

# Superselective uterine arterial embolization combined with transcatheter intra-arterial methotrexate infusion in 40 cases with fallopian tube ectopic pregnancy

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## Summary

**Purpose:** To evaluate the therapeutic results of superselective uterine artery infusion and embolization in 40 patients with fallopian tube ectopic pregnancy, and to explore the role of this minimally invasive treatment as an alternative to surgery. **Materials and Methods:** Superselective catheterization of uterine artery through cannulation of femoral artery was achieved in 40 patients with fallopian tube ectopic pregnancy (EP). Location of the lesions involved feeding arteries and active bleeding were observed through angiography. Methotrexate (MTX) diluted in saline water was slowly infused into the target artery. Small gelatin spongy particles were used to embolize the uterine artery until its branches were totally obliterated. Follow-up was undertaken to observe the results of the treatment. **Results:** Superselective uterine arterial infusion and embolization were successfully performed in all 40 patients without any related complications. Active bleeding in the peritoneum in 33 cases ceased soon after embolization. The embryos in 13 patients were confirmed to have died by ultrasound three days after the procedure. Beta-human chorionic gonadotropin ( $\beta$ -hCG) value dropped to below 15 IU/L at three to 21 days. Hemorrhage in the peritoneum dissolved after seven days in all cases. Mixed mass disappeared after one month. Hysterosalpingography was performed three months after the procedure in 19 patients and patent fallopian tubes were demonstrated in 16 patients. **Conclusions:** Superselective uterine arterial infusion and embolization is a minimally invasive procedure, which can be used to effectively treat EP by disabling the ectopic embryo and leaking arteries with the advantages of preserving the fallopian tubes.

**Key words:** Fallopian tube ectopic pregnancy; Superselective uterine artery infusion and embolization; Methotrexate; interventional radiology.

## Introduction

Approximately 1/100 pregnancies are ectopic, with the conceptus usually implanting in the fallopian tube (95.5%), which is higher in women with damage to the fallopian tubes due to pelvic infections, surgery, or previous ectopic pregnancy, and in smokers [1]. Few ectopic pregnancies (EP) resolve spontaneously, but most continue to grow and lead to rupture of the tube, and may seriously compromise women's health and future fertility [2, 3].

The treatments of EP include expectant treatment, medical management with methotrexate (MTX), and surgical interventions such as salpingotomy and laparotomy [3]. Salpingotomy by laparoscopy becomes more common in the treatment of EP, because it may lead to fewer complications and shorter recovery times compared with laparotomy, but may also be less likely to remove all the trophoblast, may eventually leading to persistent EP [4]. Surgical intervention, including laparoscopic surgery and laparotomy, is usually performed under emergency conditions, with both the risks of surgery and general anesthesia, and eventually leading to damage to fertility [5].

Several conservative methods for pregnancy termination have been suggested to avoid bleeding, preserve the uterus, and maintain fertility, such as systemic and local administration of MTX. Administered to properly selected patients, it has a success rate of up to 94% [6]. However, the adverse effects such as nausea, vomiting, gastritis, diarrhea, abdominal pain, oral mucositis, pneumonitis, bone marrow suppression, and abnormal liver function are prevalent after intravenous injection of MTX [7, 8]. It is distressing that the time for the serum beta human chorionic gonadotropin ( $\beta$ -hCG) concentration to decline to less than 15 IU/L is 33.6 days on average, but may be up to 109 days [9], which is needed by the patient to comply with post-treatment monitoring. Interestingly, the local MTX injection has been reported that it can decrease the adverse effects and is suggested as an alternative to surgery in selected cases of early unruptured tubal pregnancy [10].

Since the late 1960s, transcatheter arterial embolization, as an interventional radiology treatment, has been used for the control of pelvic hemorrhage resulting from malignancy, trauma, and radiation [11]. More recently, use of transcatheter embolization of the uterine arteries has been described for treatment of abdominal pregnancy and cervical EP [12-14]. Therefore, the authors' hypothesis is that the combination of the transcatheter intra-arterial MTX infusion and the embolization of uterine artery which feed the gestational sac may be an alternative to surgery.

\*These authors contributed equally to this work.

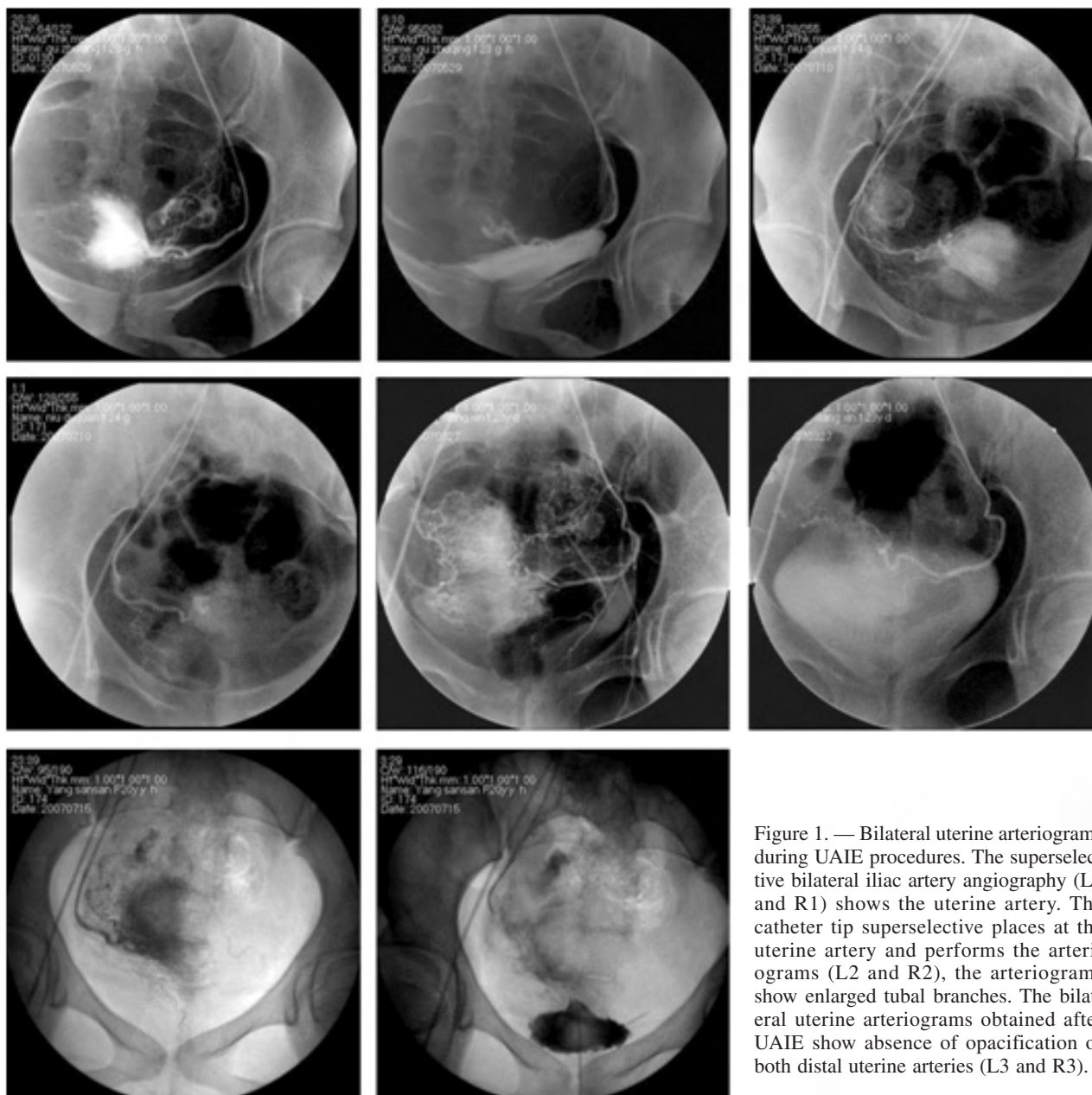


Figure 1. — Bilateral uterine arteriograms during UAIE procedures. The superselective bilateral iliac artery angiography (L1 and R1) shows the uterine artery. The catheter tip superselective places at the uterine artery and performs the arteriograms (L2 and R2), the arteriograms show enlarged tubal branches. The bilateral uterine arteriograms obtained after UAIE show absence of opacification of both distal uterine arteries (L3 and R3).

To address these issues, a retrospective study was performed evaluating the superselective uterine artery with transcatheter intra-arterial infusion and embolization (UAIE) in selected patients with fallopian tube EP, proving that UAIE is a minimally invasive procedure, which can be used to effectively treat EP by disabling the ectopic embryo and leaking arteries with the advantages of preserving the fallopian tubes.

## Materials and Methods

### Patients

Between February 2007 and March 2011, 40 patients with fallopian tubal EP entered this study. All patients willing to

accept the interventional radiology and desired future fertility; the time of suppressed menstruation < 70 days; the gestational sac has unruptured; the gestational sac has ruptured or resolved spontaneously, with abdominal bleeding, but the vital signs were still stable; transvaginal ultrasound and serum  $\beta$ -hCG test supported the diagnosis of tubal EP; the patients with shock were excluded. The demographic and clinical features of 40 patients are summarized in Table 1.

### Operation protocol

The 5F uterine artery catheter punctured the right femoral artery following the Seldinger method, and it was inserted selectively into the uterine artery of sick side. Then, the superselective uterine artery angiography was carried out to observe the feeding uterine arteries to gestational sac and active bleed-

Table 1. — Demographic and basal clinical features.

Patients	
Median age in years (range)	28 (17-38)
Median $\beta$ -hCG value IU/l (range)	2182 (269-4821)
Survival of embryos (no.) and gestational sac and its diameter (cm)	13, 0.8 - 2.5
Suppressed menstruation (days)	42 - 52
Active bleeding (no.)	18

ing. One hundred ml of MTX (100 mg MTX was diluted in 100 ml normal saline) was infused in the targeted artery, and then, the small gelatin sponge particles with size of  $0.5 \times 0.5 \times 0.5$  mm<sup>3</sup> were used to embolize the targeted uterine artery until its branches were totally obliterated, which were mixed with ten ml of contrast medium and were slowly administered. After the operation, conventional intravenous antibiotics were used for three days.

#### Detection of serum $\beta$ -hCG

A  $\beta$ -hCG test kit was used in the detection of serum  $\beta$ -hCG, and the manufacturer's instructions were followed. The venous blood samples were obtained from the subjects and allowed to clot at room temperature and aliquots of serum were obtained by centrifugation. Serums were collected and stored until analysed. Serum levels of  $\beta$ -hCG were measured by chemiluminescence.

#### Assessments

Patients were followed up with a review of medical records and telephone interviews. The follow-up periods after UAE ranged from three days to 12 months (median, four months). The authors evaluated the UAIE technique, complications, vaginal bleeding, serum levels of  $\beta$ -hCG, ultrasound examination, menstruation function, pregnancy, and delivery. Technical success was defined as disappearance of uterine arterial flow on bilateral iliac arteriography and disappearance of active vaginal bleeding on gynecologic examination after UAIE. Clinical success was defined as the disappearance of clinical symptoms; bleeding ceased, serum  $\beta$ -hCG decreased to normal levels, ultrasound examination showed disappearance or shrinkage of the mass on the annex areas, and normal menstruation ensued. The end points were defined as preservation of uterus and future fertility.

#### Statistical analysis

Categorical data are presented as absolute values and percentages, and continuous data are summarized as median and range or mean and SD. The Wilcoxon test was used for comparison of continuous variables. A value of  $p < 0.05$  was regarded as significant.

#### Results

The 40 patients all underwent UAIE procedures. The bilateral uterine artery arteriograms were obtained before UAIE to observe the gestational sac of blood supply (Figure 1). In all sessions, enlarged tubal branches to the uterus were identified (Figure 1, L1 and R2). Then, UAIE was performed with gelatin sponge particles. The bilateral uterine arteriogram obtained after UAIE shows

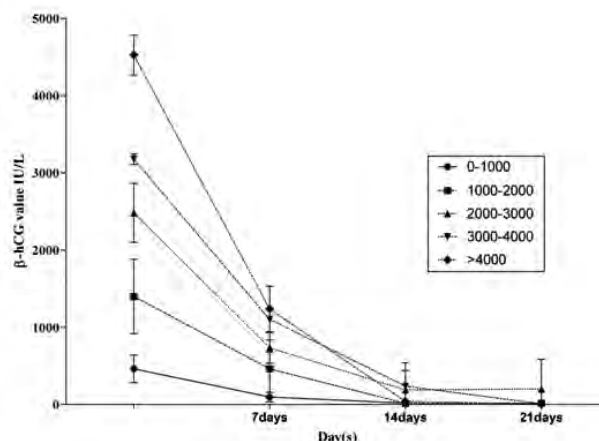


Figure 2. — The detection of serum  $\beta$ -hCG was carried out before and after UAIE at seven, 14, and 21 days.

absence of opacification of both distal uterine arteries, suggesting successful embolization (Figure 1, L3 and R3).

The clinical success was obtained in the 37 patients, among them, one patient had lesions removed because of the EP in the left fallopian tube after UAIE at one year, whose previous conceptus implanted in the right fallopian tube, and the right accessories were confirmed as well during laparoscopic surgery. Three patients finally underwent surgical treatment, two patients whose serum  $\beta$ -hCG levels that did not decline significantly had symptoms that increased, and one patient because of no willingness to comply with post-treatment monitoring.

No major complication related to UAIE was detected. Vaginal bleeding was controlled after UAIE. Ten patients had a small amount of vaginal bleeding during the three weeks after UAIE. Eighteen patients with active abdominal bleeding which showed obvious contrast agent extravasation around the annex district from the uterine artery angiography stopped bleeding after embolization.

The detection of serum  $\beta$ -hCG was carried out after the UAIE at three, seven, 14, and 21 days. The serum  $\beta$ -hCG of all 40 patients all reduced to 15 IU/l and more at 14-21 days after the UAIE (Figure 2). As shown in Figure 2, the time for the serum  $\beta$ -hCG concentration which is  $< 2,000$  IU/l to decline to normal is 14 days, the time for the serum  $\beta$ -hCG concentration which is  $> 3,000$  IU/l is 21 days.

At the forth week, ultrasound examination revealed that the mixed mass next to the uterus completely disappeared (Figure 3). Ultrasound examination revealed that the hemoperitoneum was all absorbed after embolization at three to seven days. At the third day after embolization, the ultrasonography of five patients with more pelvic blood volume (about 1,500 - 2,000 ml) showed that pelvic hemorrhage was about 300 ml, and then underwent puncture of posterior fornix of vagina and the blood removed was about 150 ml. At the seventh day after embolization, ultrasonography showed that pelvic hemorrhage was completely absorbed.

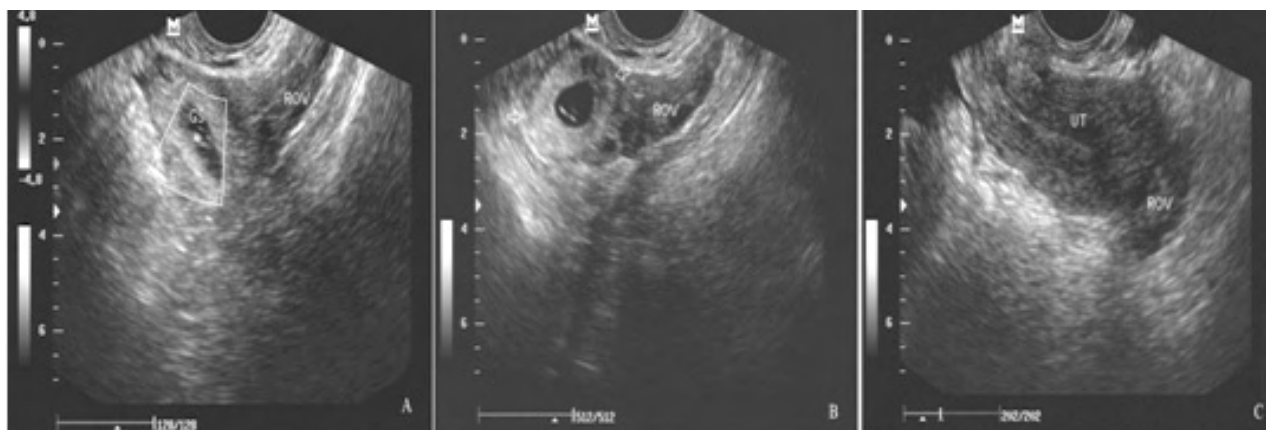


Figure 3. — Ultrasound examinations were carried out before UAIE and after UAIE at seven, and 21 days.

Nineteen patients underwent hysterosalpingography after UAIE at six months, and the result displayed a tubal patency rate of 84.2%. So far there were six patients with normal pregnancy and birth.

### Discussion

The tubal branch of uterine artery bears more than 85% of the tubal blood supply, and the ipsilateral uterine artery mainly feeds the ectopic embryo occurring in the fallopian tube, which is the anatomical basis of the transcatheter intra-arterial drugs to perform abortions and embolization to stop bleeding.

Ectopic pregnancies are today often diagnosed before the patient's condition has deteriorated such that surgical intervention is inevitable. This is partly due to an increased knowledge and awareness of risk factors among both clinicians and patients. Reliable diagnostic algorithms integrating transvaginal ultrasound and serum  $\beta$ -hCG measurement, that enable to make an accurate non-invasive diagnosis [15, 16]. As a result, the conservative management such as MTX, has been more and more accepted.

MTX, a folic acid antagonist, inhibits DNA synthesis in actively dividing cells, including trophoblasts [6]. Many researchers believe that MTX is necessary when the ectopic mass less than 3.5 cm in diameter and/or when serum  $\beta$ -hCG level exceeds no more than 3,000 IU/l [3]. Can patients without this range undergo the conservative treatment?

The frequency of MTX complications is similar to those with laparoscopy [17]. For this reason, the authors used the technology for transcatheter intra-arterial MTX infusion. The data showed that this technology effectively reduced the complications and adverse effects. In addition, as shown in Figure 2, the time for the serum  $\beta$ -hCG value to decline to normal was about 14-21 days, which greatly shortened post-treatment MTX monitoring time. The transcatheter intra-arterial MTX infusion had been used in the treatment for the cervical EP [18]. The authors believe that the transcatheter intra-arterial MTX

infusion improves MTX benefits for EP by increasing the amount of MTX delivered to the site of the gestational sac.

At three days after embolization, the ultrasonography of five patients with more pelvic blood volume (about 1,500-2,000 ml) showed that pelvic hemorrhage was about 300 ml, and then underwent puncture of posterior fornix of vagina; the blood removed was about 150 ml. At seven days after embolization, ultrasonography showed that pelvic hemorrhage was all absorbed. The ultrasonography of these five patients showed that gestational sac was ruptured. The authors embolized the abnormal side of uterine artery, which not only can arrest bleeding, interrupt the blood supply of gestational sac, but can also extend the residual time of MTX. Therefore, the authors believe that the combination uterine artery embolization with local infusion of MTX can be used to treat the patients which have an abortion, whose gestational sac has ruptured and/or in which bleeding has occurred, but the patients can still tolerate.

The initial purpose of embolization is to control the bleeding caused by abortion or rupture. The authors chose gelatin spongy particles with a size of  $0.5 \times 0.5 \times 0.5 \text{ mm}^3$  as the embolic agent, which are the temporary embolic agents. With the pelvic interventional clinical research increased, more and more literatures report that the ovarian artery participates in the abnormal blood supplying to the pelvic focus of infection [19, 20]. The ovarian artery if ignored, may lead to treatment failure caused the rebleeding. More small embolic particles can more effectively achieve the peripheral distal, and can reach the ovarian distal artery, blocking the ovarian artery, while controlling bleeding. In addition, the embolic particles within one to three mm in diameter usually cannot cause necrosis of the normal uterus.

However, one patient had active vaginal re-bleeding 45 days after UAIE and she eventually underwent salpingotomy through laparoscopy. The cause of rebleeding after UAIE is considered to be as follows: the establishment of extensive collateral circulation; the recanalization of embolized uterine arteries after UAIE using temporary

embolic agents, such as gelatin sponge, might have once again supplied blood to the uterus; some gestational tissues may have remained alive after short-time ischemia.

In conclusion, UAIE is a safe, minimally invasive, and effective procedure with a low rate of complications for tubal EP. However, the risk of vaginal rebleeding after UAIE should be recognized. Furthermore, the results of the present study show that UAIE allows the preservation of the uterus and the potential for future fertility. These results are encouraging, but the authors cannot draw firm conclusions due to the small number of patients in this study.

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