

Persistent Ectopic Pregnancy after Laparoscopic Salpingotomy: A Manageable Complication to Preserve Reproductive Tubal Function

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Objective: We evaluated whether or not persistent ectopic pregnancy (PEP) is a preventable complication after conservative laparoscopic surgery (salpingotomy) for tubal pregnancy.

Methods: We reviewed the medical records of 139 patients who underwent salpingotomy between December 1992 and December 2008.

Results: Out of 139 patients, 23 (16.5%) were diagnosed with a PEP after salpingotomy. When compared with 114 (82.5%) successfully treated patients, there were no differences in preoperative features (gestational age, serum human chorionic gonadotropin [hCG] levels, and ultrasonography findings) and postoperative reproductive potentials (ipsilateral tubal patency and pregnancy outcomes).

Conclusions: PEP, when appropriately treated, does not adversely affect tubal functions and postoperative fertility. We should uniformly perform an exact surgery paying careful attention to preserving the tubal function regardless of preoperative features.

Key words: tubal pregnancy, persistent ectopic pregnancy, laparoscopic salpingotomy, tubal function, methotrexate

INTRODUCTION

Recent advances in transvaginal ultrasonography and speedy quantification of serum human chorionic gonadotropin (hCG) have enabled us to make an early diagnosis of abnormal pregnancy, especially ectopic pregnancy. The majority of ectopic pregnancy consists of tubal pregnancy, where various therapies have been attempted to conserve the fallopian tube, providing valuable options for young women who desire to become pregnant again.

Out of the conservative therapies for tubal pregnancy (Table 1) [1], previously the surgery employed laparotomy, incision of the fallopian tube, removal of the hematoma, and microsurgical end-to-end anastomosis. Nowadays, when surgery is selected, laparoscopy should almost always be performed. Medical therapy is divided into systemic therapy (intramuscular, intravenous, or oral routes) and local tubal injection under laparoscopic or ultrasonographic guidance. Various drugs have been used, particularly methotrexate (MTX) [2]. Expectant therapy may be performed in patients with low serum hCG levels (less than 1,000 mIU/mL) [3]. Although it is still necessary for the optimum therapeutic strategy to examine the merits and demerits, as well as limitations of indications of individual regimens, laparoscopic conservative surgery (salpingotomy) is currently the most widely used [4-6].

Laparoscopic surgery has the following advantages: 1. relatively wide spectrum of indications, 2. easier operative conversion to laparotomy based on definite

diagnosis under direct view, 3. evaluation of intraperitoneal findings other than the ectopic pregnancy, and 4. lower invasiveness, which resulted in shorter hospital stay and faster return to everyday life, compared with laparotomy. However, as its disadvantage persistent ectopic pregnancy (PEP) can occur as a complication, because conservative consideration for the fallopian tube may result in the persistence of some residual trophoblasts even after the hematoma is removed [7, 8]. The reported incidence of PEP varies among studies, partly because no standardized definitions have been established. Attention should be paid to the possible occurrence of PEP because it may require additional treatment and also because, if not detected at an early stage, it may result in intraperitoneal hemorrhage and shock, which necessitates emergency surgery to resect the fallopian tube. Therefore, to predict the postoperative occurrence of PEP is a major problem that needs to be solved as soon as possible.

When detected under a stable systemic condition, PEP is mainly treated by, in addition to conservative surgery, systemic (intramuscular) therapy with MTX [9], which often results in conservation of the tubal functions. In such cases, the fallopian tube can be successfully conserved by a combination of conservative surgery and MTX therapy. On the other hand, PEP with relative low serum hCG levels, could be observed by expectant therapy without MTX.

Laparoscopic salpingotomy is a well-established procedure, and numerous studies have reported good prognoses in terms of preservation of the tubal

Table 1 Conservative treatment for tubal pregnancy

Surgical treatment
Laparotomic salpingotomy
Laparoscopic salpingotomy
Medical treatment (Methotrexate: MTX)
Systemic
Local injection
Expectant treatment

patency and successful subsequent pregnancies in successfully treated patients, i.e., those for whom ectopic pregnancy could be treated completely by surgery alone [10, 11]. However, there have been no reports on the postoperative incidence of PEP, and, therefore, no comparisons have been made between patients successfully treated by surgery alone and those who were diagnosed as having postoperative PEP. In the present study, we have elucidated the nature of PEP by a retrospective survey of the medical records in our department.

PATIENTS AND METHODS

We conducted a retrospective review of patients who underwent laparoscopic conservative surgery for tubal pregnancy between December 1992 and December 2008. Laparoscopic salpingotomy was performed under general anesthesia using the three-puncture technique: injection of vasopressin (5 units diluted in 100 ml of distilled water) into the mesosalpinx, a linear incision made at the antimesenteric site over the tubal swelling with scissor forceps, and evacuation of the contents followed by copious irrigation of the implantation site. To minimize damage to the fallopian tube, the incision was limited to 1.5 cm. All specimens were pathologically confirmed for the presence of normal trophoblastic tissue. The tubal incision was not sutured, because it is now well known that the absence of suturing is not associated with any difference in the incidence of development of postoperative tubal adhesions or the tubal patency rate [12]. Making the best use of direct observation via the laparoscope, the contralateral tube was evaluated. Additional manipulations, such as adhesiolysis, were also performed to obtain the best prognosis.

The patients were discharged on postoperative Day 3 or Day 4, and their serum hCG levels were monitored on an outpatient basis until the levels were undetectable (less than 10 mIU/mL). They were diagnosed as having PEP when the postoperative serum hCG level increased again or did not decrease for at least 1 week. Patients diagnosed as having PEP were investigated regarding the gestational age at the time of surgery, preoperative serum hCG levels, transvaginal ultrasonographic findings, and the implantation site to examine whether any of these factors might serve as predictors of PEP.

Further, patients with PEP in whom the fallopian tube could be successfully conserved were examined for postoperative tubal patency and outcome in terms

Table 2 Laparoscopic salpingotomy for tubal pregnancy

	139 Cases
Successful	114 (82.0 %)
Laparotomy (transitioned after Laparoscopy)	2 (1.4 %)
Persistent ectopic pregnancy (PEP)	23 (16.5 %)
MTX	15
Expectant	6
Salpingectomy	2

Dec. 1992–Dec. 2008

of the rate of subsequent pregnancies. The patency of the affected fallopian tube after treatment was examined by hysterosalpingography, transvaginal salpingosonography [13] or laparoscopic chromoperturbation. Postoperative pregnancy rate was calculated to 36 months. The analyzed groups consisted of patients with PEP (the PEP group), and the control group without PEP.

Statistical analysis

The results were analyzed using the χ^2 test. Statistical significance was set at the $P < 0.05$ level.

RESULTS

Of the 139 patients for whom laparoscopic salpingotomy was performed as conservative surgery for tubal pregnancy during the study period, the treatment was successful in 114 patients (82.0%). Of the remaining patients, 2 patients required intraoperative conversion to laparotomy because of hemorrhage, and 23 patients (16.5%) were diagnosed as having PEP (Table 2).

Of those 23 patients with PEP, 15 were given a systemic therapy with intramuscular MTX, 6 underwent expectant therapy, and 2 underwent additional laparoscopic salpingectomy. MTX was administered as a single dose at 50 mg/m² or 50 mg/body by intramuscular injection or in multiple doses at 20 to 25 mg/body/day for 3 to 5 consecutive days. In 21 patients for whom we attempted further conservative treatments (MTX or expectant therapy), we could preserve the affected tubes.

Fig. 1 shows the clinical course of a typical patient with PEP, in whom favorable lowering of the serum hCG was observed by postoperative Day 3, but the level subsequently increased again to about 700 mIU/mL, necessitating MTX therapy. The hCG level was measured undetectable on the 9th day after MTX administration. No difference was noted in the gestational age at the time of the surgery between the two groups with and without PEP.

PEP tended to occur more frequently in patients with relatively high serum hCG level and presence of fetal heartbeats, as detected by transvaginal ultrasonography. However, there was no statistical significance between the two groups (Tables 3, 4). No difference was noted in the implantation site between the two groups (Table 5). There was no difference in the percentage of patients with patency of the affected fallopian tube between the two groups (83.3% and 77.1%, respectively; Table 6). In regard to the posttreat-

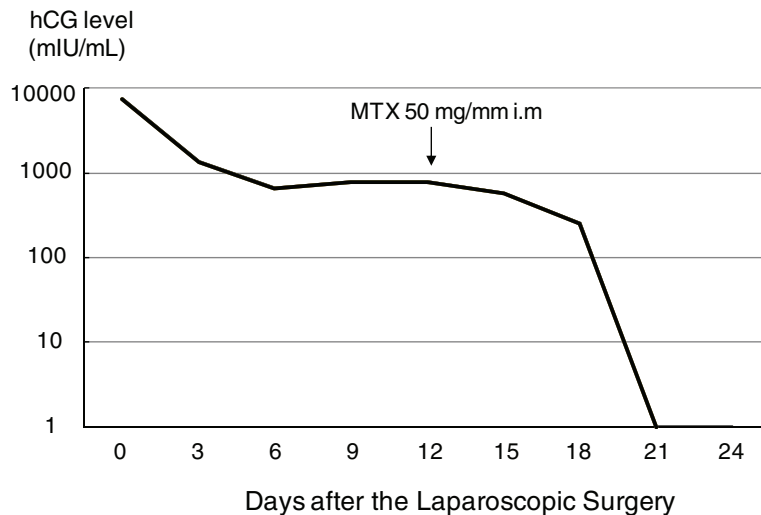


Fig. 1 A typical case of PEP

Table 3 Gestational age and hCG concentrations at the operations

	PEP (n = 23)	Control (n = 114)	p value
Gestational age (days)	47.3 ± 5.44*	48.2 ± 5.7*	NS §
hCG (mIU/mL)	6631.8 ± 8174.1*	5827.6 ± 7439.3*	NS §

*Values are mean ± standard deviation. § NS not statistically significant

Table 4 Ultrasonographic findings

	PEP (n = 23)	Control (n = 114)
Tubal GS with fetal cardiac activity	4 (17.4%)	10 (8.8%)
Tubal GS	5	24
Hematosalpinx	11	67
Intraperitoneal bleeding	2	5
Unidentified	1	8

ment outcome of subsequent pregnancies, there was no statistically significant difference in the percentage of patients who became pregnant again (44.4% and 48.9%, respectively) or that of patients who developed recurrent ectopic (tubal) pregnancies (16.7% and 17.8%, respectively) between the two groups (Table 7).

DISCUSSION

In the present patient series, PEP was noted in 16.5% of the patients who underwent laparoscopic conservative surgery for tubal pregnancy. However, there is, to date, no consensus in the definition of PEP. Seifer *et al.* [14] defined PEP as a morbid state characterized by continuous growth of villous tissue necessitating additional treatment, while DiMarchi *et al.* [15] defined it as a morbid state characterized by postoperative increase of the serum hCG levels or persistence of trophoblastic tissue in the affected fallopian tube.

We made the diagnosis of PEP in patients in whom the serum hCG levels began to increase again after

showing initial reduction, or persisted at the same level for 1 week or longer postoperatively. These circumstances are associated with persistence of trophoblastic tissue, considering that reduction of the serum hCG levels was observed immediately after the removal of trophoblastic tissue during surgery. Regarding the prediction of PEP, Spandorfer *et al.* [16] reported that less than 50% reduction of the serum hCG level on postoperative Day 1 is predictive of PEP, while Vermesh *et al.* [17] reported that a serum hCG level over 10% of the preoperative level on postoperative Day 9 is suggestive of PEP.

Is it possible to predict PEP before the operation? Kemmann *et al.* [18] reported that the likelihood of PEP was significantly increased when the serum hCG level increased more than 40% per day before surgery. However, in practical preoperative examination, tubal pregnancy is usually diagnosed by single analysis without repetition. PEP tended to occur more frequently in patients with high villous activity, as evidenced by an elevated serum hCG level and presence of fetal heart-

Table 5 Operative diagnosis with tubal location

	PEP (n = 23)	Control (n = 114)
Interstitial	1	6
Isthmus	2	7
Ampulla	20	99
Fimbria	0	2

Table 6 Ipsilateral tubal patency after treatment

	PEP (n = 12)	Control (n = 35)	p value
Patency rate	83.3% (10/12)	77.1% (27/35)	NS

Table 7 Pregnancy outcomes\$ after treatments

	PEP* (n = 18)	Control* (n = 90)	p value
Pregnancy rate	44.4% (8/18)	48.9% (44/90)	NS
Repeated tubal pregnancy rate	16.7% (3/18)	17.8% (16/90)	NS
Ipsilateral	2	9	
Contralateral	1	7	

*Excluding the IVF-ET (in vitro fertilization-embryo transfer) cases

\$ Postoperative pregnancy rate was calculated extending to 36 months.

beats in the gestational sac, as detected by transvaginal ultrasonography. However, there was no statistical significance between the two groups in the present study. PEP has also been noted to occur in patients with tubal abortion associated with low serum hCG levels. Further, PEP occurred irrespective of the implantation site, including the ampulla, isthmus, or interstitial portion of the fallopian tube. Based on these results, it seems likely that it is difficult to predict the occurrence of PEP prior to operating for an ectopic pregnancy.

Is it possible to prevent PEP? As a rule, we employ the following surgical techniques for ectopic pregnancy: vertical incision of the fallopian tube and removal of the hematoma (ectopic pregnancy mass); removal of the mass to the greatest possible extent; macroscopic confirmation of removal of the villi; laparoscopic observation of the lumen of the fallopian tube after the removal to ensure that no villous tissue remains, and copious irrigation with physiological saline solution. Despite these efforts, PEP occurred in 16.5% of the patients who underwent laparoscopic salpingotomy in the present case series. Excessive surgical techniques to prevent PEP should be avoided, because they may result in the fallopian tube incision exceeding the recommended length of 1.5 cm or excessive damage to the tubal mucosa. Preservation of the tubal functions and reproductive potential must be taken into account while performing fallopian tube conserving surgery.

Kaya *et al.* [19] reported that none of the 22 patients in their case series who received a local injection of 1 mg/kg of MTX into the fallopian tube developed PEP. Graczykowski *et al.* [20] reported that the incidence of PEP was 1.9% (1/54) in patients who received an intramuscular injection of 1 mg/kg of MTX within 24 hours postoperatively. These reports suggest that combined salpingotomy with adjuvant MTX therapy could be superior to MTX therapy administered after the development of PEP. However, if we may estimate, from these reports, that the PEP occurrence rate is 16.5%, the remaining 83.5% could be indicated to receive pharmacological treatment without the necessity

of undergoing surgery, which could be a fatal solution.

MTX therapy is intended to selectively damage villous tissue. It may be employed not only for the treatment of PEP, but also as primary treatment for tubal pregnancy. It serves as the conservative therapy of first choice for patients with tubal abortion associated with relatively low serum hCG levels [21–24]. Some authors reported, systemic MTX would offer better fertility prospects than laparoscopic salpingotomy [25]. However, informed consent must be obtained prior to administering MTX to these patients, after informing them of the possible adverse drug reactions such as, gastritis, rash, hepatic dysfunction, and bone marrow suppression, that might develop when the drug is administered as a systemic therapy or by intramuscular injection. Moreover, administration of this drug for this indication is not covered by the Japanese National Health Insurance. To avoid adverse drug reactions, PEP is sometimes treated by expectant therapy [26]. In such cases, patients are followed up without specific treatment unless the serum hCG levels show an increasing tendency. However, with expectant therapy, it tends to take a relatively long time before reduction of the serum hCG is observed, i.e., it is associated with a prolonged therapeutic period.

Does PEP adversely affect tubal functions and fertility? This is an important question, because it would be meaningless to conserve the fallopian tube unless its functions can be maintained. Therefore, it was of great significance to investigate the postoperative affected tubal patency rate and the subsequent pregnancy excluded with IVF-ET (in vitro fertilization-embryo transfer), in the present study. The results revealed the absence of any significant difference in the tubal patency rate between the two groups, with and without PEP, suggesting that PEP may not have any organic adverse effects on the fallopian tube. Similarly, there were no significant differences in the rates of subsequent pregnancies or recurrent ectopic pregnancies after the operation, which suggests that PEP may not adversely affect the tubal functions in terms of the

conservation of fertility

These results indicate, for the first time, that conservative surgery on the fallopian tube with MTX or expectant therapy should be considered in patients with ectopic pregnancy despite the risk of PEP, unless salpingectomy is indicated or intraperitoneal hemorrhage occurs. We conclude that PEP after laparoscopic salpingotomy is not a complication in terms of reproductive tubal function, as long as it is treated appropriately. Because PEP could not be predicted by preoperative features, surgeons should uniformly perform a delicate conservative operation with the complete and microscopic removal of all trophoblastic tissue.

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