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Uterine artery embolization combined with local infusion of methotrexate and 5- fluorouracil in treating ectopic pregnancy
A CONSORT-compliant article

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Abstract

Background: To compare the efficiency and safety of uterine artery embolization (UAE) combined with local infusion of methotrexate (MTX) or MTX and 5-fluorouracil (5-FU) in the treatment of ectopic pregnancy (EP).

Methods: One hundred women with EP were prospectively enrolled from December 2012 to February 2015 and randomly allocated into 2 groups. One group was treated with UAE combined MTX, and the other with UAE combined with MTX and 5-FU. Local MTX was administrated at a dose of 80 to 120 mg, based on the initial β-human chorionic gonadotropin (β-HCG) levels, and 5-FU was given intra-arterially at a uniform dose of 0.5 g.

Results: Bilateral UAE was successfully performed in all 100 patients, 88 of whom were clinically successfully treated, 45 (91.8%) in the MTX group, and 43 (87.8%) in the MTX+5-FU group; 89% of the patients achieved normalization of β-HCG below 70,000 mIU/mL within 14 to 21 days postoperatively. The time to successful β-HCG resolution was 26.74±5.57 days for patients receiving MTX+UAE treatment, and 27.57±5.08 days for those treated with additional 5-FU. Six patients had subsequent intramuscular injections of MTX and 6 had a unilateral salpingectomy after the treatment failure. Mild immediate side effects accounted for 24.5% in the sole MTX and 58.3% in MTX+5-FU group.

Conclusion: A combination of UAE and intrauterine infusion of MTX showed comparable efficiency to UAE combined with a local infusion of MTX and 5-FU in treating EP patients with the intention to preserve fertility.

Abbreviations: β-HCG = β-human chorionic gonadotropin, 5-FU = 5-fluorouracil, ANOVA = analysis of variance, CSP = cesarean scar pregnancy, EP = ectopic pregnancy, IQR = interquartile range, MTX = methotrexate, UACE = uterine artery chemoembolization, UAE = uterine artery embolization.

Keywords: 5-fluorouracil, clinical efficiency, ectopic pregnancy, methotrexate, uterine artery embolization

1. Introduction

Ectopic pregnancy (EP) is defined as an aberrant pregnancy in which the blastocyst is implanted outside the decidual area of the corpus uteri, of which, implantation in the fallopian tubes accounts for approximately 95% of EP.[1] It is reported that the incidence of ectopic or extrauterine pregnancy is 1.3% to 2.0% in all pregnancies and therefore EP represents an important risk factor for maternal mortality in early pregnancy. Currently, EP treatment options comprise expectant management, medical and surgical (mainly salpingectomy and salpingostomy) approaches.[2] However, aggressive tubal surgery may impact fertility and ovarian reserve due to its effect on the adjacent ovarian tissues.[3] Therefore, medical treatment may represent a noninvasive and reliable strategy for patients with EP wanting to preserve their fertility.

Currently, methotrexate (MTX), a folinic acid antagonist, has been widely used as a first-line therapy for hemodynamically stable patients with EP since the first report of its use in this situation by Tanaka et al.[4,5] The current systemic MTX treatment includes administration of a single-dose, double-dose, or multiple-dose of MTX in stable patients with EP. However, no consensus has reached on the clinical priority and choice of different doses of MTX in treating EP. It is documented that MTX achieves a success rate from 70% to 87%; subsequent surgery is required for patients experiencing MTX treatment failure.[1] The adverse effect of MTX on fertility is another important concern.

Uterine artery chemoembolization (UACE) is an intervention approach concurrent with uterine artery embolization (UAE) and local delivery of chemotherapeutics, which functions not only by the toxic effects of drugs but also arterial occlusion-mediated tissue ischemia. In addition, UACE allows a higher concentration and duration of MTX that targeted to the gestational sac in EP patients, causing less systemic toxic effects than systemic MTX administration.[6] Currently, combined uterine arterial MTX infusion and embolization therapy has been used in the treatment

of nontubal EP, such as cesarean scar pregnancy (CSP) and cervical pregnancy, and is considered as a viable, safe modality associated with lower morbidity, shorter hospital stay, and rapid clinical recovery.[7,8] However, the application and efficiency of UACE in tubal or uncategorized EP requires more clinical practice; 5-fluorouracil (5-FU) is an antimetabolism drug frequently used in interventional therapy, which could induce blastocyst apoptosis by inhibiting the activity of thymidylate synthase, thereby leading to interference with DNA or RNA synthesis, and inhibition of cell cycle and survival. However, whether 5-FU combined with MTX could synergistically improve the efficiency of sole MTX in EP is unknown. Therefore, our study aims to compare the efficiency and safety of concurrent UAE and perfusion of MTX or MTX + 5-FU in the treatment of EP.

2. Materials and methods

2.1. Study design and randomization

One hundred eligible female patients with EP were prospectively recruited in this randomized controlled study from December 2012 to February 2015. Major inclusion criteria were a diagnosis of EP based on the following clinical symptoms: suppressed menstruation history, abdominal pain, mild to severe vaginal bleeding, high serum levels of β-human chorionic gonadotrophin (β-HCG) over the normal threshold, and the presence of a gestational sac outside the corpus uteri detected by transvaginal ultrasound; patient who refused the surgical resection or desired to preserve the uterus; and patient who signed the informed consent. Exclusion criteria were the presence of abdominal hemorrhage and significant shock; severe cardiac, hepatic, or renal disease; unstable hemodynamic status; and noncompliance with interventional therapy. The study was approved by the Ethical Committee of Tangdu Hospital. All patients were informed about the design and potential risk of the trial before the intervention and signed informed consents. After appropriate counseling, patients willing to receive UAE and intra-arterial drug infusion were transferred to our department.

Eligible female patients were enrolled on the basis of the CONSORT Statement Extension for Randomized Controlled Trials with allocation concealment, as shown in the flowchart in Fig. 1. A computer-generated randomization table using the SAS statistical software (SAS version 9.3, Cary, NC) was used to allocate the sequentially enrolled patients into 2 equal groups by an independent statistician who was not involved in this study. The 100 consecutive patients scheduled to undergo UACE therapy were randomized into the MTX group (n = 50) and the MTX + 5-FU group (n = 50) according the random allocation number. For the allocation concealment, opaque envelopes containing the group-allocation information were sequentially numbered and closed by an individual not involved in the study. The group-allocation information was blinded to both patients and interventional radiologists who performed all the angio-
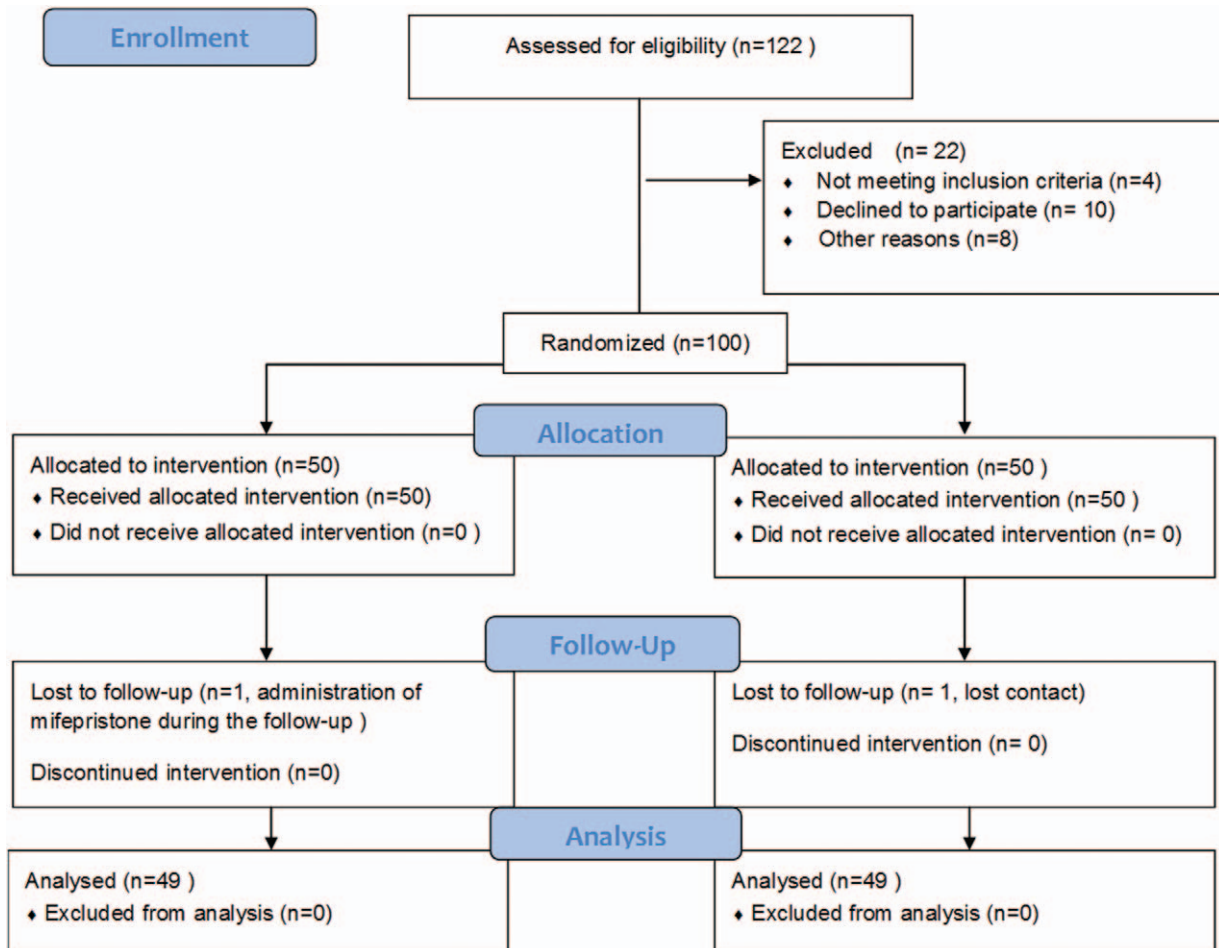

Figure 1. CONSORT flow diagram of patient selection and allocation.

graphic examinations and treatments for the duration of the study.

2.2. Medical treatment

Patients in the MTX group (n=50) were intra-arterially infused with sole MTX (Lingnan Pharmaceutical Co. Ltd., Guangzhou, China) ranging from 80 to 120 mg dissolved in 80 to 120 mL saline according to the preoperative serum level of β-HCG, that is, 80 mg for β-HCG < 10,000 mIU/mL, 100 mg for β-HCG 10,000 to 20,000 mIU/mL, and 120 mg for β-HCG > 30,000 mIU/mL. The MTX+5-FU group was given 500 mg 5-FU (Jinghua Pharmaceutical Co. Ltd., Nantong, China) intra-arterially and 80 to 120 mg MTX, as described above.

2.3. Uterine artery chemoembolization

After local anesthesia using 5% lidocaine hydrochloride injection, a 5F-catheter and guide wire (Cock, Bloomington, IN) were inserted and advanced into the uterine arteries on both sides via the right femoral artery. Digital subtraction arteriography (DSA) (Siemens, Munich, Germany) was then performed to confirm that the catheter and guide wire were correctly deployed. Then, 80 to 120 mg of MTX dissolved in 80 to 120 mL saline was infused bilaterally into the uterine arteries over 15 min in patients receiving sole MTX medical therapy. In the other group, 500 mg 5-FU was infused intra-arterially besides the MTX injection as above. Afterward, the bilateral uterine arteries in each group were embolized using gelatin sponge particles (0.5–1.0 mm). Subsequently, DSA postembolization was performed to confirm the complete obstruction of uterine arterial flow. Successful embolization was defined as the disappearance of vascularity of the gestational sac on arteriography.

2.4. Clinical efficiency evaluation

Serum β-HCG levels in all patients were examined and recorded preoperatively and 3 days postoperatively, and then weekly for the next 5 weeks, until the β-HCG was negative. The primary outcome was defined as the decreased ratio of β-HCG compared with preoperative values, against postoperative treatment time. The secondary outcomes were comprised of treatment success rate, time to successful resolution, and fallopian tube patency rate. The success of the medical management of EP was defined as β-HCG level becoming negative (<5 mIU/mL) after administration of MTX or MTX+5-FU, no signs of EP, decreased or no further increase of gestational sac size, and no internal hemorrhage. Medical management failure was signaled by symptoms indicative of tube rupture, including hemodynamic instability, increasing abdominal pain, rapidly increasing β-HCG value, and a necessity for surgical intervention. The first time point when the β-HCG level became negative was defined as the time to successful resolution. Fallopian tube patency was confirmed when contrast agents were diffused properly and no occlusions were shown in angiography. Patients who were lost to follow-up or transferred to other medications were considered censored for the outcome of time to successful resolution. Adverse effects of the 2 treatment strategies were recorded.

2.5. Sample size calculation

The sample size calculation was performed before initiation of the study based on primary endpoint in our previous pilot study. At least 40 participants should be included in each group to detect the differences with 80% statistical power and significance at 0.05. Therefore, at least 96 patients were predefined to be randomized considering a dropout rate of 20%.

2.6. Statistical analysis

Normal continuous variables were compared using repeated 1-way analysis of variance (ANOVA) followed by the Bonferroni post hoc test. Non-normally distributed variables were compared using the Kruskal–Wallis test. Differences between the 2 groups were calculated using Student t test for continuous variables and the chi-squared or Fisher exact test for categorical variables. Statistical analysis was performed using SPSS 22.0. A P value of <.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

One hundred eligible EP patients were enrolled in this prospective study and randomized into 2 groups receiving UAE interventional therapy combined with sole MTX, or UAE with MTX+5-FU. The baseline characteristics are shown in Table 1. All the patients presented to our department had symptoms of pelvic pain and vaginal bleeding. Metrorrhagia was noted in 42 patients in the MTX group and 44 in the combination medical treatment group. Women aged between 22 and 30 years were the predominant population at a 62% in this study. Six patients had previous EP, 4 in the MTX group, and 2 in the MTX+5-FU group, and all had a previous unilateral salpingectomy. Twenty-three women underwent diagnostic curettage and no chorionic placenta was found. There were 35 cases of tubal and 65 nontubal ectopic pregnancies that were mainly comprised of ovarian pregnancies (20%) and CSPs (25%). The median β-HCG at diagnosis was 13,659 mIU/mL (interquartile range [IQR] 4326, 32,506), 15,429 mIU/mL (IQR 3927, 41,203) in the MTX group, and 2687 mIU/mL (IQR 5478, 36,410) in the MTX+5-FU group. Seventeen patients had absolutely higher β-HCG levels over 30,000 mIU/mL. By ultrasonography, diameter of the gestational sac diameters was ranging from 0.7 to 2.9 cm; the embryo within the gestational sac could be seen in 30 patients, and 17 had fetal cardiac activity; in the remaining 13 patients, only a yolk sac was identified. No significant differences were found in baseline characteristics between the 2 groups.

3.2. β-HCG decrease after UACE treatment

β-HCG level was monitored at 3 days preoperatively and weekly thereafter in all women who underwent bilateral UACE. The mean decreased ratio of β-HCG, normalized to that of the preoperative value, was substantially lowered within the first postoperative 7 days by approximately 50% in the MTX group and 42% in the MTX+5-FU group. We noticed that 89% of the patients achieved normalization of β-HCG below 7 mIU/mL within 14 to 21 days postoperatively. No significant difference was seen in the effects of the 2 medications on the inhibition of β-HCG levels during the observation periods using repeated ANOVA ($F=0.284$, $P=.597$) (Fig. 2). Moreover, no statistically significant interaction was noted between medication strategies and monitoring time ($F=0.826$, $P=.418$) (Table 2). The time to successful resolution was 26.74 ± 5.57 days for patients receiving MTX treatment combined with UAE, and 27.57 ± 5.08 days for those treated with the combination of MTX and 5-FU along with UAE ($P>.05$).

Table 1

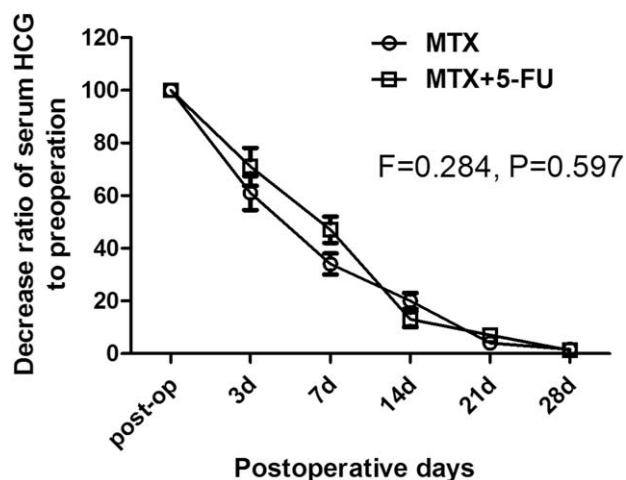**Baseline characteristics of the patients in the 2 groups.**

Characteristics	Total (n=100)	Sole MTX (n=50)	MTX+5-FU (n=50)	P
Age, y	30.5±10.3	32.6±12.5	29±13.2	.536
<22	8	4	4	.432
22–30	62	30	32	
>30	30	16	14	
BMI, kg/m^2	22.6±4.9	21.9±5.2	23.1±4.1	.152
Reproduction history, n	38	18	20	.680
Gravidity	2.6±1.4	2.6±1.4	2.7±1.5	.502
Parity	1.22±0.41	1.09±0.28	1.21±0.19	.265
Previous ectopic pregnancy	6	4	2	.400
History of unilateral salpingectomy	6	4	2	.400
Menstruation cessation time, d	32–71	48 (32–71)	44 (33–70)	.189
Medical sites				.477
Fallopian tube	35	18	20	
Interstitial pregnancy	4	2	2	
Cervical pregnancy	10	6	4	
Ovarian pregnancy	20	11	9	
Cesarean scar pregnancy	25	13	15	
Previous HCG, mIU/mL	1023–142,311	1023–142,311	1125–93,265	—
<10,000	21	10	11	.661
10,000–30,000	62	33	29	
>30,000	17	7	10	
Pelvic pain	100	50	50	—
Vaginal bleeding	100	50	50	—
Metrorrhagia	86	42	44	.564
Fetal heart activity	17	8	9	.790
Gestational sac diameters, cm	1.64 (0.7–2.9)	1.72 (0.7–2.8)	1.89 (0.8–2.9)	.243

HCG = human chorionic gonadotropin.

3.3. Clinical outcomes

Bilateral UAE was successfully performed in all the patients. As presented in Fig. 3, the gestational sac was surrounded by numerous arterial branches for blood supply before embolization, as shown in the angiography; after the embolization, both uterine arteries were obstructed and the vascularity of the gestational sac completely disappeared. The time for total lesion disappearance was 29.7±4.0 (5–56) days in the whole population. Finally, 88 patients were successfully clinically treated, 45 in the MTX group and 43 in the MTX+5-FU group,

Figure 2. The ratio of β-human chorionic gonadotropin (%) normalized to initial levels in the 2 groups of patients with ectopic pregnancy within 4 weeks.

and no significant difference was seen in the clinical recovery efficiency between the 2 groups. One patient in MTX group was lost to the follow-up and 1 patient was excluded due to administration of mifepristone during the follow-up. It was also noted that the clinical success rate de-escalated against the level of preoperative β-HCG with treatment priority shown in patients with a preoperative β-HCG of <10,000 mIU/mL (Fig. 4). Eighty patients with EP had a salpingography and 4 cases of tube occlusion were seen. No substantial difference was noted in tube patency ratio in the 2 groups (P=.646). Finally, 6 patients had a subsequent intramuscular injection of MTX and 6 had a unilateral salpingectomy due to treatment failure (Table 3). No severe adverse effects of the 2 treatment strategies were recorded; only mild abdominal pain, gastrointestinal disorders, oral ulcers, and hepatic injury were seen in both groups, which were substantially improved when symptom-specific treatments were administered. No severe immediate side effects, such as internal vascular bleeding, sepsis, and early liver or renal failure were observed. The supplement of 5-FU might increase the risk of these adverse events (P=.001).

Table 2

Statistical analysis of the interaction between treatment strategy and time on the effect of postoperative β-human chorionic gonadotropin levels.

Variables	DF	DF (adjusted)	SS	MS	F	P
Observation time	5	1.605	38.057	23.711	115.143	.000
Observation time × treatment	5	1.605	0.273	0.170	0.826	.418
Error	235	75.437	15.534	0.206		

Figure 3. Representative digital subtraction angiograms in a patient with ectopic pregnancy who received uterine arterial embolization.

4. Discussion

EP is a gynecologic acute abdominal disease that may seriously compromise women's health and future fertility; early diagnosis and effective treatment are crucial. However, decision making for the treatment of EP is still challenging especially when MTX treatment fails and subsequent surgery is needed. Our study showed comparable efficiency of UAE combined with MTX, or MTX and 5-FU in treating EP with success rates of 90% and 86%, respectively.

UAE was initially considered as a conservative treatment for various obstetric and gynecological conditions, such as postpartum hemorrhage and uterine myomas, which has been used in the management of EP in this decade. UAE is a minimally invasive surgical procedure in treating EP by blocking blood flow in the uterine arteries, decreasing the vascularization surrounding the pregnancy and promoting trophoblastic degeneration.[9] Currently, the potential use of UAE has been explored mainly in nontubal ectopic pregnancies such as CSP. Transcatheter arterial chemoembolization has been shown to be more effective than systemic MTX treatment for termination of CSP.[10] Moreover, adjunctive therapy with embolization has significantly reduced the duration of hospital stay than when MTX is used alone.[11] Krissi et al[8] reported that a combination of uterine arterial MTX infusion and embolization with systemic MTX is an effective and safe treatment for nontubal ectopic pregnancies in women who try to conceive. Shen et al[6] demonstrated that the mean time until normalization of the serum β-HCG was 37.7 days, and the mean time until CSP mass disappearance was 33.3 days after MTX administration combined with UAE. In the overall EP population in our study, the mean time to successful resolution was 26.74 days, and 29.7 days until the mass disappearance for patients receiving MTX treatment and UAE. Notably, uterine arterial infusion and embolization were successfully performed in all patients without any related complications. Active bleeding in
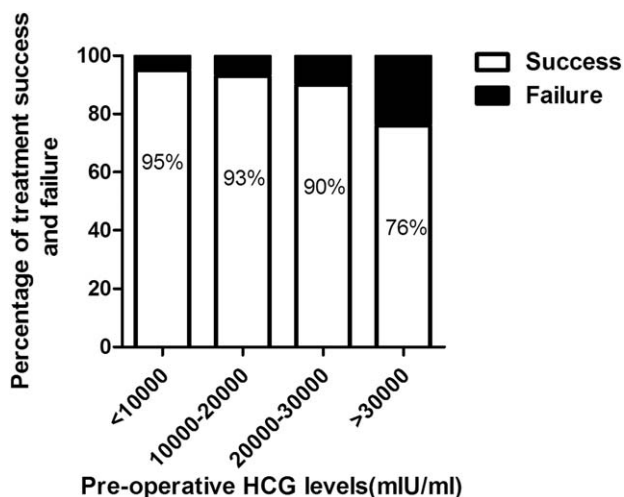

Figure 4. Treatment success rate in patients with various initial serum β-human chorionic gonadotropin.

Table 3

Clinical outcomes of the 2 groups of patients.

Characteristics	Total (n=98)	Sole MTX (n=49)	MTX+5-FU (n=49)	P
Success rate (%)	88 (89.8%)	45 (91.8%)	43(87.8%)	.505
Postembolization surgery	6	2	4	.646
MTX intramuscular injection	6	3	3	1.000
Hospital stay	10.35±3.16	10.26±2.84	10.56±3.45	.754
Time to successful resolution	27.03±4.95	26.74±5.57	27.57±5.08	.596
Normal in 2 wk	64	34	30	
Normal beyond 2 wk	25	11	13	
Fallopian tube patency	93	47	46	.646
Adverse effects	40 (40.8%)	12 (24.5%)	28 (58.3%)	.001
Pelvic pain	19	7	12	
Gastrointestinal disorders	15	2	13	
Medulla suppression	1	1	0	
Oral ulcer	3	2	1	
Hepatic injury	2	0	2	

the peritoneum in 33 cases ceased soon after embolization. The embryos in 30 patients were confirmed by ultrasound to have died 3 days after the procedure. The β-HCG value dropped to below 15 mIU/mL at 3 to 21 days. Hemorrhage in the peritoneum dissolved after 7 days in all cases. The mixed mass disappeared after 1 month. Hysterosalpingography was performed 3 months after the procedure in 19 patients and patent fallopian tubes were demonstrated in 16 patients in Gong's report.[12]

The 5-FU is an inhibitor of thymidylate synthase and is a commonly used intervention therapy. The 5-FU can induce blastocyst apoptosis by inhibiting the activity of thymidylate synthase, thereby leading to interference with DNA or RNA synthesis, and inhibition of cell cycle and survival. It is documented that gestational trophoblastic neoplasms show high sensitivity and specificity to 5-FU monotherapy and combination therapy with actinomycin D.[13,14] Our study investigated whether 5-FU combined with MTX could synergistically improve the efficiency of sole MTX in EP. As the data showed, the additional supplement of 5-FU did not have a further positive impact on the success rate, β-HCG normalization time or the time to mass disappearance, compared to the use of sole MTX with UAE. However, the addition of 5-FU might increase the risk of side effects associated with the dose–effect of this cytotoxic drug. Therefore, other treatment modalities that complement to UAE, aside from MTX, should be further discussed.

The present study is limited to the small sample size and its nature of single center study. In addition, our study concluded that additional application of 5-FU did not show priority to the UAE + MTX therapy in treating overall EP. However, whether the conclusion varies for tubal and nontubal EP should be further confirmed. Besides, 5-FU was used at an indicated dose in the current study, and we still do not know whether optimal synergistic effect could be observed in treatment efficiency of EP when changing 5-FU dosage or 5-FU/MTX ratio according to the individual β-HCG level.

Our study compared the treatment efficiency of UAE and infusion with sole MTX, or MTX combined with 5-FU, in treating ectopic pregnancies. The results showed that UAE and concomitant local infusion of MTX was effective in addressing ectopic pregnancies with the intention to preserve fertility. Moreover, intrauterine arterial embolization and infusion of MTX combined with 5-FU had comparable effects to UAE with sole MTX. However, the extra addition of 5-FU may increase the risk of adverse effects.

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