CLINICAL STUDY

Uterine artery embolization in association with methotrexate infusion for the treatment of tubal ectopic pregnancy

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ABSTRACT

Objective To investigate the safety, feasibility, and effectiveness of uterine artery embolization in association with methotrexate (MTX) infusion for the treatment of tubal ectopic pregnancy.

Methods Fifty-one patients with tubal ectopic pregnancy were referred for interventional management. All patients received super-selective arteriography of the uterine artery, were infused with 50–100 mg methotrexate (MTX) through a catheter, and underwent embolization of the uterine artery with a gel-foam pledge. Clinical presentation, findings of physical examination, β-HCG values, and the size of the ectopic mass were documented for comparison. The concentration of MTX in blood was evaluated at 0.5, 6, 12, 24, 36, and 48 hours after the procedure.

Results Forty-seven out of the 51 patients had clinical resolution of their tubal pregnancy (92.2%). The average time for the β-HCG value to decrease and come back to normal was 9.16 ± 2.54 days (mean +/− SD). MTX levels in peripheral blood could not be detected for patients who received 50 or 75 mg MTX at 36 hours after the procedure, while the MTX level was 0.01 μmol/L at 48 hours after the procedure for patients who received 100 mg. Out of the 4 cases whose ectopic mass size was ≥5 cm, 3 failed to respond to the treatment; however, those whose ectopic mass size was ≤5 cm responded positively to the treatment, regardless of the β-HCG concentration and abdominal bleeding, except for 1 patient who had to undergo laparoscopy for severe abdominal pain and who showed a reduction in her β-HCG level.

Conclusion Uterine artery embolization in association with methotrexate infusion is safe and effective in the treatment of tubal ectopic pregnancy, especially for those women with mild to moderate bleeding, or for those at risk of a major hemorrhage. The selection criterion of mass size >5 cm should, therefore, be carefully considered.

Keywords: radiology, interventional; tubal, pregnancy; embolization, therapeutic.

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INTRODUCTION

The most common location of ectopic pregnancy is the fallopian tube. Surgery is still the preferred first-line treatment for tubal pregnancy. Since ectopic pregnancy is now being diagnosed earlier and more frequently than a few decades before, management has shifted from emergency laparotomy to laparoscopy to even more conservative methods in select cases (1). For example, the use of methotrexate (MTX) can successfully result in the resolution of some cases without operative intervention. However, it must not be forgotten that ectopic pregnancy accounts for 0.67%–4.38% of maternal deaths, and should, therefore, still be considered a potentially life-threatening condition (2,3). Uterine artery embolization has been available for more than 20 years in the treatment of various gynecologic and obstetric conditions, especially in patients with postpartum hemorrhage (4). The use of such a technology certainly avoids hysterectomy and maintains normal reproductive function in these women.

Although the application of uterine artery embolization and MTX infusion in the treatment of ectopic pregnancy have shown an increasing trend in the recent days (5-7), there are some questions that require clarification, which include the indication, efficacy of the treatment modality, and safety issues during the treatment process. We attempted to investigate and provide clarification on these issues by performing MTX infusion along with uterine artery embolization on 51 patients who experienced tubal pregnancy.

PATIENTS AND METHODS

Clinical materials

From May 2002 to March 2018, 51 voluntary patients 22 to 39 years of age (average, 27 years) agreed to undergo MTX infusion and uterine artery embolization for the treatment of tubal pregnancy. All procedures were performed after receiving approval by our institutional review board and obtaining informed consent from all patients. The duration of menolipsis in these patients was from 42 to 90 days (average, 59 days). Thirty-one cases were left tubal pregnancies and 20 were right. Thirteen cases experienced their first pregnancy and 38 patients were multipara. Twenty-eight cases had a history of induced abortion and 23 cases used contraceptive devices. Eighteen of the 51 cases never experienced uterine rupture; while 33 cases showed signs of internal hemorrhage, 27 of which had experienced puncture at the utero-rectal fossa. The puncture resulted in a pumping volume of incoagulable blood between 15 and 40 mL. Four cases exhibited a mass size of ≥5 cm and the other cases were ≤5 cm as measured by ultrasonography. The β-HCG value measured before treatment was <5000 mIU/mL in 16 cases, between 5000 and 10000 mIU/mL in 21 cases, and 10000–64000 mIU/mL in 14 cases.

Methods

We adapted a modified Seldinger technique to the catheterization of the femoral artery; and after the catheter super-selectively reached the uterine arteries, angiography was performed with a DSA machine. Angiographic features of the tubal pregnancy were then divided into 3 different vascular architectures (or types I, II, and III). We chose the MTX dosage depending upon vascular type in the interventional treatment. The dosage allocation in the 3 types were 50 mg for type I, 75 mg for type II, and 100 mg for type III. MTX was injected slowly after dilution with 100 mL of physiologic saline. After infusion, the uterine arteries were subsequently embolized with gelfoam particles (1 mm × 2 mm × 2 mm). We performed angiography again to clarify the embolic situation, and embolization was halted when we observed stasis of the contrast medium.

Observation after treatment

After removing the catheter, the puncture site was handled with localized pressure and bandaging. The patients were asked to remain supine with legs extended, and not to move or walk for at least 12 hours. Symptoms and signs such as abdominal pain and vaginal bleeding were then carefully observed after returning from the DSA room. Serum β-hCG concentrations, abdominal bleeding, and the size of the ectopic mass were closely evaluated. Patients with β-HCG levels that rose progressively, that

showed fetal cardiac activity, or that exhibited severe abdominal pain were monitored for the possibility of rupture and bleeding of the gestational sac. Under either of these conditions, operation or laparoscopy was performed immediately.

Observation index

Serum β-HCG was measured every 2 days in all patients, and the evaluation of β-HCG lasted until the values returned to normal. The volume change in the sacs was observed by ultrasonography. Peripheral blood concentrations of MTX were monitored dynamically 0.5, 6, 12, 24, 36, and 48 hours after the interventional procedure. Routine blood tests and liver function tests were performed 7 and 14 days after the procedure. The recovery time until the next menstruation was observed after the procedure. Follow-up salpingography was requested and performed in some cases during follow-up.

Statistical analysis

For clinical data, the independent sample t-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. A *P*-value <0.05 indicated a statistically significant difference. All statistical analyses were performed using statistical software (SPSS version 25.0 for OS, SPSS, Chicago, IL).

RESULTS

Technical approach

Catheterization and uterine artery embolization in association with methotrexate infusion were technically successful in all 51 cases. The average time for manipulation on the DSA table was 45.7 min (range, 25–71), and the average fluoroscopic time was 2.8 min (range, 1.5–5.3).

Therapeutic effects

Forty-seven tubal pregnancies were successfully terminated by treatment, with a success rate of 92.1% (47/51). Serum B-HCG levels in these patients dropped to normal levels within 9.16 ± 2.54 days after the procedure; and pelvic hematoceles in all patients were absorbed 7 to 28 days after. Pelvic masses in 46 patients (with a mass size of ≤5 cm) also disappeared 11 days to 6 months after treatment. However, 3 of 4 cases with a mass size ≥5 cm and 1 of 47 cases with a mass size ≤5 cm were unsuccessful after the procedure, and were then treated operatively or at laparoscopy; the latter case underwent laparoscopy for severe abdominal pain, but with a reduction in β-HCG. The 3 former cases manifested no therapeutic effects, with a progressive rise in serum β-HCG and extant fetal cardiac activity.

The recovery time to menstruation in these patients was 28 to 43 days, and the salpingographic findings in 23 patients showed that their tubes were patent at the follow-up time of 3–15 months.

Adverse reactions after treatment

Eighteen of 51 cases suffered from remarkable distension and pains in the hypogastric zone during the procedural period and were treated with Dolantin (75 mg) injection. Sixteen of 51 cases had the same aforementioned symptoms at some location after the procedure and recovered well after analgesic symptomatic treatment with an indomethacin rectal suppository. Eighteen of 51 cases were febrile, with a body temperature of approximately 38.5 ℃–39.0 ℃. The causes of the fever were considered to be heat absorption or an embolic syndrome; and body temperature returned to normal 1 week later without special treatment. During the hospitalization period of 7 to 14 days after treatment, we found no evidence of bone marrow suppression or liver function damage in the peripheral blood of these patients. There were also no gastrointestinal reactions among the patients.

Features of angiography

Angiographic features of tubal pregnancy can be divided into 3 different vascular architectures: types I, II, and III. We observed no positive angiographic features in our type 1 cases (9 cases, 17.6%), and angiographic features reflecting type II (18 cases, 35.3%) were exhibited as follows. The tubal branches of the uterine arteries increased, thickened, and became circuitous, and no supply artery to the gestational sac was observed. An irregular patchy and villiform vascular staining was found at the tubal area of the parametrium in the parenchymal phase of DSA. Angiographic features of type III (24 cases, 47.1%) were observed as follows. The tubal branches of the uterine arteries increased markedly and became much more circuitous than with type II, and the small branches off the tubal branch were observed to

supply the gestational sac. Using angiography of the parenchyma, we observed in our typical cases round abnormal vascular staining of the tubal area, and round masses surrounded by small vessels from the tubal arteries.

The mean concentration of MTX in peripheral blood 0.5 hours after injection was 0.99 μmol/L (MTX dosage, 50 mg), 1.22 μmol/L (with 75 mg), and 1.76 μmol/L (with 100 mg). Six hours later, the mean blood concentrations of MTX remained at 10% of the concentrations at 0.5 hours. Twenty-four hours later, the mean concentrations were only 1% of those observed at 0.5 hours. Thirty-six hours after injection, no MTX was found in the blood of groups administered 50 or 75 mg. In the 100-mg group, we quantified 0.01 μmol/L in the blood 48 hours later.

DISCUSSION

The incidence of tubal ectopic pregnancy has risen up of late. However, because of the development of advanced medical techniques, current treatment methods of ectopic pregnancy are conservative therapy or the use of methotrexate, instead of traditional salpingectomy. The combination of intra-uterinoarterial infusion and embolization is an updated interventional method that has been developed in 2010s (5-7).

Tubal arteries comprise umbrella branches of the ovarian artery and the tubal branch of the uterine artery. These branches anastomose mutually and form 20 to 30 small branch vessels that distribute to and supply blood to the tubal wall. The blood supply to the embryo primarily comes from these small branch vessels; in addition, because they provide more than 85% of the blood supply to the fallopian tubes (8,9), the tubal branches of the uterine artery are the principal supply arteries to the pregnancy sac within the tube. The above description is, therefore, the basic theoretical principle underlying intra-uterinoarterial infusion and embolization that we adopted (9,10). We believed that it was thus reasonable to apply this method to treat any fertile embryo that developed at any site within the oviducts. Our results showed that using uterine artery embolization in association with methotrexate infusion to treat tubal pregnancy was very effective.

MTX is a commonly used agent that can result in embryonic loss by interfering with the synthesis of DNA through inhibition of dihydrogen folic acid reductase (also known as dihydrofolate reductase). However, there was no difference in the outcome between a single vs. repeated administration of MTX at the same dose. Calcium folinate (CF) must be used to reverse the toxicity resulting from marrow and gastric mucosal reactions caused by high doses of MTX. CF, however, should not be used if injecting MTX through the uterine artery; as the concentration of MTX was always less than 10 μmol/L in the peripheral blood when the dosage used was 50–100 mg.

Drug biodistribution to the fallopian tubes is not influenced by redistribution of the systemic blood when injecting the MTX via the uterine arteries (8,11). Although villus vessels in embryonic tissues within the tubes may receive the maximal dosage of infused MTX, because of the low binding of pharmaceutical proteins in this manner in veins, the concentration of free bioactive MTX may increase 2–22 fold, resulting in a quick embryonic death. In addition, artificial uterine embolism can cause a higher retention of MTX and obstruct the supply of blood to the embryonic tissues, similarly resulting in rapid necrosis and degeneration of the embryo. In addition, this technique can prevent the rupture of the embryonic sac and lethal hemorrhaging by stopping blood loss from tubal vessels. Therefore, we recommend that indications for the interventional method be expanded to not only include non-rupture of the embryonic sac and when life signs are stable, but also for those individuals with rupture of the embryonic sac who are at risk for inherent hemorrhaging or massive bleeding.

The determination of MTX dosage in the treatment of tubal pregnancy unfortunately lacks a feasible and unified standard. Kiss et al. (12) reported that there was no relationship between the absolute concentrations of β-HCG in the blood of women with tubal pregnancies and Ki-67, an index that represents the activity of the trophocyte. However, Ki-67 exhibits a strong relationship with dynamic changes in β-HCG. Such results may help to explain the success of interventional treatment with respect to our tubal pregnancy patients who showed high β-HCG levels, and the failure of the method on patients with low β-HCG levels. Dynamic changes in β-HCG may therefore predict the outcome of conservative treatment better than absolute β-HCG values (13). Natale et al. (14) studied the relationship between the depth of wall penetration by trophoblast

cells in tubal pregnancies with the days of menolipsis, the size of the associated mass, and serum β-HCG concentrations; and the authors found that the days of menolipsis and the size of the associated mass were not significantly correlated with the depth of tubal wall penetration among the different involved depths exhibited by tubal trophoblast cells. In other words, these 2 types of indices do not indicate the depth of tubal wall involvement by trophoblast cells, and serve little function in monitoring the therapeutic effects of conservative treatment on ectopic pregnancy. The dynamic fluctuations in β-HCG levels rather than mass size also appeared to demonstrate a close relationship with successful treatment in an ultrasonographic study (15). However, determining the MTX dosage from β-HCG levels or the size of the gestational sac is not statistically relevant; we determined the MTX dosage primarily by angiographic observations of the tubal pregnancy. To the type-II patients who showed notable gestational sac staining, we added to the dosage of MTX in order to destroy the fertile embryo via its rich supply of blood vessels. We recommend that the appropriate time to perform uterine artery infusion of MTX will not be later than 8 weeks of pregnancy, as the gestational sac at that time would have implanted in the deep mucosal or muscularis layers of the tubal wall, which have a rich blood supply and vital chorionic tissue. Such important endpoints could then become the statistical dependent variables that might in turn indicate the preferred dosage of certain chemotherapeutic drugs.

We found that the concentration of MTX in peripheral blood was very low after uterine artery embolization and methotrexate infusion; and that there were, in fact, very few toxic side-effects in our patients. We therefore believe that it is safe to use 100 mg of MTX despite not injecting calcium folinate.

Based upon our findings, restoration of the tubal wall would not be affected by uterine artery embolization in association with methotrexate infusion in patients with tubal pregnancy. After treatment the tube would therefore remain patent, with menstruation restored in these patients. Treatment may also not result in hypofunction of the ovaries or in avascular necrosis because the ovarian vascular bed is not embolized permanently by gelfoam grain. Ovarian hypofunction occurred in some of our patients using the conservative method--possibly resulting from overdosing with MTX, and potentially inhibiting follicular development. This effect could be avoided and controlled by using appropriate MTX doses as determined by angiographic features and β-HCG levels before the procedure. Using 50–100 mg of MTX, 47 cases in our study recovered their menstrual function without ovarian hypofunction.

Forty-seven of the 51 cases had their conditions resolved by our method, although when the ectopic mass size was ≥5 cm, 3 of 4 cases failed treatment; and thus the overall resolution rate for these patients was very low. However, when the mass size was ≤5 cm, regardless of how high the serum β-HCG concentration was and regardless of whether abdominal bleeding occurred or not, the resolution rate was very high [97.87% (46/47)]. Only 1 patient underwent laparoscopy for severe abdominal pain with a reduction in β-HCG levels, although her β-HCG concentration was ≤10000 mIU/mL and there was no abdominal hemorrhaging. Thus, we considered that the mass size in her case of more than 5 cm would not provide a good indication, while the higher β-HCG concentration would not be contraindicative.

During the procedures described herein, close attention must of course be given to minimizing the amount of radiation to which the mother and fetus are exposed during fluoroscopy. Skillful catheter manipulation, use of collimators, pulsed acquisitions, and limited total exposure time will guarantee achievement of this goal.

The advantages of our method lie in its minimal invasiveness, safety, efficacy, and few side-effects. Uterine artery embolization in association with methotrexate infusion can maintain adequate ovarian function and can therefore be an ideal alternative treatment for tubal pregnancy patients, especially for those at risk of massive hemorrhaging.

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