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Prophylactic Single-Dose Systemic Methotrexate Therapy for High-Risk Group in Persistent Ectopic Pregnancy After Laparoscopic Conservative Surgery of Tubal Pregnancy

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Abstract:

Backgroud: to evaluate whether the incidence of persistent ectopic pregnancy after laparoscopic conservative surgery can be reduced or prevented by prophylactic single-dose systemic methotrexate (MTX) in high-risk group.

Methods: Women who underwent laparoscopic conservative surgery for treatment of unruptured ectopic pregnancy, who agreed to participate in the study and who had risk factors for persistent ectopic pregnancy (n = 112) were randomly assigned to the prophylaxis or control group. In the prophylaxis group (n = 72), patients received a single dose of MTX, 1.0mg/kg intramuscularly, within 24 hours postoperatively. No treatment was used in the control group (n = 40). Both groups were followed with serial serum β-hCG titers; titers were measured on the frist postoperative day, then every 72 hours until levels were lower than 5mIU/ml.

Results: Four women had persistent ectopic pregnancy, no in the prophylaxis group (0%) and four among the controls (10%); this difference was statistically significant (P < 0.01). One women (1.4%) reported mild side effects after MTX, but these resolved spontaneously.

Conclusions: The incidence of persistent ectopic pregnancy was significantly reduced after a single prophylactic dose of systemic MTX administered postoperatively in high-risk group. This regimen is safe and can be used to decrease the extent of postoperative monitoring after conservative treatment of unruptured ectopic pregnancy.

Key words: high-risk group of persistent ectopic pregnancy/laproscopic conservative surgery/single-dose methotrexate.

Introduction

Ectopic pregnancy is very common gynecologic disease that needs urgent surgery and its incidence has been gradually increased. The reason of this recent increase of rate is unclear yet, but it seems to be related to the increase of artificial abortion, pelvic inflammatory disease, intrauterine device application and tubal ligation.

Traditionally salpingectomy has been used as classic treatment for ectopic pregnancy. However recently the conservative surgeries such as salpingostomy or fimbrial squeezing has been tried in infertility patients or in women who want to conceive more, because ectopic pregnancy can be detected earlier before tubal rupture by development of good diagnostic techniques. Furthermore, according to development of good laparocopic instruments and skill of laparoscopic operation, laparoscopic conservative operation can be successfully performed for ectopic pregnancy. Recently, laparoscopic conservative operation for ectopic pregnancy is more increased than the past, because it was reported that laparoscopic conservative operation had more advantages than laparotomy.

However, in some cases of conservative operation for ectopic pregnancies, persistent tubal pregnancies were found and further treatments were needed. The incidence of persistent ectopic pregnancy has been reported to range from 3% to 20%. There are some reports that systemic MTX treatment were effective in some cases for persistent ectopic pregnancies. However, MTX treatment after recognizing of persistent ectopic pregnancy needs long follow-up of serial checking β-hCG and high failure rate due to large tubal gestational product, and so it makes economic and psychological problems for the patients.

Therefore, it can be considered that the prevention of persistent ectopic pregnancy is better than treatment after development of persistent ectopic pregnancy. Recently for prediction of persistent ectopic pregnancy, there are several reports about the high risk groups of persistent ectopic pregnancy. If we can decrease the rate of persistent ectopic pregnancy by injection of MTX just after conservative surgery in this high-risk group, it will be very helpful and useful for prevention of persistent ectopic pregnancy.

Our study was performed to evaluate in a prospective and randomized manner whether the incidence of persistent ectopic pregnancy after laparoscopic conservative surgery can be reduced or prevented by prophylactic postoperative administration of a single intramuscular (IM) dose of MTX in high- risk group.

Material and Method

1. Material

All women who underwent laparoscopic conservative surgery for tubal gestation at Chonnam University Medical School were invited to participate in the study. Those with severe anemia, active liver or kidney disease, leukemia, bone marrow abnormalities, or allergy to MTX were excluded.

The criteria of high risk were as follows; 1) Not easily detached Gestational sac from the tube and profuse bleeding tendency during operation, 2) Hematosalpinx larger than 3 cm, 3) Cases treated by fimbrial milking, 4) Preoperative serum progesterone level exceeding 35 nmol/L, 5) Preoperative daily serum β-hCG changes above 100 mIU/ml or more than 40% of prior day level, 6) Preoperative serum β-hCG level greater than 3,000 mIU/ml. These criteria were made by modification of previous other reports.

Women who met the inclusion criteria and who agreed to participate gave informed consent were randomly assigned to either the prophylaxis group or the control group. Subjects in the prophylaxis group received a 1.0 mg/kg IM injection of MTX within 24 hours after completion of the operative procedure. The controls received no treatment. The postoperative follow-up was identical for both groups. Each woman was questioned about any symptoms and possible side effects related to medication and was instructed to return every third day thereafter for serum β-hCG assessment until levels became undetectable (less than 5 mIU/mL). The percent change of the β-hCG level was calculated between every two consecutive measurements. Persistent ectopic pregnancy was considered to be present when either the serum level of β-hCG increased or the decline was less than 20% between two consecutive measurements taken 3 days apart.

2. Laparoscopic conservative surgery (Figure 1.)

Operations were performed under general endotracheal anesthesia and dorsal lithotomy position. Three-puncture techniques were used for laparoscopic operations with one 10 mm umbilical and two 5 mm lateral suprapubic incision. We used 10 mm diameter and 0° panoview telescope (Richard Wolf, Germany) with CCD camera system (Toshiba, Japan).

After injection of 1:20 diluted vasopressin into the expanded part of tube by ectopic pregnancy, tubal wall of expanded portion was incised about 2-3 cm by using the needle bovie with 30-40 watt cutting-current at the opposite side of the mensentery. After then, the conception material was removed carefully by using suction-irrigator and grasping forceps. Bleeding point was controlled with using a microbipolar coagulator and a needle diathermy. Incision sites were sutured only in case that the bleeding was severe. In fimbrial pregnancy cases, conceptus was squeezed out by gentle tubal pressure.

After cleaning peritoneal cavity by warm lactated Ringer's solution, we filled the abdominal cavity with hydrocortisone and large amount of high molecular dextran in order to prevent adhesion.

3. Statistical analysis

The difference in the occurrence of persistent ectopic pregnancy between the study groups was analyzed using Fisher's exact test and χ^2 test. The differences in the mean age, durations of amenorrhea before operations, serum β-hCG levels before and after operation, and the durations until their serum β-hCG levels returned to the normal ranges were analyzed using student *t*-test.

Results

Among the 112 women who were enrolled, 72 were randomly assigned to the prophylaxis group and 40 to the control group. The mean ± standard deviation (SD) age of the women was 31.2 ± 3.27 years in the prophylaxis group and 130.66 ± 3.27 years in the control group; the groups did not differ statistically. In addition, the mean days of amenorrhea before operations (51.83 ± 7.93 and 49.2 ± 4.93 days in the prophylaxis and control groups, respectively), the mean serum β-hCG level just before operations (8902 ± 5155.4 and 9110.3 ± 9210.8 mIU/mL), and the mean serum β-hCG level which was measured on the first day after operations (2094.2 ± 3411.5 and 3843.7 ± 3072.3 mIU/mL) were not statistically different between the groups.

Of the 40 women in the control groups, four (10%) developed persistent ectopic pregnancy. But, none (0%) of the 72 who were treated MTX after laparoscopic conservative surgery developed persistent ectopic pregnancy. The difference in the incidence of persistent ectopic pregnancy between the groups was statistically significant ($P < 0.01$). Of the 4 women who developed persistent ectopic pregnancy in control group, three women were successfully treated with single-dose systemic MTX and the other one woman required a second laparoscopic operation due to failed MTX therapy.

The mean ± SD length of time required for the β-hCG level to decline below the detectable level was 29.6 ± 7.84 days for the patients in the prophylaxis group and 17.56 ± 4.68 days in the control group who had not persistent tubal pregnancy. This difference was statistically significant ($P < 0.01$). Only one subject (1.4%) in the prophylaxis group experienced side effect related to MTX: Leukopenia was developed. The side effects resolved spontaneously after 1 week and did not require any medical intervention.

Discussion

As a consequence of the current widespread availability of early diagnosis for ectopic pregnancy, the surgical attitude toward ectopic pregnancy has become more conservative, with an emphasis placed on tubal preservation. One consequence of this is an increased risk of postoperative complications, in the majority of cases because of persistent trophoblastic activity. Persistent ectopic pregnancy following laparoscopic conservative surgery has an incidence rate varying between 3 and 20%.

Persistent ectopic pregnancy may lead to life-threatening complications, such as intraperitoneal bleeding and tubal rupture, and may require a second surgical procedure. Therefore, it is important to define pre- and postoperative characteristics to identify patients at increased risk of having residual trophoblastic tissue after laparoscopic conservative surgery for tubal pregnancy. If preoperative serum β-hCG level is more than 3,000 mIU/ml or serum β-hCG level increases more than 40% per day, persistent ectopic pregnancy rate is increased due to lesser necrotic gestational sac and more invasiveness of trophoblast. Persistent ectopic pregnancy rate is also increased in patients with more severe bleeding tendency during the operation. It was also reported that the progressing rate to persistent ectopic pregnancy was more in fimbrial milking case than salpingotomy or salpingostomy. Hagstrom et al. reported that persistent ectopic pregnancy rate was increased if preoperative serum progesterone level was more than 35 nmol/L and daily change of serum β-hCG level was more than 100 mIU/ml.

Graczykowski and Mishell reported that MTX prophylaxis after linear salpingotomy reduced the incidence of persistent ectopic pregnancy. However, to prevent a few cases of persistent ectopic pregnancy, many women might be treated unnecessarily with systemic MTX. Therefore, we used the single-dose systemic MTX for the prevention of persistent ectopic pregnancy only in high risk group. Although the prophylactic use of MTX did not eliminate the need for postoperative follow-up, it contributes to the reduction of health care costs and may diminish patient discomfort. In addition, the prophylactic use of MTX may be very useful in the management of a noncompliant patient or one who is not available for postoperative follow-up. Another benefit of the prophylactic use of MTX after linear salpingostomy is an increase in the woman's chance to preserve the affected tube by reducing the risk of tubal damage or salpingectomy resulting from persistent ectopic pregnancy. This application may be especially useful in patients who have an unruptured ectopic pregnancy in the only functioning oviduct.

In our investigation, 10% of patients who did not treated with prophylactic systemic MTX were suffered from persistent ectopic pregnancy. But, persistent ectopic pregnancy was not developed in patients who treated with preventive single-dose systemic MTX. Only one patient in the prophylaxis group developed side effect related to MTX.

In conclusion, a single-dose systemic MTX therapy in high risk group after conservative laparoscopic surgery was found to be effective for prophylaxis against persistent ectopic pregnancy. The addition of prophylactic MTX, which is capable of reducing the occurrence of persistent trophoblastic activity, increases the effectiveness of laparoscopic conservative surgery for the conservative management of tubal pregnancy.

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