (Fig. 1). All clinical data used for research purposes were approved by the Ethics Committee of Affiliated Maternity and Child Health Care Hospital of Nantong University.

The serum β -hCG was quantified 11–14 days following embryo transfer. In the event that serum β -hCG was positive, a vaginal ultrasound was conducted 28 days after embryo transfer with the objective of confirming the IUP. A further ultrasound examination was conducted two weeks after the diagnosis of IUP to exclude the occurrence of EP. Moreover, ultrasound evaluations were administered promptly if the patient reported abdominal discomfort and vaginal hemorrhage.

General intravenous anaesthesia was used for laparoscopic surgery, with a CO₂ pneumoperitoneum pressure of below 12 mmHg. The hematocele in the pelvic area was initially removed, followed by the localisation of the EP mass for surgical procedures. The fallopian tubes were removed for tubal pregnancy, while cornuostomy was conducted for the treatment of cornual pregnancy. Oral dydrogesterone (10 mg tid) was administered after surgery until 10 weeks of gestation. The patient was discharged 3 days after surgery with no abnormalities in ultrasonography. A telephone call was made to each patient to inquire about the progress of her pregnancy.

Statistical analysis was conducted using SPSS Statistics 21.0 (IBM SPSS Statistics, Inc., Armonk, NY, US). Measurement data were presented as mean \pm standard deviation ($X \pm S$).

3. Results

3.1. General characteristics of patients with HP

Table 1 delineates the general characteristics of 21 patients with HP undergoing in vitro fertilization (IVF) for conception. Among these, 3 cases involved the transfer of fresh embryos, while 18 cases involved the

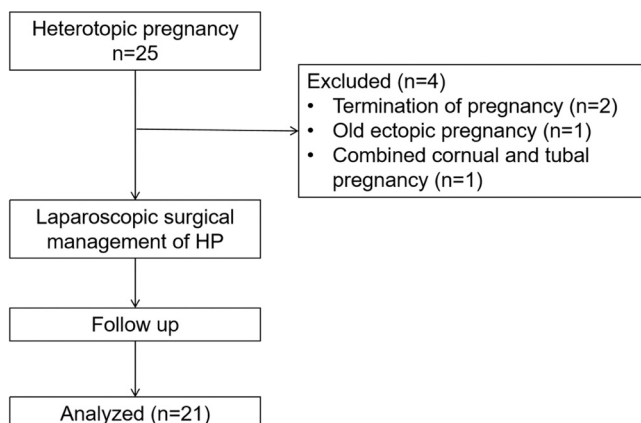


Fig. 1. Flow diagram.

Table 1
Baseline characteristics of IVF-ET patients with HP.

Variables	No. (%) of patients
Age, mean \pm SD (range), yr	30.3 \pm 4.3
BMI (Kg/m ²)	21.5 \pm 2.5
Type of infertility, n (%)	
Primary	5(23.8 %)
Secondary	16(76.2 %)
History of EP (n%)	
N = 0	13 (61.9 %)
N = 1	6 (28.6 %)
N = 2	2 (9.5 %)
History of pelvic surgery, n (%)	
Tubal surgery	15(71.4 %)
Non-tubal surgery	2(9.5 %)
No surgery	4(19.1 %)
Infertility factor	
Tubal factor	15(71.4 %)
Other factor	6(28.6 %)
Method of IVF-ET, n (%)	
Fresh non-donor embryo	3(14.3 %)
Frozen-thawed embryo	18(85.7 %)

Values are expressed as mean standard deviation \pm SD, and percentages. Abbreviations: HP: heterotopic pregnancy; EP: ectopic pregnancy; BMI: body mass index; IVF-ET: in vitro fertilization and embryo transfer.

Table 2
Clinical and surgical characteristics of patients with HP.

Variables	No. (%) of patients
Clinical manifestations, n (%)	
Abdominal discomfort and/or vaginal hemorrhage	11(52.4 %)
Asymptomatic	10(47.6 %)
Hypovolemic shock	3(4.8 %)
Gestational age at diagnosis(d)	49.1 \pm 11.1
Site of ectopic pregnancy, n (%)	
Tubal	11(52.4 %)
Interstitial	4(19.0 %)
Corner	6(28.6 %)
Management of HP, n (%)	
Surgical management	21(100 %)

Values are expressed as mean standard deviation \pm SD, and percentages.

Table 3
Pregnancy outcomes of patients with HP.

Variables	No. (%) of patients
Rupture after treatment	0
Clinical outcomes, n (%)	
Abortion	8 (38.1 %)
Live birth	13 (61.9 %)
Mode of delivery, n (%)	
Vaginal delivery	8 (61.5 %)
Cesarean section	5 (38.5 %)

Values are expressed as mean standard deviation \pm SD, and percentages.

transfer of frozen embryos. The ages ranged between 21 and 37 years, with an average of (30.3 \pm 4.3) years and a BMI of 21.5 \pm 2.5. Eight cases had a history of ectopic pregnancies, with two cases having experienced two ectopic pregnancies. Fifteen cases (71.4 %) had a history of pelvic surgeries, including procedures such as tubal patency restoration, tubal anastomosis, and tubal resection. 71.4 % of the patients underwent IVF for conception due to tubal factors.

3.2. Clinical and surgical characteristics of patients with HP

Eleven cases (52.4 %) of patients exhibited clinical manifestations such as abdominal pain and/or vaginal hemorrhage, with three cases (4.8 %) encountering hypovolemic shock requiring blood transfusions for management. Ten cases (47.6 %) remained asymptomatic, and all

patients received a definitive diagnosis of HP through surgical procedures. The average duration for diagnosing hydrosalpinx was 49.1 ± 11.1 days.

All 21 patients underwent laparoscopic surgery. Ectopic pregnancies were situated in distinct locations: the ampullary section of the fallopian tube in nine cases (60 %), the isthmic portion in two cases (13.4 %), the interstitial area of the tubal canal in four cases (26.6 %), and within the uterine cornua in six cases. All patients made a full recovery and were discharged from the medical facility.

3.3. Pregnancy outcomes of patients with HP

Among the 21 cases, there were 8 instances of miscarriage (6.15 %), with 6 occurring before the 12th week of gestation, 1 at the 13th week, and 1 at the 22nd week due to cervical insufficiency. Among the live births, there were 12 full-term deliveries (92.3 %), 1 preterm birth (7.7 %), 5 cesarean sections (38.5 %), and 8 vaginal deliveries (61.5 %). Thirteen neonates showed no anomalies at birth, with no deformities detected.

4. Discussion

Reports have detailed that approximately half of HP patients may either exhibit no symptoms due to regular luteal support or present symptoms such as abdominal discomfort and/or vaginal hemorrhage, indicative of a threatened abortion within an IUP [7]. Simple gastrointestinal disturbances, like nausea and vomiting, might also manifest in certain cases. Some patients may even experience hemorrhagic shock as a direct aftermath of EP [8]. Our research findings revealed that roughly 52.4 % of patients displayed abdominal pain or vaginal bleeding before their diagnosis. Consequently, for individuals undergoing assisted reproductive technology and standard luteal support, it is thoughtless to presume a threatened abortion without solid evidence or to escalate luteal support without further substantiation. Rather, it is imperative to exclude the possibility of EP. Given the unique clinical variations of HP, meticulous ultrasound examinations play a pivotal role. Immediate ultrasound evaluations are recommended for symptomatic patients. Prior studies have noted instances occurring as early as 20 days post-embryo transfer, with our study identifying diagnoses as swiftly as 24 days post-transfer [9]. As for asymptomatic individuals, ultrasound assessments are advised between 4 to 5 weeks post-embryo transfer.

Ovulation induction and the transfer of multiple embryos create conditions conducive to embryo implantation at multiple sites. Additional risk factors for EP encompass fallopian tube dysfunction [10]. Previous research has established that a prior history of EP correlates with an elevated risk of experiencing EP in subsequent pregnancies and also increases the likelihood of encountering HP. The likelihood of facing another EP can be as substantial as 15 % to 20 % among individuals who have undergone a single salpingotomy in the past and can escalate to 32 % for those with a history of two ectopic pregnancies [11]. Consistent with the conclusions drawn from preceding studies, 38.1 % of the participants in this investigation had a history of EP. Moreover, 71.34 % of them had undergone fallopian tube surgeries, which encompassed procedures such as tubal dredging, tubal ligation, and salpingectomy. The underlying mechanism stems from the compromised function of the fallopian tubes, leading to aberrant transport mechanisms within these tubes, alongside an anomalous expression of molecules that impede embryo implantation within the fallopian tubes. These anomalies ultimately promote embryo implantation within the fallopian tubes [12,13].

As a result, it is imperative to implement effective measures to prevent the incidence of HP. Contrasted with single embryo transfers, the practice of transferring multiple embryos can elevate the risk of EP. Hence, elective single embryo transfer is strongly recommended [14]. A retrospective cohort study conducted in 2014 unveiled an ectopic pregnancy incidence of 2.22 % in frozen-thawed embryo transfer cycles

and 4.62 % in fresh embryo implantation cycles [15]. These results underscored the substantial reduction in EP rates associated with frozen-thawed embryo transfers in comparison to fresh blastocyst transfers. One potential rationale behind this observation is that the endometrium during the frozen-thawed embryo cycle assumes a natural or naturally simulated state, fostering heightened endometrial receptivity and synchronization, thereby creating a more favorable environment for the implantation of frozen-thawed embryos [16]. Consequently, determining the optimal approach to assisted reproductive technology (ART) transplantation remains an ongoing subject of exploration and discourse.

The determination regarding the management of HP is predominantly shaped by the presence of an IUP and the patient's inclination to uphold the IUP. Should the IUP exhibit dysplasia or if the decision is made not to sustain it, the course of treatment mirrors that utilized in cases of EP. In instances where the IUP progresses favorably and preservation is warranted, the approach for addressing the ectopic gestational sac hinges on factors such as the location and size of the sac, whether there is rupture and bleeding, the levels of hCG, and the patient's vital signs. Given the pressing urgency expressed by patients, the removal of ectopic gestational sacs while safeguarding the IUP holds paramount significance [17]. Upon accurate diagnosis and appropriate management of EP, the survival rate of the IUP can reach as high as 70 % [18]. Treatment modalities encompass surgical intervention, pharmaceutical therapy, and conservative monitoring. Among these choices, surgery stands as the primary recourse, offering the potential for favorable outcomes [19].

In the early 1990s, due to the limited application of laparoscopy in clinical practice, pregnancy was considered a contraindication for the use of laparoscopy. With the introduction of guidelines for laparoscopic surgery during pregnancy, the safety of laparoscopic surgery in pregnancy has been acknowledged [20]. The laparoscopic approach provides a broad field of view, reduces surgical time, minimizes uterine stimulation from open surgery, limits intraoperative anesthesia use, lowers the risk of postoperative miscarriage in intrauterine pregnancies, and promotes faster patient recovery. The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) recommends strict control of intra-abdominal pressure < 12 mmHg and surgery performed by experienced laparoscopic surgeons for patients requiring continued intrauterine pregnancies to reduce surgical duration and carbon dioxide abdominal damage. During surgery, efforts are made to select anesthetics that are non-teratogenic to the fetus, avoid the use of monopolar electrocautery to prevent current backflow affecting the intrauterine fetus, and aim to expel as much carbon dioxide from the abdominal cavity post-surgery [21]. Additionally, previous studies have shown no adverse effects on pregnancies in women who underwent laparoscopic appendectomy or cholecystectomy in early pregnancy [22,23]. This study reports cases treated with laparoscopic surgery, with all 21 patients receiving timely treatment, achieving a live birth rate of 61.9 %, and with no newborn abnormalities observed.

Given the persistence of EP or the risk of miscarriage or premature birth due to the sequelae of tubal inflammatory exudation following conservative surgery for tubal ampullary or isthmic EP, ipsilateral salpingectomy is performed during the operation [24]. Cornuostomy and cornual resection are commonly used surgical procedures for interstitial or cornual pregnancies. Due to the ongoing development of intrauterine pregnancies, cornual resection may increase the risk of uterine rupture during pregnancy due to its impact on uterine integrity. Therefore, Cornuostomy is preferred over cornual resection [25]. In this study, patients with interstitial tubal and cornual pregnancies underwent Cornuostomy to remove the gestational tissue, followed by continuous closure of the wound using 1–0 absorbable sutures. Electrocautery for hemostasis was minimized during surgery to avoid tissue necrosis, and care was taken to prevent excessive uterine traction, with hemostatic materials used when necessary. All procedures were performed by experienced senior physicians. Cornuostomy may disrupt the integrity of

the uterine muscle layer, increasing the risk of uterine rupture during the antenatal and postnatal periods. A review of literature reporting intrauterine interstitial and cornual pregnancies from 2000 onwards did not find any reports of uterine rupture during pregnancy or persistent ectopic pregnancies in all surgical patients [24]. In this study, seven cases of intrauterine interstitial tubal or cornual pregnancies underwent Cornuostomy. These patients were closely monitored during pregnancy, and none experienced uterine rupture during pregnancy or delivery.

Maternal hypotension can lead to fetal hypotension and hypoxemia, resulting in inadequate cerebral perfusion in the fetus. Fetal compensatory mechanisms through the autonomic and sympathetic nervous systems can help mitigate mild to moderate hypoxia [26,27]. Shinji Nomura et al. reported a case of a 7-week pregnant woman who underwent laparoscopic salpingectomy following shock to remove the affected fallopian tube and subsequently delivered a healthy baby via full-term cesarean section. In this study, three patients presented with shock symptoms, with pelvic bleeding exceeding 1500 ml in two cases. Despite these challenges, two patients and their families strongly advocated for maintaining the intrauterine pregnancies. Post-surgery, both patients successfully delivered two healthy babies at full term. These findings suggest that in cases of complex pregnancies complicated by shock, preserving the IUP can still be considered. Moreover, all three cases of shock patients were treated with laparoscopic surgery, achieving favorable outcomes. However, due to the scarcity of shock cases, a comparative analysis between laparotomy and laparoscopic surgery outcomes, obstetric complications, and live birth rates cannot be conducted.

The prognosis of heterotopic pregnancies primarily focuses on maternal and fetal complications during the perinatal period, such as spontaneous abortion, preterm birth, uterine rupture during pregnancy, recurrent bleeding during pregnancy, postpartum hemorrhage, and fetal malformations. Due to the low incidence of heterotopic pregnancies and the predominance of individual case reports, it is challenging to accurately estimate prognosis. Limited data mostly center around intrauterine pregnancies with concurrent tubal pregnancies. A retrospective analysis of 56 cases of heterotopic pregnancies undergoing surgical treatment revealed a spontaneous abortion rate of 17.86 % and a live birth rate of 82.14 %, with seven cases resulting in preterm births. No congenital malformations were observed in the newborns at birth, except for one case diagnosed with mild cerebral palsy at age one [28]. Another study of 12 cases of heterotopic pregnancies reported a live birth rate of 75 % with favorable fetal outcomes [29]. Soriano et al. followed up with 12 cases of heterotopic pregnancies, where 11 cases underwent laparoscopic surgery and one case underwent conservative treatment with medication. Among them, eight had live births, two were still pregnant, and two experienced spontaneous abortions, with no reports of fetal malformations [30]. These results indicate a relatively high live birth rate in cases of intrauterine concurrent tubal pregnancies, with no significant increase reported in the rates of preterm births, fetal malformations, recurrent bleeding during pregnancy, or postpartum hemorrhage.

As a single-center retrospective study, inherent biases are present. The low prevalence of the condition results in a limited patient cohort, thereby restricting the statistical power of our research findings. Furthermore, this study noted three cases of shock in which laparoscopic surgery proved successful, yielding a high rate of live birth. In the future, Prospective multicenter clinical studies can be conducted to explore the impact of laparoscopic surgical treatment on the outcomes and fetal well-being of patients with shock-associated HP.

In conclusion, despite the low incidence rate of heterotopic pregnancies, there is a possibility of intrauterine and extrauterine heterotopic pregnancies in patients undergoing ovulation induction or assisted reproduction with embryo transfer, especially those with a history of EP. This should be of significant concern to clinicians. Detailed ultrasound examinations are crucial, encompassing every specific site such as the cervical canal, uterine cornua, interstitial region, residual fallopian

tube, and abdominal cavity, rather than solely focusing on the adnexal area. Experienced surgeons performing laparoscopic procedures exhibit minimal impact on intrauterine pregnancies, with most cases achieving favorable pregnancy outcomes.

CRedit authorship contribution statement

Wei-wei Ma: Writing – original draft, Visualization, Investigation, Data curation. **Yi Zhu:** Supervision, Resources, Investigation. **Ya Shen:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

All authors disclosed no relevant relationships.

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