

Clinical Analysis of 47 Cases of Heterotopic Pregnancy After Assisted Reproductive Technology

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Research Article

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Abstract

Background:

Heterotopic pregnancy is rare in natural pregnancy. In recent years, with the development of assisted reproductive technology, the incidence of heterotopic pregnancy is increasing. Heterotopic pregnancy not only affects the development of intrauterine embryo, but also threatens the life of patients. There is no unified standard for the treatment of heterotopic pregnancy until now. So we research the clinical features and the effect of different intervention time on pregnancy outcome in patients with heterotopic pregnancy (HP) after assisted reproductive technology (ART).

Methods:

A retrospective analysis was conducted on the patients who were diagnosed as HP in Shanghai first maternal and infant hospital after conception through ART from January 2014 to June 2019. We analyzed the clinical characteristics, therapeutic method and intervention time to explore their impact on the outcome of HP.

Results

47 patients with HP after ART were treated in our hospital and have complete clinical data.

Among them, 18 cases treated with conservative therapy and 29 cases treated with operation. 29 cases delivered (including 3 cases of pre-term birth and 26 cases of full-term birth) and 18 cases aborted. In HP patients, β Human chorionic gonadotropin (β -HCG, 0.617) and extrauterine mass size (0.242) are not much guiding significance for the treatment. Transvaginal ultrasonography (TVS) examination on admission found that different conditions of ectopic (anechoic area, adnexal mass, heart beat, yolk sac) was independent risk factors of different treatment methods ($P=0.005$). And the intervention time before six weeks can get better pregnancy outcome ($p=0.034$).

Conclusions

Patients with ART should be examined by TVS as early as possible. If abnormal TVS (anechoic area, adnexal mass, heart beat, yolk sac) results are found, patients should be operated by laparoscopy. And the best intervention time of laparoscopy is before 6 weeks.

Background

Heterotopic pregnancy (HP) refers to the simultaneous development of two or more embryos in different parts of the reproductive system, at least one of which belongs to intrauterine normal pregnancy, and the rest is ectopic pregnancy [1]. In natural pregnancy, the incidence of HP is 1/30000 [2]. In recent years, with the increase of female infertility incidence rate [3], the proportion of women who assisted pregnancy through assisted reproductive technology has increased, which has led to a rising trend in the incidence

of HP [4]. Due to the existence of intrauterine pregnancy, ectopic pregnancy is often ignored. However, When HP happens, the level of β -HCG is often higher than ectopic pregnancy, increasing the risk of mass rupture in ectopic pregnancy. Therefore, it is very important to diagnosis HP early.

At present, ultrasound is still the main diagnostic method for HP. Typical ultrasound findings of HP: gestational sac can be seen in the uterine cavity, and the echo of gestational sac can be seen outside the uterine cavity, but some HP were missed because of the lack of typical ultrasound findings [5]. The ultrasonic manifestations of HP ectopic lesions can be divided into direct signs (gestational sac, yolk sac, even germ and fetal heart) and indirect signs (mixed echo mass and abdominal pelvic effusion). The diversity of ultrasonic manifestations leads to the uncertainty of ultrasonic diagnosis [6,7].

The treatment of HP includes conservative treatment and surgical treatment [8,9]. With the development of laparoscopic technology, laparoscopic surgery is the first choice for patients who have reached the surgical indications. Laparoscopic surgery has the advantages of fast postoperative recovery, small trauma, and greatly reducing the incidence of intestinal adhesion [10]. HP has its particularity: it is necessary to ensure the normal development of intrauterine embryos and the safety of patients. Whether conservative treatment with Methotrexate (MTX) has teratogenic effect on intrauterine embryos remains unclear.

HP is seen rarely, there is no unified standard for the treatment and intervention time of HP patients in the previous literature. For patients with heterotopic pregnancy, we should not only ensure the development of intrauterine gestational sac, but also ensure the safety of patients. It's a challenge for treatment. HP mainly occurs in ART, we analyzed HP after ART cases in Shanghai First Maternity and Infant Hospital, our study aims to explore the influence of different factors on the choice of treatment and the best intervention time.

Methods

Participants

We retrospectively analyzed 47 cases of HP patients after ART treated in Shanghai first Maternity and Infant hospital. Our hospital is one of the earliest medical institutions to develop assisted reproductive technology in Shanghai. Furthermore, our hospital is a specialized hospital of Obstetrics and Gynecology, which has a large number of patients every year. Ultrasound doctors have rich experience in the diagnosis of ectopic pregnancy.

The inclusion criteria were: HP patients were pregnant through ART; Intrauterine fetal heart rate can be seen by B-ultrasound; HP patients were discharged from hospital after regular treatment and delivered in our hospital. The data included patient characteristics, pregnancy characteristics and clinical symptoms.

Data collection

We collected clinical data of patients including age, Body Mass Index (BMI), number of previous ectopic pregnancies, the reason of maternal infertility, menopause days, embryo implantation days, fertilization method, embryo type, number of uterine cavity operation, location of HP, diagnosis time, mean haemoglobin count, ultrasound findings when admission and β -HCG level when admission.

Different treatment methods were selected according to β -HCG level, TVS, clinical symptoms and clinical experience of doctors. Surgical treatment includes laparoscopic surgery and open surgery. All patients received general anesthesia. Patients with tubal pregnancy underwent salpingectomy on the affected side and cornual pregnancy patients underwent partial cornectomy as well as salpingectomy on the affected side. The pathological examination was performed after the cut tissue was dissected and the villi was found. During laparoscopic surgery, about 2.7-3.6L carbon dioxide (CO₂) was injected through the Veress needle. No matter which kind of operation method, the patients were treated with fetal protection after operation.

The diagnosis was made by clinical symptoms and TVS examination, and the operation was confirmed by pathological findings in pathological examination. Blood routine examination was performed on the first day after operation. In order to reduce the human error of postoperative hemoglobin value, the operation was performed by experienced doctors.

Statistical analysis

Descriptive statistical analysis of patients and treatment characteristics. SPSS 25.0 was used for statistical analyses. The counting data were expressed as cases and percentages, and the measurement data were in accordance with normal distribution uses mean \pm SD denotes, the description that does not conform to the normal distribution uses the median. For categorical variables, description adoption rate (%) is used. The comparison between groups was performed by t test χ^2 Inspection. The Kaplan–Meier survival curve was used to detect the tendency between the different intervention time and cumulative full-term birth percentage. In all analyses, two-sided $P < 0.05$ was considered to be statistically different.

Results

From January 2014 to June 2019, among the patients who were conceived by ART and treated in our hospital, 357 cases were diagnosed as ectopic pregnancy, only 57 cases were HP. 2 cases automatic discharge during treatment and 8 cases have incomplete information of pregnancy outcome, so we study only 47 cases of HP after ART. The study flowchart is presented in Figure 1.

29 patients had live birth and 18 patients had pregnancy loss (including fetal stopped growth and spontaneous abortion). The age of the conservative treatment group was 32.39 \pm 5.03 years old, range from 27 to 43 years old, BMI was 20.96 \pm 2.46 kg/m². The age of the operation treatment group was 31.45 \pm 3.05 years old, range from 25 to 37 years old, BMI was 21.53 \pm 2.63 kg/m². There was no significant difference between the groups number of previous ectopic pregnancies, site of ectopic pregnancy, menopause days, embryo implantation days, fertilization method, types of transferred

embryos and number of uterine cavity operation (Table 1). All the patients were transplanted with 2 embryos.

Among the 18 patients with conservative treatment, there were 10 case (55.6%) had no clinical symptoms before admission, only TVS found abnormalities, while among the 29 cases who treated by operation, 24 cases had clinical symptoms (bleeding, abdominal pain and bleeding with abdominal pain), 88.9% (16/18) cases TVS examination only found fallopian tube mass in conservative treatment, 51.7% (15/29) cases had positive findings including anechoic area, heart beat and yolk sac. There were significant differences between two groups. The median diagnosis time of conservative treatment was 30.5 days and operation treatment was 29 days after embryo implantation, there was no significant difference between the groups of location of HP, diagnosis time, mean haemoglobin count on admission, β -HCG level on admission and mass size by ultrasonography (Table 2).

The patients who met the operation indications were treated by operation, all the specimens were examined by pathology. Among the patients who underwent surgery, the last TVS examination before operation showed that 7 cases had extrauterine yolk sac, 7 cases had extrauterine heart beat, 2 cases had extrauterine anechoic area and 13 cases only had extrauterine adnexal mass. The median pelviche morrhage was 100ml and intervention time was 48 days. Mean blood loss was 17.31 ± 8.34 g/L and mass size was 3.78 ± 1.31 centimetres (cm) during the operation (Table 3).

Because there are few patients at 3, 8, 9 and 15 weeks of gestation, so we analysed the cases at 4, 5, 6 and 7 weeks of gestation. In order to determine the appropriate time of laparoscopic treatment, 24 cases were divided into birth and pregnancy loss group, analysis found that there were significant differences between two group (Table 4), and the cumulative survival rate was analyzed by Kaplan–Meier method (Figure 2).

Discussion

In recent years, due to the increasing pressure of people's life, increased exposure to electronic equipment radiation and other factors, infertility patients showed an obvious upward trend. The development of assisted reproductive technology has brought hope for infertility patients, so that infertility patients have the opportunity to conceive their next generation. Globally, in vitro fertilization and embryo transfer (IVF-ET) technology generally transfers 2 or more embryos at a time to improve the pregnancy rate, but it also increases the probability of multiple pregnancy and ectopic pregnancy [11]. There are many causes of ectopic pregnancy, including abortion history, pelvic inflammatory disease, intrauterine device, fallopian tube factors [12]. At present, it is recognized that the main cause of infertility and HP after assisted reproductive technology is fallopian tube dysfunction caused by fallopian tube lesions [13]. In this study, 45 cases of 47 patients were conceived by IVF due to tubal factors, 13 patients had a history of ectopic pregnancy and 32 patients had a history of intrauterine operation. Embryo transfer is to put the embryo directly into the uterine cavity with the transfer tube. The embryo entering the uterine cavity still needs to swim for about 3 days. It is completely embedded in the endometrium after three processes of

localization, adhesion and invasion, while some embryos swim into the fallopian tube. If some pathological changes of fallopian tube or pelvic cavity lead to abnormal peristaltic function of fallopian tube, such as damaged fallopian tube epithelium, narrow lumen, loss of cilia or hydrosalpinx, the embryo is easy to stay in the fallopian tube for implantation and development, resulting in tubal pregnancy.

In the natural physiological state, the embryo development is synchronized with the "implantation window" of the endometrium [14]. In IVF-ET, the time of embryo transfer into uterine cavity in cleavage stage was 2 to 3 days earlier than that in natural pregnancy. Three days later, the embryo can not be implanted in the uterine cavity immediately. Under the action of oviduct peristalsis, cilia swing and corpus luteum, most of the embryos will move back to the uterine cavity, but some of them can migrate outside the uterine cavity to produce ectopic pregnancy [15]. Previous studies have shown that the ectopic pregnancy rate in blastocyst transplantation cycle is lower than that in cleaved embryo transplantation cycle [16]. In this study, among the 47 patients with HP after embryo transfer, 18 were at the cleavage stage on the 3rd day, 6 were blastocysts on the 5th day, and 23 were frozen thawed embryos. In addition to the above reasons, the occurrence of ectopic pregnancy is also related to the volume of transfer fluid, injection pressure and the depth of embryo from uterine cavity during transfer [17].

When ectopic pregnancy occurs, β -HCG often does not double well, and progesterone level is generally 10-25ng/ml lower than intrauterine pregnancy. Transvaginal ultrasound is the main examination method, the choice of treatment method for ectopic pregnancy should be combined with HCG level and B-ultrasound results, Expectant treatment, MTX embryo killing treatment and surgical treatment can be adopted. However, due to the existence of intrauterine pregnancy, the HCG value of HP is similar to or higher than that of intrauterine pregnancy, and the level of progesterone is similar to intrauterine pregnancy. If intrauterine pregnancy is found by ultrasonography, it is easy to be missed if the ultrasonographic features of ectopic pregnancy are not typical. When HP occurs, the HCG level is often high, the embryo has a strong activity, and the risk of ectopic pregnancy rupture is significantly increased. If the ectopic pregnancy embryo is found too late, it will not only affect the outcome of intrauterine pregnancy, but also cause hemorrhagic shock due to the rupture of ectopic embryo, which will threaten the lives of patients. Therefore, for patients with assisted reproductive technology pregnancy, even if intrauterine pregnancy is found, we should carefully check the situation of ectopic embryos. Study has reported that the β -HCG level on day 14 (HCG_{14}) and day 21 (HCG_{21}) was higher than 290mIU/ml and 2790mIU/ml respectively, with the decrease of HCG_{21} / HCG_{14} ratio ranging from 10-15 [18].

Typical clinical symptoms of HP are similar to those of ectopic pregnancy, including abdominal pain, irregular vaginal bleeding, peritoneal irritation and uterine enlargement [19]. In this study, all patients were after embryo transfer, and they paid more attention to vaginal bleeding, abdominal pain and other clinical manifestations than patients with natural pregnancy. They all went to the hospital earlier for examination and treatment, and the diagnosis time was 19-104 days after embryo transfer. Immediate hCG and B-ultrasound examination made the signs of HP mild, in our research, there are 32 patients had clinical symptoms while 15 cases had no clinical symptoms. So TVS is an important basis for the diagnosis of HP [6]. Typical ultrasound findings of HP: gestational sac can be seen in the uterine cavity, and the echo

of gestational sac can be seen outside the uterine cavity, but some HP were missed because of the lack of typical ultrasound findings [5]. The ultrasonic manifestations of HP ectopic lesions can be divided into direct signs and indirect signs: the direct signs are the gestational sac, yolk sac, even germ and fetal heart with ectopic pregnancy; the indirect signs include mixed echo mass and abdominal pelvic effusion. The diversity of ultrasonic manifestations leads to the uncertainty of ultrasonic diagnosis [6,7]. Therefore, the diagnosis of HP should be combined with the patient's history, clinical manifestations and ultrasound findings. In particular, the first follow-up of B-ultrasound should pay attention to the presence of gestational sac like structure, mixed mass, abdominal and pelvic effusion. If the pregnant person has sudden abdominal pain, irritability and vaginal bleeding during pregnancy, it should be checked whether it is HP [20].

Patients with suspected HP should be hospitalized as soon as possible. In 47 cases of HP patients in our hospital, the median intervention time was 48 days. Intraoperative visual observed that gestational sac size was 3.78 ± 1.31 cm. Previous studies have found that the probability of have better pregnancy outcome the laparoscopic treatment is higher than that of conservative treatment patients in HP. Conservative treatment avoids the risks associated with surgery, however, conservative treatment of HP patients with ectopic pregnancy mass rupture rate of 20%. Therefore, For HP patients with high HCG and obvious clinical symptoms, laparoscopic surgery should be used as early as possible, and the best treatment time is before 6 weeks, but not before 4 weeks, too early surgical treatment can easily lead to abortion. For the postoperative patients, routine use of fetal drug. To extend the pregnancy week of intrauterine pregnancy as far as possible when the patient's vital signs are stable.

Conclusion

In summary, laparoscopic surgery should be performed as early as possible for HP patients with clinical symptoms and typical extrauterine manifestations, the best intervention time was before 6 weeks, but not less than 4 weeks. For HP patients with no obvious symptoms or atypical TVS examination, conservative treatment is feasible.

Abbreviations

HP: heterotopic pregnancy

ART: assisted reproductive technology

TVS: Transvaginal ultrasonography

β -HCG: β Human chorionic gonadotropin

MTX: Methotrexate

BMI: Body Mass Index

CO₂: carbon dioxide

cm: centimetres

IVF-ET: in vitro fertilization and embryo transfer

Declarations

Ethics approval and consent to participate

This study was performed according to the Declaration of Helsinki and approved by the institutional review boards of Shanghai First Maternity and Infant Hospital (KS20230), and we have obtained oral/written informed consent from each patient to participate the research.

Consent for publication

we have obtained consent to publish from each patient.

Availability of data and materials

The first author can provide the data analyzed during the current study on reasonable request.

Author information

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SX designed the study, HL collected the patients' information, QB performed statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Clinical characteristics for heterotopic pregnancy with different treatment			
Variable	Conservative treatment (n=18)	Operation treatment (n=29)	P-value
Age (years)	32.39±5.03	31.45±3.05	0.481
BMI (kg/m ²)	20.96±2.46	21.53±2.63	0.459
Previous ectopic pregnancies (n, %)			0.321
0	15	19	
≥1	3	10	
Site of ectopic pregnancy (n, %)			1.000
Tubal factor	17	28	
Male factor	1	1	
menopause days	52.72±10.92	52.79±17.41	0.988
Embryo implantation days	33.67±7.72	31.93±14.62	0.645
Fertilization method (n, %)			1.000
IVF	17	28	
ICSI	1	1	
Embryo (n, %)			0.964
Fresh	7	11	
Frozen	9	14	
blastocysts	2	4	
uterine cavity operation (n, %)			0.409
0	4	11	
1	6	10	
≥1	8	8	

BMI body mass index

Table 2 Diagnostic information

Variables	Conservative treatment (n=18)	Operation treatment (n=29)	P-value
Clinical manifestations before diagnosis (n, %)			0.006
Yes	8	24	
No	10	5	
Location of HP, n			0.561
Left tubal	8	14	
Right tubal	8	13	
Cornual	1	1	
Cervix	1	0	
Diagnosis time, days	30.5	29	0.721
Mean haemoglobin count (g/dL)	122.11±12.53	129	0.510
Ultrasound findings when admission			0.005
Anechoic area	2	5	
adnexal mass	16	14	
Heart beat	0	5	
Yolk sac	0	5	
β-HCG level when admission (mIU/ml)			0.617
<2000	0	1	
≥2000	18	28	
mass size by ultrasonography (mm)			0.242
<30	13	16	
≥30	5	13	

HP Heterotopic pregnancy

Table 3 Surgical information

Variables	Patient with HP treated by operation (n=29)
Extrauterine ultrasound findings when operation intervention	
Anechoic area	2 (6.90)
adnexal mass	13 (44.83)
Heart beat	7 (24.14)
Yolk sac	7 (24.14)
Pelvic hemorrhage, ml	100
Intervention time, days	48
Mean blood loss	17.31±8.34
mass size	3.78±1.31

Table 4 Intervention time and pregnancy outcome

Variables	Birth	Pregnancy loss	P-value
Gestational age at operation (weeks)			0.034
4	5	4	
5	6	1	
6	4	1	
7	0	3	

Figures

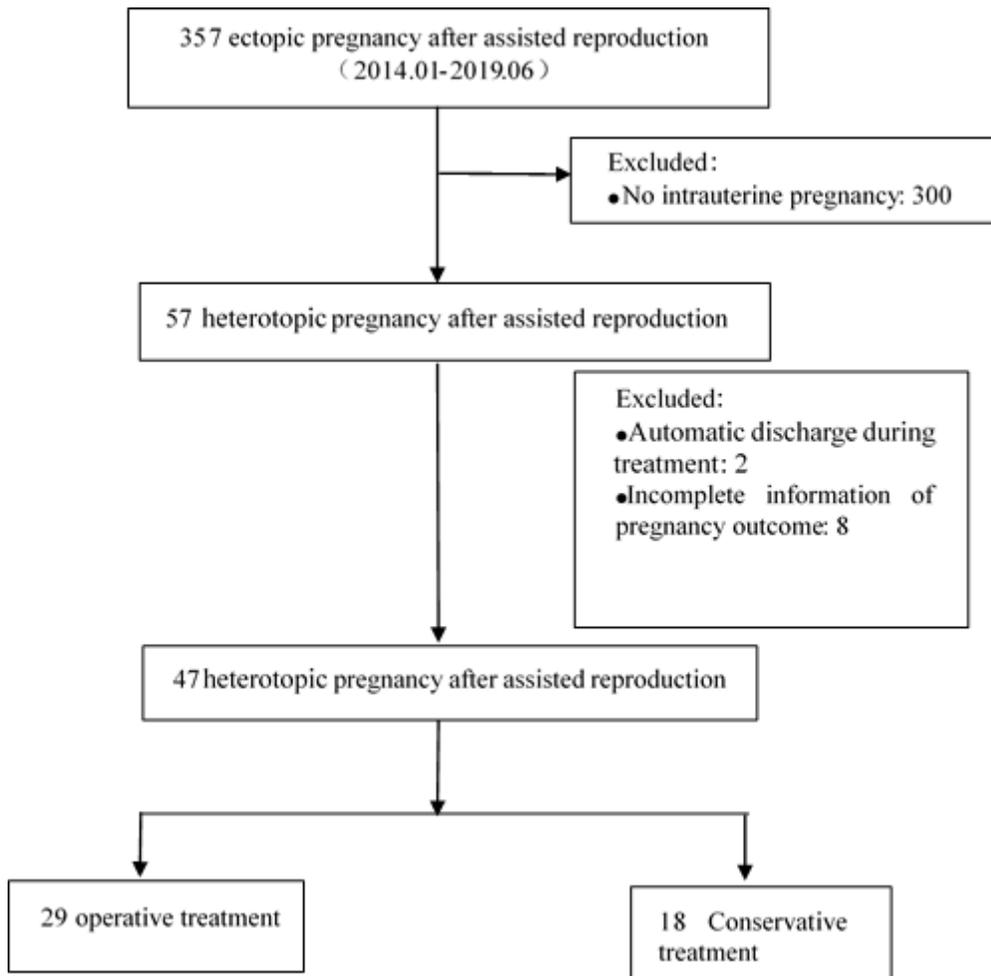


Figure 1

Flowchart of patients included in this study.

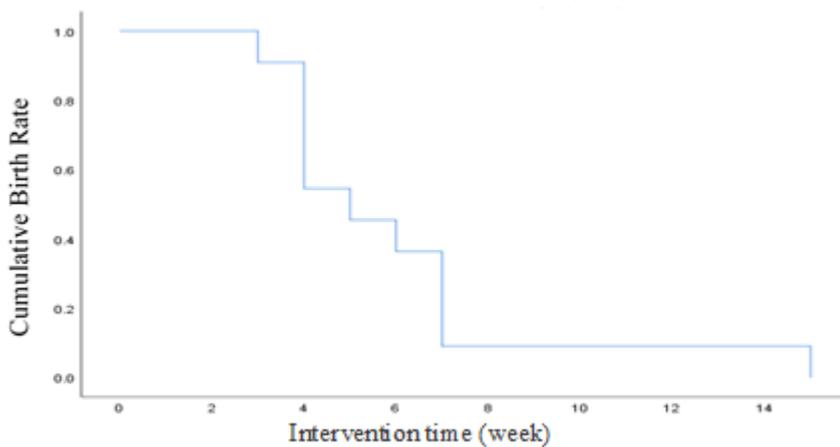


Figure 2

Cumulative delivery rate at different gestational weeks. Kaplan–Meier method analysis of HP patients undergoing laparoscopic surgery and successful delivery of live infants.