Treatment of tubal heterotopic pregnancy with viable intrauterine pregnancy: a retrospective study

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Abstract

Objective The aim of our study was to analyze surgical treatment and expectant treatment of tubal heterotopic pregnancy (HP) with viable intrauterine pregnancy (IUP). Study Design This was a retrospective analysis of 65 tubal HP with viable IUP patients. Patients were divided into surgical treatment group or expectant treatment group. Main outcome measures were abortion rate, rescue treatment rate, complication rate and ectopic pregnancy (EP) rupture rate. Results The abortion rate, rescue treatment rate and complication rate in the expectant treatment group were 8.69% (2/23), 30.43% (7/23) and 0.00%, compared to 16.67% (7/42), 0.00% and 2.38% (1/42), respectively, in the surgical treatment group. Five patients in the expectant treatment group suffered tubal EP rupture. Subgroup analysis of the expectant treatment group revealed that the rescue treatment rate in patients with an EP mass enlargement ≥50% was 80% (4/5), which was significantly higher than that in patients with an EP mass enlargement <50% (6.25%, 1/16, P =0.028). In the surgical treatment group, lower abortion rates were demonstrated in the laparotomy subgroup, salpingectomy subgroup and ≥49 days gestational age subgroup, with abortion rates of 0.00%, 12.12% (4/33) and 6.25% (1/16), respectively. Conclusions Both surgical and expectant treatments are optional treatment modalities for tubal HP with viable IUP. The abortion rate was low in the expectant treatment patients. EP mass enlargement ≥50% can be a predictor of rescue treatment in expectant treatment patients. Laparotomy surgery and salpingectomy would be more preferable in surgical treatment patients.

Introduction

Heterotopic pregnancy (HP) is the coexistence of intrauterine pregnancy (IUP) and ectopic pregnancy (EP), which is a rare type of pathological pregnancy [1, 2]. It is estimated that the incidence rate of HP in spontaneous pregnancies is approximately 1/30000 to 1/4000, while the risk increases to 1/100 in women who conceived via assisted reproductive technology (ART) [2]. The exact etiology of HP is still unknown. Many risk factors, including pelvic inflammatory disease, previous tubal surgery, ovarian stimulation, and ART, have been demonstrated to contribute to the occurrence of HP [3]. The ectopic gestational sac of HP can be located at the fallopian tube, uterine corner, cervix, cesarean section scar, or even abdomen; of these, tubal HP is the most common type [4].

An early and correct diagnosis of tubal HP is difficult. Symptoms of tubal HP include abdominal pain, vaginal bleeding or hypovolemic shock resulting from tubal EP rupture; however, some patients can be asymptomatic [5, 6]. Due to its nontypical clinical presentations, a diagnosis of tubal HP may be delayed, missed or misdiagnosed as threatened abortion [7, 8]. Serum beta-human chorionic gonadotropin (β-hCG) levels are of low value in the diagnosis of tubal HP because of the coexistence of viable IUP. Transvaginal (TVS) or transabdominal sonography plays a critical role in the diagnosis of tubal HP, and studies suggest that 76% to 92.4% of HP could be correctly diagnosed with early TVS [8–10].

According to the literature, treatment modalities of tubal HP with viable IUP include surgical removal of EP tissues, expectant management, medical treatment with local or systemic methotrexate and

sonographically-guided transvaginal aspiration of ectopic gestational embryos with or without embryo-killing drug treatment (embryo aspiration treatment) [5–7, 9–12]. Medical treatment with methotrexate should not be considered due to its indicated teratogenic effects on viable IUP [13]. Embryo aspiration treatment is not recommended since the risk of failure can reach 55%14]. Surgery and expectant management were first-line treatment modalities of HP patients with viable IUP in most publications [2, 6, 9, 15, 16]. However, due to the rarity of tubal HP, most publications regarding HP are case reports or retrospective studies of case series from single medical center, and consensus on the optimal treatment modality of tubal HP with viable IUP has not been reached.

Thus, the objective of this study was to analyze the surgical treatment and expectant treatment of tubal HP patients with viable IUP.

Materials And Methods

A total of 97 patients were diagnosed with HP in our center between January 2003 and June 2016, among them, 92 patients were tubal HP, 5 patients were IUP coexisted with uterine cornual pregnancy. All medical records were reviewed to exclude patients without viable IUP and patients who opted for embryo aspiration treatment; 65 patients were finally included in this study, as presented in the patient flow chart (Figure 1). The diagnostic criteria of tubal HP were based on TVS presentations, including the coexistence of an IUP and typical EP confirmed by sonography [8].

According to the primary treatment, patients were divided into a surgical treatment group (N = 42) and an expectant treatment (N = 23) group. All patients, excluding 2 patients who were in the state of haemorrhagic shock, were properly informed about their situations and the benefits and risks of each optional treatment modality, and final treatment was confirmed based on their clinical presentation, hemodynamic situation and personal preferences. Written informed consent was obtained from all individual participants included before treatment. The basal clinical characteristics of all patients are presented in Table 1.

In the surgical treatment group, emergency surgery was performed on patients with unstable hemodynamic situations or those for whom EP rupture was suspected; elective surgery was performed on patients with stable hemodynamic situations. In the expectant treatment group, patients underwent intensive observation for clinical presentations that could indicate the rupture of EP, and repeated TVS examinations were performed to monitor changes in the tubal EP mass. Once rapid enlargement of the EP mass or EP cardiac activity was indicated in repeated TVS examinations, rescue treatment was performed immediately.

The outcome measures for both groups were abortion rate, rescue treatment rate and complication rate. The EP rupture rate was also analyzed in the expectant treatment group. We performed subgroup analyses for both groups to identify potential risk factors for the measured outcomes.

A chi-squared test was used to compare rates, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 17.0.

This retrospective observational study was approved by the Clinical Research and Experimental Animal Ethics Committee of our hospital.

Results

The symptoms, hemodynamic situation, diameters of EP mass at diagnosis, fetal cardiac activity and gestational age at diagnosis of all patients are presented in Table 1. The incidence of tubal HP was 92/47502 per pregnancy in our hospital. All patients except 1 conceived via ART, 1 patient conceived via artificial insemination with husband's sperm, 63 patients conceived via in vitro fertilization and embryo transfer (IVF-ET). Among patients conceived via IVF-ET, 3 embryos were transferred in 9 patients, 2 embryos were transferred in 48 patients, numbers of embryo transferred was unknown in 6 patients. 32 patients had previous pelvic surgery, 16 patients had previous tubal EP, 33 patients had a history of abortion, and the average gravidity of all patients was 2.08±1.24.

The pregnancy and maternal outcomes in the expectant treatment group are presented in Table 2. Two patients experienced abortion during hospitalization, and the abortion rate was 8.69% (2/23). Seven patients were transferred for emergency surgery, and the rescue treatment rate was 30.43% (7/23). Among the patients who underwent rescue treatment, 1 patient presented EP cardiac activity, and 1 patient showed rapid enlargement of the EP mass in repeated TVS examinations. Five patients suffered EP rupture, and the EP rupture rate was 21.74% (5/23). In the subgroup analysis, we found that the rescue treatment rate and EP rupture rate in patients with an EP mass enlargement <50% were lower than those in patients with an EP mass enlargement ≥50%, with $P = 0.004$ and $P = 1.000$, respectively. A lower rescue treatment rate and EP rupture rate were also observed in patients with gestational age at diagnosis <49 days, with $P>0.05$. No complications were observed in this group.

In the surgical treatment group, 11 patients presented an unstable hemodynamic situation at diagnosis, 14 patients had an estimated blood loss ≥ 500 ml before surgery, and 7 patients needed blood transfusion. The pregnancy and maternal outcomes in the surgical treatment group are presented in Table 3. Seven patients suffered abortion postoperation, and the abortion rate was 16.67% (7/42). No patients needed rescue treatment. One patient suffered urinary retention postoperation, and the complication rate was 2.38% (1/42). Seven patients needed blood transfusion due to hemorrhagic shock. In the subgroup analysis, the average operation time for the salpingotomy subgroup and salpingectomy subgroup was 56.39 ± 24.28 min and 77.50 ± 30.35 min, respectively, with $P<0.05$. The abortion rate for the <49 days gestational age at diagnosis subgroup was higher than that in the ≥49 days subgroup (23.08% versus 6.25%). No statistical differences were observed for estimated blood loss, surgical type, timing of surgery, gestational age, resection of fallopian tube, operation time and abortion rate in the subgroup analyses.

Discussion

Treatment of tubal HP with viable IUP is difficult and challenging. First, tubal EP is a gynecological emergency that may cause severe maternal morbidity and occasional mortality if the treatment is delayed or inappropriate. Second, the coexisting viable IUP may be at high risk of abortion if inappropriate treatment is administered. In our study, most tubal HP patients conceived via ART, similar to previous studies [4–6, 8, 10, 15, 16]. Considering that ART patients have a strong desire to preserve the viable IUP, we should evaluate the influences of every treatment modality and find a balance between risk to the patient and preservation of the viable IUP when deciding treatment therapies.

Surgery is a first-line treatment option for tubal HP patients; surgery can be the primary treatment or a rescue treatment complementary to the failure of other treatment modalities [6, 9, 16, 17]. Indications of surgical treatment of tubal HP include 1. hemodynamic instability or indicated rupture of the EP mass, 2. active EP fetal cardiac activity, 3. clinical presentations or TVS examinations indicating EP mass rupture, 4. failure of other treatment modalities, and 5. patient preferences. Although the risk of adverse pregnancy outcomes associated with surgery during pregnancy was low, data from several large-scale retrospective observational studies found that the risk of abortion was higher in patients with nonobstetric abdominal surgery during pregnancy [18–20]. In our study, the abortion rate in the surgical treatment group (7/42, 16.67%) was higher than that in the expectant treatment group (2/28, 7.14%), similar to the above studies. These results indicate that surgical treatment of tubal HP may lead to a higher risk of abortion.

When surgery is necessary, either laparotomy or laparoscopy can be considered. Compared to laparotomy, laparoscopy has the advantages of being minimally invasive with a rapid recovery time, a short operation time and little blood loss [21]. However, in our study, the abortion rate in patients who underwent laparoscopic surgery was higher than that in those who received a laparotomy (25.93% versus 0.00%). The same result was observed in another study, with an abortion rate of 33.33% (2/6) in patients who underwent laparoscopic surgery and 7.14% (1/14) in patients who received a laparotomy [10]. Two additional large-scale studies also found that patients who underwent laparoscopic surgery during pregnancy had a higher abortion rate than those who received a laparotomy [19, 20]. Thus, we think that laparotomy surgery would be more appropriate in tubal HP patients who want to preserve the viable IUP.

In our subgroup analysis, the abortion rate in the salpingectomy subgroup was lower than that in the salpingotomy subgroup (11.12% versus 33.33%); these results have not been reported in previous studies. We speculate that the reasons were the shorter operation time and the easier surgical procedure in the salpingectomy subgroup than those in the salpingotomy subgroup. One study showed that tubal EP patients who selected salpingotomy had a risk of persistent trophoblasts, and up to 20% of patients were transferred to salpingectomy because of persistent tubal bleeding during surgery [22]. Therefore, we suggest that salpingectomy is more appropriate for tubal HP patients with viable IUP. A reduced abortion rate was also observed in the ≥49 days gestational age group, indicating that the surgical procedure should be performed after the first 49 days if the patient is stable. Additionally, a decreased abortion rate

was also observed in patients with an estimated blood loss >500 ml who received elective surgery. The potential reasons for this result are unknown, and more studies are needed.

Expectant management is another treatment option for certain tubal HP patients with viable IUP [1, 23]. The indications of expectant treatment are as follows: 1. patients are hemodynamically stable, and patients have no signs of EP rupture, 2. EP cardiac activity is negative upon TVS examination, 3. patients are aware of the risks of failure and EP rupture, and 4. emergency surgery can be performed immediately upon suspicion of EP rupture. It was reported that the success rate of expectant management was 50–88% in selected tubal EP patients [1, 23, 24]. Successful expectant management of tubal HP has been previously reported [6, 17, 25]; however, failures of expectant management of HP patients with viable IUP have also been reported by many researchers [6, 8, 23]. In our study, the success rate of expectant management was 63.57%; up to 30.43% (7/23) of patients needed rescue management, and 21.74% (5/23) of patients suffered EP mass rupture. These results indicate the possibility of failure in the expectant management of tubal HP. Thus, patients who opt for expectant management should receive intensive clinical observation, and a timely rescue treatment should be performed if there are any indications of EP rupture. A relatively low abortion rate (8.69%, 2/23) was observed in our study; we speculate that the reason for the low rate was that expectant management avoided the potential harmful risk factors associated with surgery.

Previous studies demonstrated that the initial serum β-hCG level was a predictor of positive outcomes in tubal EP patients who opted for expectant management [23, 24, 26], and a serum β-hCG level < 1500 IU/L was always representative of tubal miscarriage [23]. However, due to the coexistence of a viable IUP in tubal HP patients, serum β-hCG levels were of low predictive value for the expectant treatment group. According to one review, there is no consensus regarding the acceptable diameter of an EP mass determined by TVS at diagnosis that is suitable for determining expectant management in tubal EP patients [21]]. In our subgroup analysis, we demonstrated that the rescue treatment rate and EP rupture rate were comparable among different EP mass diameters, indicating that the size of EP mass was not a contraindication of expectant management for tubal HP patients. Further, in our subgroup analysis, we found that the rescue treatment rate was associated with the enlargement of the EP mass; up to 57.14% of patients needed rescue treatment in tubal HP patients who presented EP mass enlargement ≥50% in repeated TVS examinations. This indicated that EP mass enlargement ≥50% can be a predictor of rescue treatment in expectant management patients.

Although our study showed a relatively low abortion rate in expectant treatment patients, it was not comparable between the surgical treatment group and the expectant treatment group due to their different basic clinical characteristics. Treatment of tubal HP with viable IUP should be individualized based on the hemodynamic situation, EP fetal cardiac activity and patient preference. Tubal HP patients with viable IUP should be informed of the benefits and risks of those two treatment modalities. More prospective clinical studies are needed.

Conclusion

Both surgical and expectant treatments are optional treatment modalities for tubal HP with viable IUP. The abortion rate was low in the expectant treatment patients. EP mass enlargement ≥50% can be a predictor of rescue treatment in expectant treatment patients. Laparotomy surgery and salpingectomy would be more preferable in surgical treatment patients.

Declarations

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Tables

Table 1 Basal clinical characteristic of all tubal HP patients

Characteristic	All patents	Expectant treatment group (N=23)	Surgical treatment group (N=42)
Age (years)	30.91±3.27	30.05±2.43	31.65±3.14
Risk factors			
Previous pelvic surgery	32	9	23
History of abortion	33	14	19
Previous tubal EP	16	6	10
Symptoms			
Asymptomatic	12	3	9
Vaginal bleeding	6	4	2
abdominal pain	28	9	19
Vaginal bleeding and abdominal pain	19	7	12
Hemodynamic situation at diagnosis			
Stable	54	23	31
Instable	11	0	11
Diameters of EP mass at diagnosis[a]			
<30mm	21	9	12
31-40mm	12	5	7
>40mm	25	9	16
Fetal cardiac activity [b]			
Yes	10	0	10
No	55	23	30
Gestational age at diagnosis (days)			
<49	34	8	26
≥49	31	15	16

[a] Diameters of EP mass at diagnosis were unknown in 7 patients in Surgical treatment group. [b] Fetal cardiac activity of EP in Surgical treatment group was unknown in 2 patients. EP: ectopic pregnancy

Table 2 Maternal and pregnancy outcomes in expectant treatment group

	Cases	Rescue treatment rate		Rupture of EP rate,		Abortion rate	
	NO.	N (%)	*P* value	N (%)	*P* value	N (%)	*P* value
Diameter of EP mass at diagnosis(mm)							
<30	9	3(33.33%)	0.538	3(21.43%)	-	0	-
30-40	5	2(40.00%)		0		0	
≥40	9	2(22.22%)		2(22.22%)		2(22.22%)	
Gestational age at diagnosis (days)							
<49	8	2(25.00%)	1.000	1(12.50%)	1.000	1(12.50%)	1.000
≥49	15	5(33.330%)		4(26.67%)		1(6.67%)	
EP mass enlargement [a]							
<50%	16	1(6.25%)	**0.004**	2(12.50%)	1.000	2(12.50%)	-
≥50%	5	4(80.00%)		1(20.00%)		0	

Table 3 Maternal and pregnancy outcomes in surgical treatment group

	Case No.	pregnancy outcome		Maternal outcome	
		Abortion, N (%)	*P* value	Complication, N (%)	*P* value
Estimated blood loss before surgery					
≥500ml	14	2 (14.29%)	1.000	0 (0.00%)	-
<500ml	28	5 (17.86%)		1 (3.57%)	
hemodynamic situation					
Stable	31	5 (16.13%)	1.000	1 (3.22%)	-
Instable	11	2 (18.18%)		0 (0.00%)	
Timing of surgery					
Emergency surgery	18	2 (11.11%)	0.679	0 (0.00%)	-
Elective surgery	24	5 (20.83%)		1 (7.14%)	
Surgical type					
laparoscopy	27	7 (25.93%)	-	1 (3.70%)	-
Laparotomy	15	0 (0.00%)		0 (0.00%)	
Fallopian tube					
salpingotomy	9	3 (33.33%)	0.155	0 (0.00%)	-
salpingectomy	33	4 (12.12%)		1 (3.03%)	
Gestational age (days)					
<49	26	6 (23.08%)	0.222	1 (11.11%)	-
≥49	16	1 (6.25%)		0 (0.00%)	

Figures

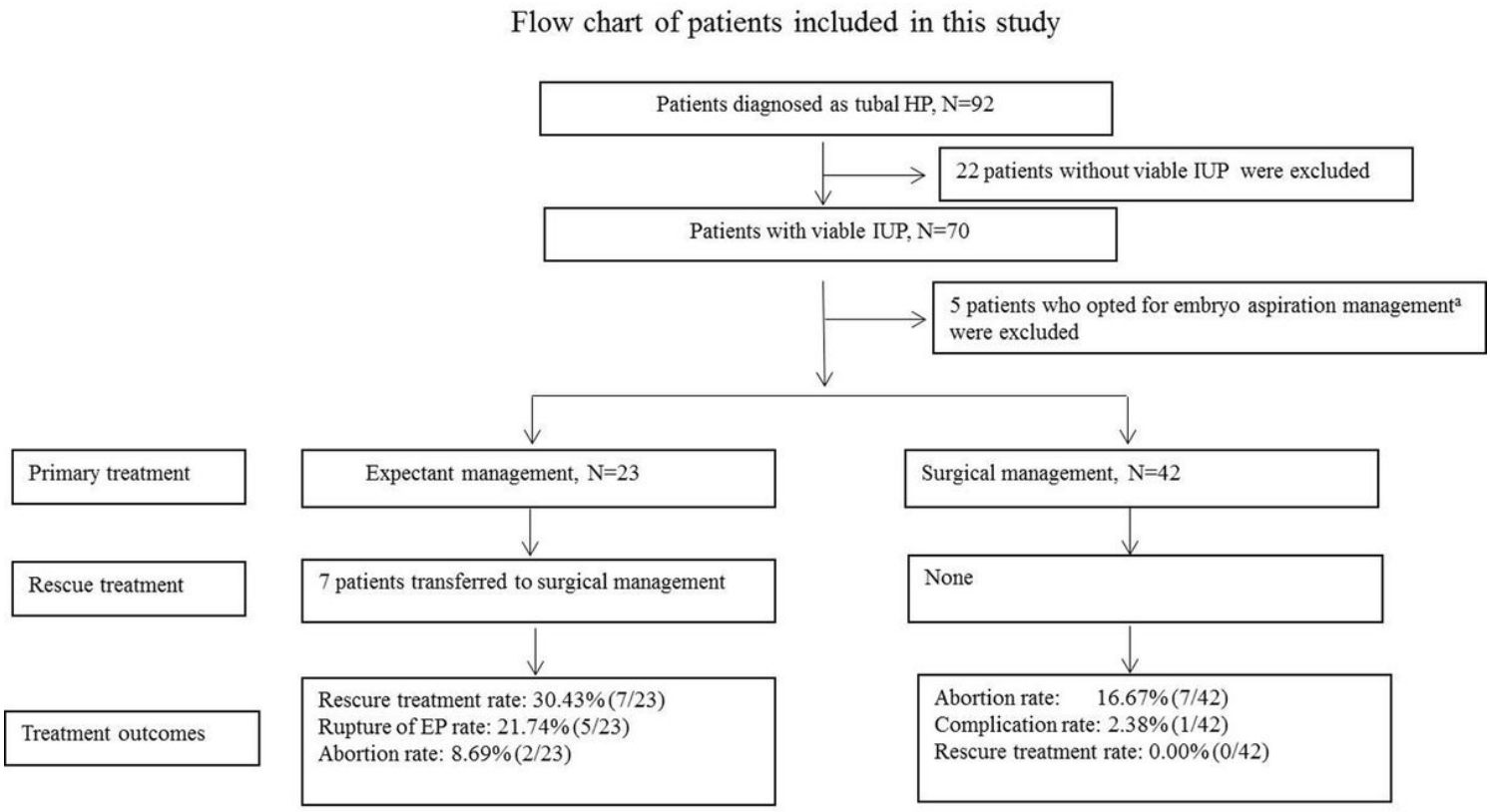

Figure 1

Figure 1: Flow chart of patients included in this study. a Embryo aspiration: Transabdominal sonographic guided transvaginal aspiration of ectopic gestational embryo with or without embryo-killing drugs. HP: Heterotopic pregnancy. IUP: Intrauterine pregnancy. EP: Ectopic pregnancy.