

Management of Heterotopic Pregnancy

Experience From 1 Tertiary Medical Center

Jin-Bo Li, MD, Ling-Zhi Kong, MD, Jian-Bo Yang, MD, Gang Niu, MD, Li Fan, MD, Jing-Zhi Huang, MD, and Shu-Qin Chen, MD, PhD

Abstract: The objective of this study is to summarize the experiences of our department in the management of heterotopic pregnancy (HP) and to analyze the influence of different treatment modality on the viable intrauterine pregnancy.

There were 64 patients diagnosed as HP in the Department of Gynecology and Obstetrics in our hospital between January 2003 and June 2014, 52 HP patients with viable intrauterine pregnancy were included and analyzed in our study. Interventions included expectant management, surgical management and transabdominal sonographic guided transvaginal aspiration of ectopic gestational embryo (embryo aspiration) management.

Main outcome measures are maternal outcome and pregnancy outcome.

In expectant management group, 4 patients suffered rupture of ectopic pregnancy, 6 patients transferred to surgical management, 1 patient suffered a fever of 40.4°C, the abortion rate was 5% (1/20). In surgical management group, emergency surgery was performed in 9 patients with unstable hemodynamics and 3 patients with stable hemodynamics, 1 patient suffered uterine rupture 5 weeks later and dead fetus was demonstrated, 1 patient suffered urinary retention postoperative, the abortion rate was 14.8% (4/27). In embryo aspiration management group, 1 patient needed another embryo aspiration, all patients were eventful and no abortion was observed.

In our retrospective study, transabdominal sonographic guided aspiration of ectopic gestational embryo has the best maternal outcome and the lowest abortion rate, surgical management group shows the highest abortion rate, and expectant management presents the worst maternal outcome.

(*Medicine* 95(5):e2570)

Abbreviations: ART = assisted reproductive technology, Embryo aspiration = transabdominal sonographic guided transvaginal aspiration of ectopic gestational embryo, EP = ectopic pregnancy, HP = heterotopic pregnancy, IUP = intrauterine pregnancy, MTX = methotrexate.

Editor: Liang Hong.

Received: July 1, 2015; revised: November 25, 2015; accepted: December 25, 2015.

From the Department of Gynecology and Obstetrics, The First Affiliated Hospital of Sun Yat-Sen University, Guangdong, Guangzhou, P.R. China. Correspondence: Shu-Qin Chen, Department of Gynecology and Obstetrics, The First Affiliated Hospital of Sun Yat-Sen University, 58# Zhong Shan Road II, Guangzhou 510080, P.R. China (e-mail: chenshuqin1021@163.com).

J-BL and L-ZK contributed to this work equally.

This retrospective study is approved by the Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-Sen University.

The authors have no funding and conflicts of interest to disclose.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial License, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000002570

INTRODUCTION

Heterotopic pregnancy (HP) refers to the simultaneous presence of intrauterine pregnancy (IUP) and ectopic pregnancy (EP), which is very rare but a potentially life-threatening condition.¹ HP can be spontaneous or the subsequence of assisted reproductive technology (ART), the spontaneous incidence of HP in general population is thought to be about 1 in 30,000,² but with the widespread of ART, the incidence of HP in woman with ART raises to about 0.09% to 1.00%.^{3–6}

The actual etiology of HP is still unknown, many researches have demonstrated that pelvic inflammatory disease, previous tubal surgery, ovarian stimulation, and ART are high risk factors of HP; however, some HP patients can be totally absent of these risk factors.^{2,7} The ectopic gestational sac of HP can be located at fallopian tube, uterus corner, uterus cervix, previous cesarean scar, or even abdomen.^{7–10}

Clinical presentations of HP are atypical, common presentations include vaginal bleeding, acute abdominal pain, and hypovolemic shock, while 1 report points out that about 50% HP patients can be totally asymptomatic.^{1,2,5,7,11} Human beta chorionic gonadotropin is unimportant in the establishment of HP due to the co-existence of the IUP. Transvaginal sonographic examination plays an important role in the diagnosis of HP, which presents as an IUP co-existed with a separated adnexal mass, gestational sac, or ring sign.^{6,12} However, even transvaginal sonographic examination has performed, the EP may also be missed or misdiagnosed as hemorrhagic corpus luteum cyst.^{2,6,12,13} In fact, it is estimated that about 58.93% to 73.75% cases of HP are not confirmed before surgery.^{1,14} So, it is a consensus that an early and accurate diagnosis of HP is often difficult.

Management of HP is still controversial.^{1,9,15} According to literatures, treatment modalities of HP include expectant management, surgical management, and sonographic guided embryo aspiration with or without embryo-killing drugs.^{1,7,9,15–17} However, due to the rarity of HP, most publications about HP are case report or small case series, treatment experiences are limited, so there is no consensus on the preferred treatment modality of HP.

The objective of this retrospective study is to summarize the experiences of our department in the management of HP and to analyze the influence of different treatment modality on the viable IUP.

MATERIALS AND METHODS

There were 64 patients diagnosed as HP in the Department of Gynecology and Obstetrics in our hospital between January 2003 and June 2014. The diagnostic criteria of HP were: in expectant management patients, HP was diagnosed mainly on the presence of an IUP and typical EP sonographic characteristics; in other patients, HP was diagnosed based on the intraoperative findings and histological examination of suspected EP

tissues. All medical records and sonographic pictures are collected and reviewed carefully to exclude the misdiagnosis. Since 1 objective of our study is to retrospectively analyze the influence of different treatment modality on the viable IUP, 12 patients without viable IUP before treatment are excluded, thus 52 patients are finally included in our study.

Patients are divided into 3 groups according to the treatment modality they received, those are expectant management group, surgical management group, and transabdominal sonographic guided transvaginal aspiration of ectopic gestational embryo (embryo aspiration) management group. All patients except those unconscious were well informed about their situation and the potential advantages and disadvantages of each treatment modality, the final treatment modality was confirmed based on the presentations, hemodynamic situation, and patients' choice. Basic demographics, such as pregnancy history, conception mode, gestational age, clinical presentations, location, sonographic characteristic, and hemodynamics situation, of all patients are presented in Tables 1–3.

In expectant management group, patients were under strict observation on any signs of the rupture of EP, such as the progression of abdominal pain and unstable hemodynamic presentations. Transvaginal sonographic re-examinations were performed weekly to monitor the changes of EP mass and clues of hemoperitoneum. When the rupture of EP was suspected, rapid enlargement of EP mass was demonstrated or cardiac activity was presented, surgery was performed immediately to have good maternal results.

In surgical management group, emergency surgery, either laparotomy or laparoscopy, was performed to those patients with unstable hemodynamic situations and to those rupture of EP were suspected. To those patients with stable hemodynamic situations, selective surgery was performed. Antibiotic was applied preoperatively and postoperative for 2 days to avoid infection.

In embryo aspiration management group, patients received transvaginal sonographic re-examinations postoperative weekly to monitor the changes of EP mass and clues of hemoperitoneum. If enlargement of EP mass was demonstrated, another embryo aspiration or surgery would be performed. And if there was any sign of rupture, surgery was needed to rescue patient's life.

The luteal support strategy of all patients was determined by ART experts.

The endpoint of follow-up was the termination of this pregnancy. Maternal outcome and pregnancy outcome were main therapeutic measurements. Other therapeutic measurements included the transfer to other treatment modality, operation time, blood transfusion, and complications.

This retrospective study was approved by the Medical Ethics Committee of our hospital, all patients and (or) their husbands were well informed about their situation, and written informed consents were received before treatment.

RESULTS

Maternal outcome and pregnancy outcome of patients in expectant management group were showed in Table 1. Four patients suffered rupture of EP during hospitalization, the rupture rate was 20% (4/20). Among them, 3 patients suffered tubal rupture and another patient suffered uterine corner rupture, emergency surgery was performed timely in these 4 patients. One patient showed cardiac activities of the EP and another patient showed gradual enlargement of ectopic

gestational sac during weekly sonographic re-examinations, surgery was performed in both patients. One patient suffered a fever of 40.4°C, she was uneventful after the application of antibiotic for 3 days. One patient ended up with abortion during observation 1 week later, the total abortion rate was 5% (1/20) during observation. Three patients, with ongoing living IUP before check out, lost follow-up because of the change of contact information.

Maternal outcome, pregnancy outcome, and operative data in surgical management group were presented in Table 2. Emergency surgery was performed in 9 patients with unstable hemodynamics; among them, 6 patients needed blood transfusion, 2 patients suffered abortion during follow-up; the abortion rate in patients with unstable hemodynamics was 22.22% (2/9). Three patients with stable hemodynamics received emergency surgery because of the rupture of EP. Two patients with stable hemodynamics suffered abortion postoperative, the abortion rate was 11.11% (2/18). Total abortion rate in surgical management group was 14.8% (4/27) during observation. One patient suffered uterine rupture 5 weeks later after corner resection, dead fetus was demonstrated in the following surgery. One patient suffered a complication of urinary retention. Two patients lost follow-up with viable IUP because of the change of contact information.

Maternal outcome and pregnancy outcome of patients in embryo aspiration management group were showed in Table 3. One patient showed obvious enlargement of the ectopic gestational sac by weekly sonographic re-examination 1 week later, another procedure was performed to avoid the rupture of ectopic gestational sac. The other 4 patients were all eventful. No abortion was observed in this group.

DISCUSSION

An early and accurate diagnosis of HP is often difficult and challenging due to the rarity of HP, the delay or failure of diagnosis may lead to potential life-threatening conditions such as the rupture of EP, hypovolemic shock or even loss of life,^{1,6} so the early and accurate diagnosis of HP is extremely critical. Though the sensitivity of transvaginal sonographic examination, ranged from 26.3% to 92.4%, in the definitive diagnosis of HP is still debatable,^{1,6} a routine transvaginal sonographic examination at 4 to 6 weeks after ART to exclude EP and HP is recommended.^{7,15,18} So, an early transvaginal sonographic examination is recommended in early pregnancy, especially those patients conceived via ART or those with other risk factors.

Unlike those patients with EP only, most HP patients are conceived via ART and have a strong desire to preserve the viable IUP, so the key point of treatment is to preserve the viable IUP and to resolve the EP, this makes the treatment of HP difficult and challenging.^{1,18}

To those patients with stable hemodynamic situation and asymptomatic, expectant management could be considered.^{6,10,15,16} The main advantage of expectant management is that it avoids all potential complications related to the surgery and transabdominal sonographic guided transvaginal aspiration of ectopic gestational embryo.^{6,10} Nevertheless, expectant management should not be considered in patients with viable EP or unstable hemodynamic situation.¹⁰ As the risks of continued growth and rupture of EP still exist, failures of expectant management have been reported.⁶ In our research, 20% patients in expectant management group suffered rupture of EP eventually, 1 patient presented cardiac activities of EP and another

TABLE 1. Characteristics of Patients Treated With Expectant Management

Patient No.	Gravity, Parity, Abortion, and Ectopic Pregnancy	Mode of Conception	Gestational Age at Diagnosis, d	Clinical Presentations	Location of Ectopic Pregnancy	Fetal Heart		Diameters of Gestational Mass, mm	Treatment of the Ectopic Pregnancy	Maternal Outcome	Secondary Treatment	Pregnancy Outcome
						Beats of Ectopic Pregnancy	Beats of Ectopic Pregnancy					
1*	G1P0A0	IVF-ET	50	Abdominal pain	Right tube	-	-	57	Expectant	Tubal rupture with hemoperitoneum up to 800 mL	Emergency laparotomy and salpingectomy	Term delivery, CS
2*	G1P0A0	IVF-ET	53	Abdominal pain and vaginal bleeding	Right tube	-	-	53	Expectant	Tubal rupture	Emergency laparotomy and salpingectomy	Lost follow-up, live fetus with normal NT 1 wk later
3	G3P0A1E1	IVF-ET	39	Abdominal pain and vaginal bleeding	Right tube	-	-	22	Expectant	Tubal rupture	Emergency laparoscopy and salpingostomy	Term delivery, CS
4	G4P0A2E1	IVF-ET	47	Asymptomatic	Right corner	-	-	15	Expectant	Right corner rupture and shock, hemoperitoneum up to 1200 mL	Emergency laparotomy and right corner incision, 350 mL CRBC was transfused	Term delivery, CS
5	G3P0A2	IVF-ET	46	Vaginal bleeding	Left tube	-	-	32	Expectant	Gradual enlargement of ectopic gestational sac	Laparoscopy and salpingostomy	Lost follow-up, live twin pregnancy 3 wk postoperative by ultrasound
6	G3P0A2	IVF-ET	54	Abdominal pain and vaginal bleeding	Right tube	-	-	37	Expectant	Transvaginal sonography showed heart beats of ectopic pregnancy 1 wk later	Laparoscopy and salpingostomy	Preterm delivery, CS (twin pregnancy)
7 ^{bc}	G3P1A1	IVF-ET	50	Vaginal bleeding	Right tube	-	-	62	Expectant	Fever of 40.4°C	Antibacterial treatment	Term delivery
8	G2P0A0E1	IVF-ET	38	Abdominal pain and vaginal bleeding	Left tube	-	-	22	Expectant	Uneventful	None	Term delivery, CS (macrosomia)
9*	G1A0P0	IVF-ET	54	Vaginal bleeding	Right tube	-	-	41	Expectant	Uneventful	None	Term delivery, CS (breech presentation)
10	G1P0A0	Spontaneous pregnancy	37	Abdominal pain	Left tube	-	-	31	Expectant	Uneventful	None	Term delivery, CS (severe preeclampsia)
11	G1P0A0	AIH	50	Asymptomatic	Right tube	-	-	28	Expectant	Uneventful	None	Term delivery, CS (twin pregnancy)
12c	G2P1A0	IVF-ET	68	Abdominal pain and vaginal bleeding	Right tube	-	-	33	Expectant	Uneventful during hospital	None	Lost follow-up, live fetus by ultrasound 5 wk later
13 ^c	G1P0A0	IVF-ET	63	Abdominal pain	Right tube	-	-	29	Expectant	Uneventful	None	Term delivery
14 ^{cd}	G1P0A0	IVF-ET	44	Abdominal pain	Right tube	-	-	50	Expectant	Uneventful	None	Term delivery, CS (suspected fetal distress)
15 ^{cde}	G1P0A0	IVF-ET	49	Asymptomatic	Right tube	-	-	30	Expectant	Uneventful	None	Term delivery, CS
16*	G1P1A0	IVF-ET	77	Abdominal pain and vaginal bleeding	Right tube	-	-	50	Expectant	Uneventful	None	Term delivery, CS
17*	G1P0A0	IVF-ET	50	Abdominal pain	Left tube	-	-	53	Expectant	Uneventful	None	Abortion
18	G1P0A0	IVF-ET	46	Abdominal pain	Left tube	-	-	18	Expectant	Uneventful	None	Term delivery, CS
19c	G1P0A0	IVF-ET	51	Abdominal pain	Left tube	-	-	20	Expectant	Uneventful	None	Term delivery, CS
20	G2P0A0E1	IVF-ET	56	Abdominal pain	Left tube	-	-	26	Expectant	Uneventful	None	Term delivery, CS

AIH = artificial insemination by husband, CRBC = concentrated red blood cells, CS = cesarean section, IVF-ET = in vitro fertilization and embryo transfer, NT = nuchal translucency thickness. * Patient refused to surgical management; b = misdiagnosed as threatened abortion, c = those patients were concomitant with ovarian hyper-stimulation syndrome, d = culdocentesis was done in those patients to exclude the rupture of ectopic pregnancy, e = this patient was hospitalized for severe ovarian hyper-stimulation syndrome, typical sonography characteristics of ectopic pregnancy were showed during regular ultrasound examination.

TABLE 2. Characteristics of Patients Treated With Surgical Management

Case No.	Gravidy, Parity, Abortion, and Ectopic Pregnancy	Mode of Conception	Gestational Age at Diagnosis, d	Clinical Presentations	Location of Ectopic Pregnancy	Fetal Heart Beats of Ectopic Pregnancy	Diameters of Gestational Hemodynamics	Situation	Treatment of the Ectopic Pregnancy	Blood Loss, mL	Operation Time, min	Blood Transfusion	Maternal Outcome	Pregnancy Outcome
1*	G1P0A0	IVF-ET	43	Abdominal pain	Right tube	Unknown	Unknown	Unstable	Emergency laparotomy and salpingectomy	50, 500 mL hemoperitoneum	73	850 mL CRBC and 600 mL plasma	Uneventful	Term delivery, CS
2	G2P0A0E1	IVF-ET	35	Abdominal pain	Left tube	-	Undescribed	Unstable	Emergency laparotomy and salpingectomy	50, 800 mL hemoperitoneum	65	200 mL CRBC and 200 mL plasma	Uneventful	Term delivery
3	G3P0A1E1	IVF-ET	40	Abdominal pain and shock	Right tube	-	27	Unstable	Emergency laparotomy and salpingectomy	50, 1500 mL hemoperitoneum	95	None	Uneventful	Term delivery, CS
4 [†]	G1P0A0	IVF-ET	46	Vaginal bleeding and shock	Right tube	-	Undescribed	Unstable	Emergency laparotomy and salpingectomy	No estimate, 2000 mL hemoperitoneum	90	1400 mL CRBC and 400 mL plasma	Uneventful during hospital	Lost follow-up with live intrauterine pregnancy
5	G1P0A0	IVF-ET	46	Vaginal bleeding and abdominal pain	Right tube	-	80	Unstable	Emergency laparotomy and salpingectomy	30, 500 mL hemoperitoneum	50	None	Uneventful	Term delivery, CS (suspected fetus distress)
6	G0P0A0	IVF-ET	52	Abdominal pain and shock	Left tube	-	Undescribed	Unstable	Emergency laparoscopy and salpingectomy	No estimate, 1200 mL hemoperitoneum	40	1600 mL CRBC	Uneventful	Abortion
7	G2P0A1	IVF-ET	35	Shock	Left tube	-	54	Unstable	Emergency laparoscopy and salpingectomy	50, 1500 mL hemoperitoneum	80	900 mL whole blood	Uneventful	Term delivery
8*	G3P0A2	IVF-ET	58	Shock	Right tube	Unknown	Unknown	Unstable	Emergency laparotomy and salpingectomy	50, 1750 mL hemoperitoneum	90	800 mL CRBC and 650 mL plasma	Uneventful	Term delivery, CS
9 [†]	G1P0A0	IVF-ET	37	Vaginal bleeding and abdominal pain	Left tube	-	25	Unstable	Emergency laparoscopy and salpingectomy	50, 800 mL hemoperitoneum	50	None	Uneventful	Abortion
10	G1P0A0	IVF-ET	59	Vaginal bleeding and abdominal pain	Right tube	+	63	Stable	Laparotomy and salpingectomy	50, 50 mL hemoperitoneum	40	None	Uneventful during hospital	Lost follow-up, live fetus with normal NT
11	G2P0A0E1	IVF-ET	91	Asymptomatic	Left uterus corner	+	71	Stable	Emergency laparotomy and uterus corner resection	800	145	None	None	Uterine rupture 5 wk later
12	G3P0A0E2	IVF-ET	42	Asymptomatic	Right uterus corner	+	31	Stable	Lap	50	25	None	Uneventful	Term delivery
13	G4P0A1E2	IVF-ET	52	Asymptomatic	Right uterus corner	+	19	Stable	Laparoscopy and uterus corner resection	30	25	None	Uneventful	Term delivery, CS
14	G1P0A0	IVF-ET	47	Vaginal bleeding and abdominal pain	Left tube	+	Undescribed	Stable	Laparotomy and salpingectomy	30	35	None	Uneventful	Term delivery, CS
15	G3P0A2	IVF-ET	53	Asymptomatic	Left tube	+	17	Stable	Laparotomy and salpingectomy	100	55	None	Uneventful	Term delivery, CS
16	G3P0A1E1	IVF-ET	41	Asymptomatic	Right tube	-	29	Stable	Laparotomy and salpingectomy	50	60	None	Uneventful	Term delivery, CS
17	G1P0A0	IVF-ET	37	Abdominal pain	Left tube	-	59	Stable	Emergency laparotomy, left salpingectomy, and right tubal ligation	100, 500 mL hemoperitoneum	110	None	Uneventful	Term delivery, CS
18	G5P1A1E2	IVF-ET	51	Asymptomatic	Right tube	-	46	Stable	Laparoscopy and salpingectomy	20, 50 mL hemoperitoneum	40	None	Uneventful	Term delivery, CS
19	G1A0P0	IVF-ET	48	Abdominal pain	Right tube	-	67	Stable	Emergency laparotomy and salpingectomy	20, 150 mL hemoperitoneum	70	None	Uneventful	Term delivery, CS
20 [†]	G2P0A1	IVF-ET	46	Abdominal pain	Right tube	-	24	Stable	Laparoscopy and salpingectomy	80	50	None	Postoperative fever (38.6)	Term delivery, CS (partial placenta previa)
21	G4P1A2	IVF-ET	41	Vaginal bleeding and abdominal pain	Bilateral tube	-	Right: 43; left: 18	Stable	Laparoscopy and salpingectomy	50	65	None	Urinary retention	Abortion

Case No.	Gravity, Parity, Abortion, and Ectopic Pregnancy	Mode of Conception	Gestational Age at Diagnosis, d	Clinical Presentations	Location of Ectopic Pregnancy	Fetal Heart		Diameters of Gestational Hemodynamics	Treatment of the Ectopic Pregnancy	Operative Data				
						Beats of Ectopic Pregnancy	Beats of Gestational Hemodynamics			Blood Loss, mL	Operation Time, min	Blood Transfusion	Maternal Outcome	Pregnancy Outcome
22	G3P1A1	IVF-ET	60	Asymptomatic	Right tube	-	41	Stable	Laparoscopy and salpingectomy	10	30	None	Uneventful	Term delivery, CS (suspected fetus distress)
23	G3P1A1	IVF-ET	45	Abdominal pain	Right tube	-	24	Stable	Laparotomy and salpingotomy	50, 350 mL hemoperitoneum	75	None	Uneventful	Preterm delivery, CS (PROM at 29 + 2 wk)
24	G2P0A1	IVF-ET	40	Vaginal bleeding	Left tube	-	35	Stable	Laparoscopy and salpingectomy	50	30	None	Uneventful	Term delivery, CS
25	G2P1A0	IVF-ET	45	Vaginal bleeding and abdominal pain	Right tube	-	25	Stable	Laparoscopy and salpingectomy	20, 300 mL hemoperitoneum	45	None	Uneventful	Term delivery, CS (breach presentation)
26	G4P1A2	IVF-ET	42	Vaginal bleeding and abdominal pain	Right tube	-	43	Stable	Laparoscopy and salpingotomy	50	65	None	Uneventful	Abortion
27	G2P0A1	IVF-ET	63	Asymptomatic	Left tube	+/-	34/30 (85)	Stable	Laparoscopy and salpingectomy	5	30	None	Uneventful	Term delivery, CS

CRBC = concentrated red blood cells, CS = cesarean section, IVF-ET = in vitro fertilization and embryo transfer, NT = nuchal translucency thickness, PROM = premature rupture of membrane.

* Sonographic examination was not taken in those patients.

† Concomitant with ovarian hyper-stimulation syndrome.

1 patient showed the enlargement of EP mass. Those facts suggest that regular ultrasonographic re-examinations and close observations are essential for patients chosen expectant management. Once there are any clues indicating rupture or enlargement of EP, other rescue treatment is recommended to have a good maternal outcome.

Surgical management, either laparotomy or laparoscopy, is a feasible treatment modality for HP.^{7,9} To those patients with unstable hemodynamic situation or with any signs indicating rupture of the EP, emergency surgery is strongly recommended to rescue the patient. Selective surgery is only suitable for those HP patients with stable hemodynamic situation. Surgical removal of the EP mass includes salpingectomy, salpingostomy, cornual resection, oophorectomy, and even total abdominal hysterectomy.^{1,9} Surgical management gains the advantage of complete removal of the EP mass, while there might be a higher abortion rate of the IUP.⁵ In our research, total abortion rate in surgery management group was up to 14.8%, obviously higher than the other 2 groups.

Transabdominal sonographic guided aspiration of ectopic gestational embryo with or without embryo-killing drug, which is thought to be minimally invasive, has been performed as treatment modality of EP for years, its safety and effectiveness have been well demonstrated.¹⁹⁻²¹ The difficulty of this treatment modality in the management of HP depends on the location of the ectopic gestational sac, it should be attempted only when the ectopic gestational sac is clearly visualized.¹ Both potassium chloride and hyperosmolar glucose can be used as embryo-killing drugs in the management of HP, while methotrexate (MTX) should be avoided because of its teratogenic effects on the viable IUP.¹⁵ Since rupture of the EP after this procedure have been reported,²¹ repeated sonographic examination and strict observation are strongly advised till the ectopic gestational sac becomes stable. And if the enlargement of EP is demonstrated, a repeat procedure or change to surgery management is recommended.

MTX is widely used in the conservative management of EP due to its highly effective to halt trophoblast proliferation.²² But evidence of MTX-related teratogenicity has already been observed in surviving intrauterine fetus after failed medical abortion or other treatment.^{23,24} Though there are researches showed good therapeutic effect and no negative pregnancy outcomes with medical treatment of MTX,^{7,16,25,26}; we hold the attitude that the use of MTX, no matter systematically or locally, should be avoided in the treatment of HP.

One report pointed out that about 31.4% HP were end up with natural spontaneous abortion,⁵ in our research, the total abortion rate is 26.56% (17/64) in all HP patients, which is lower than previous reported, we speculate the reason is that part of HP are missed before diagnosis. Clayton pointed out that 63.3% of IUP kept on living when HP cases were treated properly and the miscarriage rate of HP patient underwent surgery was up to 31.25% (25/80).⁵ While in our research, at least 78.85% (41/52) HP patients finally delivered 1 or more babies and the abortion rate in surgery management group was 25.93% (7/27) at the most. We speculate this owns to the multi-team endeavor of gynecologist and experts in ART in our center.

Due to the rarity of HP, it is difficult to conduct a randomized controlled trial. The limitation of our retrospective study is that patients enrolled in each group are indeed uncomparable in some basal clinical characteristics, it is difficult to point out which is the preferred treatment modality for most HP patients, so the treatment of HP should be individualized, and more researches are needed to be performed.

TABLE 3. Characteristics of Patients Treated With Transabdominal Sonographic Guided Transvaginal Aspiration of Ectopic Gestational Embryo

Patient No.	Gravity, Parity, Abortion and Ectopic Pregnancy		Gestational Age at Diagnosis, d	Clinical Presentations	Location of Ectopic Pregnancy	Fetal Heart Beats of Ectopic Pregnancy	Diameters of Gestational Mass, mm	Treatment of the Ectopic Pregnancy	Maternal Outcome	Pregnancy Outcome
	Mode of Conception	Pregnancy								
1*	G1P0A0	IVF-ET	54	Asymptomatic	Left tube	+	38	Transabdominal sonographic guided transvaginal aspiration of gestational sac (twice)	Uneventful	Preterm delivery, CS (severe preeclampsia)
2	G2P0A1	IVF-ET	42	Vaginal bleeding and abdominal pain	Left tube	+	41	Transabdominal sonographic guided transvaginal aspiration of gestational sac	Uneventful	Term delivery, CS (POPP)
3	G3P0A1E1	IVF-ET	44	Asymptomatic	Left tube	+	22	Transabdominal sonographic guided transvaginal aspiration of gestational sac	Uneventful	Preterm delivery
4	G6P0A5	IVF-ET	45	Abdominal pain	Left tube	+	Undescribed	Transabdominal sonographic guided transvaginal aspiration of gestational sac	Uneventful	Term delivery, CS (severe preeclampsia)
5	G1P0A0	IVF-ET	45	Asymptomatic	Right tube	+	32	Transabdominal sonographic guided transvaginal aspiration of gestational sac	Uneventful	Term delivery, CS (DCDA)

CS = cesarean section, DCDA = double chorion double amniotic sac, IVF-ET = in vitro fertilization and embryo transfer, POPP = persistent occipito transverse position.

* This patient had another transabdominal sonographic guided transvaginal aspiration of gestational sac for the enlargement of the ectopic gestational sac showed by regular sonographic re-examination 1 week later.

CONCLUSIONS

In our retrospective study, transabdominal sonographic guided aspiration of ectopic gestational embryo has the best maternal outcome and the lowest abortion rate, surgical management group shows the highest abortion rate, and expectant management presents the worst maternal outcome.

ACKNOWLEDGMENTS

The authors thank Miss Jia Wang and Prof Ke-Xuan Liu for their assistance in language modification of this work.

REFERENCES

1. Barrenetxea G, Barinaga-Rementeria L, de Lopez LA, et al. Heterotopic pregnancy: two cases and a comparative review. *Fertil Steril*. 2007;87:417–419.
2. Talbot K, Simpson R, Price N, et al. Heterotopic pregnancy. *J Obstet Gynaecol*. 2011;31:7–12.
3. Perkins KM, Boulet SL, Kissin DM, et al. Risk of ectopic pregnancy associated with assisted reproductive technology in the United States, 2001–2011. *Obstet Gynecol*. 2015;125:70–78.
4. Wang LL, Chen X, Ye DS, et al. Misdiagnosis and delayed diagnosis for ectopic and heterotopic pregnancies after in vitro fertilization and embryo transfer. *J Huazhong Univ Sci Technolog Med Sci*. 2014;34:103–107.
5. Clayton HB, Schieve LA, Peterson HB, et al. A comparison of heterotopic and intrauterine-only pregnancy outcomes after assisted reproductive technologies in the United States from 1999 to 2002. *Fertil Steril*. 2007;87:303–309.
6. Li XH, Ouyang Y, Lu GX. Value of transvaginal sonography in diagnosing heterotopic pregnancy after in-vitro fertilization with embryo transfer. *Ultrasound Obstet Gynecol*. 2013;41:563–569.
7. Yu Y, Xu W, Xie Z, et al. Management and outcome of 25 heterotopic pregnancies in Zhejiang, China. *Eur J Obstet Gynecol Reprod Biol*. 2014;180:157–161.
8. Yeh J, Aziz N, Chueh J. Nonsurgical management of heterotopic abdominal pregnancy. *Obstet Gynecol*. 2013;121:489–495.
9. Eom JM, Choi JS, Ko JH, et al. Surgical and obstetric outcomes of laparoscopic management for women with heterotopic pregnancy. *J Obstet Gynaecol Res*. 2013;39:1580–1586.
10. Sentilhes L, Bouet PE, Gromez A, et al. Successful expectant management for a cornual heterotopic pregnancy. *Fertil Steril*. 2009;91:911–934.
11. Sun SY, Araujo JE, Elito JJ, et al. Diagnosis of heterotopic pregnancy using ultrasound and magnetic resonance imaging in the first trimester of pregnancy: a case report. *Case Rep Radiol*. 2012;2012:Article ID 317592.
12. baron KT, Babagbemi KT, Arleo EK, et al. Emergent complications of assisted reproduction: expecting the unexpected. *Radiographics*. 2013;33:229–244.
13. Varras M, Akrivis C, Hadjopoulos G, et al. Heterotopic pregnancy in a natural conception cycle presenting with tubal rupture: a case report and review of the literature. *Eur J Obstet Gynecol Reprod Biol*. 2003;106:79–82.
14. Tal J, Haddad S, Gordon N, et al. Heterotopic pregnancy after ovulation induction and assisted reproductive technologies: a literature review from 1971 to 1993. *Fertil Steril*. 1996;66:1–12.
15. Baxi A, Kaushal M, Karmalkar H, et al. Successful expectant management of tubal heterotopic pregnancy. *J Hum Reprod Sci*. 2010;3:108–110.
16. Chin HY, Chen FP, Wang CJ, et al. Heterotopic pregnancy after in vitro fertilization-embryo transfer. *Int J Gynaecol Obstet*. 2004;86:411–416.
17. Ocal P, Erkan S, Cepni I, et al. Transvaginal ultrasound-guided aspiration and instillation of hyperosmolar glucose for treatment of unruptured tubal heterotopic pregnancy. *Arch Gynecol Obstet*. 2007;276:281–283.
18. Buca DI, Murgano D, Impicciatore G, et al. Early diagnosis of heterotopic triplet pregnancy with an intrauterine and bilateral tubal pregnancy after IVF: a case report. *J Obstet Gynaecol*. 2015;35:755–756.
19. Lang PF, Weiss PA, Mayer HO, et al. Conservative treatment of ectopic pregnancy with local injection of hyperosmolar glucose solution or prostaglandin-F2 alpha: a prospective randomised study. *Lancet*. 1990;336:78–81.
20. Wang M, Chen B, Wang J, et al. Nonsurgical management of live tubal ectopic pregnancy by ultrasound-guided local injection and systemic methotrexate. *J Minim Invasive Gynecol*. 2014;21:642–649.
21. Goldstein JS, Ratts VS, Philpott T, et al. Risk of surgery after use of potassium chloride for treatment of tubal heterotopic pregnancy. *Obstet Gynecol*. 2006;107:506–508.
22. Marion LL, Meeks GR. Ectopic pregnancy: history, incidence, epidemiology, and risk factors. *Clin Obstet Gynecol*. 2012;55:376–386.
23. Hyoun SC, Obican SG, Scialli AR. Teratogen update: methotrexate. *Birth Defects Res A Clin Mol Teratol*. 2012;94:187–207.
24. Piggott KD, Sorbello A, Riddle E, et al. Congenital cardiac defects: a possible association of aminopterin syndrome and in utero methotrexate exposure? *Pediatr Cardiol*. 2011;32:518–520.
25. Sijanovic S, Vidosavljevic D, Sijanovic I. Methotrexate in local treatment of cervical heterotopic pregnancy with successful perinatal outcome: case report. *J Obstet Gynaecol Res*. 2011;37:1241–1245.
26. Deka D, Bahadur A, Singh A, et al. Successful management of heterotopic pregnancy after fetal reduction using potassium chloride and methotrexate. *J Hum Reprod Sci*. 2012;5:57–60.