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Preservation of tubal function following methotrexate treatment for ectopic pregnancy

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To evaluate methotrexate (MTX) administration as a conservative treatment for ectopic pregnancy, we reviewed the medical records of 248 cases (210 patients) of MTX treatment for tubal pregnancies at our department between December 1985 and December 2003, and compared its pregnancy prognosis with that of laparoscopic salpigotomy (59 patients). With the MTX treatment, 185 patients were successfully treated, and the subsequent pregnancy rate and ectopic pregnancy rate were 48.4 % and 18.4 %, respectively, while those rates were 49.2 % and 18.6 %, respectively, after the salpigotomy. These results suggest that MTX treatment is comparable to the more conservative operation. To clarify the (dys/) function of the ectopic implantation tubes and MTX-treated tube (s), we excluded patients who had a contralateral healthy tube, and extracted 40 patients as "the affected tube group", where the pregnancy-related parameters were not adversely affected. The findings suggest that MTX is not necessary to preserve tubal function.

Key words : tubal function, methotrexate, ectopic pregnancy, infertility, laparoscopy

INTRODUCTION

While salpingectomy is the traditional treatment for ectopic pregnancy, various conservative treatments are available for future fecundity [1, 2]. In the past, conservative abdominal surgery involved salpingotomy with hematoma removal, or partial salpingectomy with end-to-end anastomosis by microsurgery under laparotomy. Recent technological advances have enabled operations under laparoscopy, and standardized those methods for conservative surgery. On the other hand, pharmacological therapy is an alternative conservative method for ectopic pregnancy, primarily involving methotrexate (MTX), whether by systemic or local administration. The most conservative approach is an expectant management to observe the natural course without any active treatment, particularly in patients with low hCG levels.

We have systemically administered MTX, especially in cases of tubal pregnancy, expecting a favorable affect on tubal function to increase future fecundity. Even after the successful management of ectopic pregnancy by MTX, an important and difficult question is the extent to which tubal function was preserved, which should be fairly evaluated in this context. While prognostic pregnancies after treatment have been reported, these reports do not strictly assess the fecundity of the affected tube in as far as these cases include analysis of the healthy (unaffected by ectopic implantation) tube, i.e., the contralateral MTX-treated tube. In the present study, we analyzed previous records of ectopic pregnancies to determine the extent to which tubal function can be preserved following MTX treatment, paying careful attention to

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the fecundity of MTX-treated tubes in post-ectopic pregnancy.

The data was compared with the results of laparoscopic salpigotomy, which is thought to be a more conservative procedure in surgical treatment.

SUBJECTS AND METHODS

We reviewed the medical records of MTX treated tubal pregnancies at our department between December 1985 and December 2003.

We have systemically administered MTX, particularly in cases of tubal pregnancy, to utilize its specific pharmacological inhibitory action on chorionic tissue. This non-surgical approach to the treatment of the ectopic pregnancy might favor the preservation of tubal function after treatment, with a possible increase in future fecundity. The most common protocol of MTX administration is the multiple dose regimen, where intramuscular MTX of 20-25 mg/body/day is administered for 3 to 5 days [3-5], while another is the single dose regimen, where intramuscular MTX of 50 mg/m^2 of body is administered once [6-9]. Although patients were commonly managed under hospitalization, sometimes patients were treated in the out-patient clinic. Since MTX treatment does not have an immediate effect, and tends to have long therapeutic duration, its indication should be limited in cases of (1) unruptured gestational region, (2) relatively low hCG titer, (3) undetectable fetal heart movement by ultrasonic visualization, and (4) stable intraperitoneal bleeding upon frequent assessment. In addition, its side effects must also be taken into account, the most common of which is oral erosion or dermatitis, and rarely, liver dysfunction and bone marrow suppression of mild severity. In the period analyzed, 59 patients received laparoscopic salpigotomy, the indication of which was decided using the MTX criteria mentioned above.

We analyzed 248 cases of 210 patients, of which 214 cases (86.3 %) of 185 patients were successfully managed by MTX treatment alone, but 34 cases (13.7 %) required a subsequent surgical procedure (Table 1). The patients enrolled in this study were between 23 and 40 years old (31.9±4.6; Mean±S.D.) at their first MTX treatment, with a body mass index (BMI) of 21.7±1.2 (Mean±S.D.). At the first MTX treatment, 62.5 % had no past history of pregnancy, and the rest had already experienced previous pregnancy including ectpic pregnancy (20.5 %), live-birth delivery (12.5 %), and abortion (7.5 %). To evaluate pregnancy prognosis, the next pregnancy was monitored up to 60 months in longer cases.

Of the 185 patients successfully managed by MTX treatment, we excluded patients who had a contra-lateral healthy (unaffected by ectopic implantation) tube, and extracted 40 patients as "the affected tube group", who had only ectopic implantation-affected and MTX-treated tube (s), and analyzed the prognosis of their next pregnancy. Of these 40, 29 patients had a single MTX-treated tube after contra-lateral salpingectomy and 11 patients had double MTX-treated tubes after repeated ectopic pregnancy. Pregnancy prognosis was compared between the affected group and overall case analyzed at first.

To evaluate the efficacy of MTX treatment, analyzed data were compared with those of the cases treated by laparoscopic salpigotomy, as a representative procedure of conservative surgical treatment.

Statistical Analysis.

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

RESULTS

Pregnancy prognosis following MTX-treated ectopic pregnancy

Of the 185 patients successfully managed with MTX treatment alone, pregnancies were confirmed in 114 (61.6 %), 70.5 % of which were confirmed within 1 year following the MTX treatment (Table 1). Of these pregnancies, 77 were after natural coitus or intrauterine insemination (IUI), 25 were after *in vitro* fertilization and embryo transfer (IVF-ET), and the remaining 12 were after both (Table 2a; middle column). Excluding the IVF-ET cases, 89 patients (48.1 %) became pregnant after the treatment. In the subsequent pregnancies of these 89 patients, 55 patients had intra-uterine pregnancies, 21 had repeated ectopic pregnancies and the remaining 13 experienced both. Hence (Table 2b; middle column), the intra-uterine pregnancy rate

Table 1 Patients received systemic MTX# treatment for ectopic pregnancy.

Period	1985.Dec.～2003.Dec.	
	210 patients	(248 cases)
Age (years)*	31.9 ± 4.6 $	
BMI**	21.7 ± 1.2 $	
Successful MTX treatment	(185 patients)	214 case (86.3%)
1 set (20～25 mg for 3～5 days)		173
2 sets		28
3 sets		4
Single-dose (20 mg/m²)		9
Unsatisfactory MTX treatment	(25 patients)	34 cases (13.7%)
Resection after MTX (laparotomy)		11
Conservative operation after MTX (laparotomy)		8
Conservative operation after MTX (laparoscopy)		15

methotrexate

*Age when she was diagnosed as ectopic pregnancy at the first time.

** Body mass index (kg /m²)

$ Mean ± S.D..

Table 2 (a) Pregnancy following MTX# treatment

Patients	All n = 185	Affected tube group n = 40
Pregnancy	114	24
After normal coitus, or IUI*	77	15
After IVF-ET**	25	5
After either of the above	12	4
Total pregnancy rate	61.6 % (114/185)	60.0 % (24/40)
Pregnancy (except IVF) rate	48.1 % (89/185)	47.5 % (19/40)

methotrexate

* Intrauterine insemination of hasband's semen.

** In vitro fertilization and embryo transfer.

(b) Pregnancy after natural coitus or IUI* following MTX# treatment

Patients	All n = 185	Affected tube group n = 40
After natural coitus or IUI*	89	19
Intra-uterine	55	10
Intra- and extra-uterine	13	3
Extra-uterine	21	6
Intra-uterine pregnancy rate	36.8 % (68/185)	32.5 % (13/40)
Ectopic pregnancy rate	18.4 % (34/185)	22.5 % (9/40)

methotrexate

* Intrauterine insemination of husband's semen.

Table 3 (a) Pregnant cases following MTX[#] treatment

Method for pregnancy	Pregnancy	Intra-uterine	Extra-uterine
Natural coitus, or IUI*	127	90	37 (29.1 %)
IVF-ET**	50	42	8 (16.0 %)
Total	177	132	45 (25.4 %)

[#] methotrexate

* Intrauterine insemination of husband's semen.

** In vitro fertilization and embryo transfer.

(b) Pregnant cases following MTX[#] treatment in affected tube group

Method for pregnancy	Pregnancy	Intra-uterine	Extra-uterine
Natural coitus, or IUI*	25	16	9 (36.0 %)
IVF-ET**	14	10	4 (28.6 %)
Total	38	26	13 (33.3 %)

[#] methotrexate

* Intrauterine insemination of husband's semen.

** In vitro fertilization and embryo transfer.

Table 4 Pregnancy prognosis following conservative treatments

	MTX[#] (n=185)	Laparoscopic (n=59)
Pregnancy rate	48.4 % (89/185)	49.2 % (29/59)
Intra-uterine pregnancy rate	36.8 % (68/185)	40.7 % (24/59)
Ectopic pregnancy rate	18.4 % (34/185)	18.6 % (11/59)

[#] methotrexate

for subsequent pregnancies was 36.8 % (per patients) and the repeated ectopic pregnancy rate for subsequent pregnancies was 18.4 % (per patients).

Data presented above (and below) express the patient-base in the conventional manner. While some patients experienced repeated ectopic pregnancy, the number of patients was not equal to case count. Pregnancy-related rates are summarized in Table 3 (middle column).

Affected tube group

Pregnancies were confirmed in 24 of 40 patients (60.0 %) in the affected tube group. Of these pregnant patients, 15 pregnancies were after natural coitus or IUI, 5 were after *in vitro* fertilization and embryo transfer

(IVF-ET), and the remaining 4 were after both. Excluding the IVF-ET cases, 19 of the 24 patients (47.5 %) became pregnant after the treatment (Table 2a; right column). Of the next pregnancies of these 19 patients, 10 were intra-uterine pregnancies, 6 were repeated ectopic pregnancies and the remaining 3 experienced both types. Hence (Table 2b; right column), the intra-uterine pregnancy rate for subsequent pregnancies was 32.5 % (per patients) and the repeated ectopic pregnancy rate for subsequent pregnancies was 22.5 % (per patients).
Pregnancy-related rates are summarized in Table 3 (right column).

Comparison with cases treated with the laparoscopic salpigotomy

To evaluate the efficacy of MTX treatment, the key data analyzed above was compared with that of the cases treated with laparoscopic salpigotomy, as a representative procedure of conservative surgical treatment (Table 4).

DISCUSSION

Systemic administration of MTX for ectopic pregnancy is one of the pharmacological, non-surgical, treatments. We analyzed 248 such cases, where the patients hoped to have children, and the size of this cohort is second only to that of Lipscomb *et al*. [8]. MTX treatment was first designed to preserve tubal function, and thus outcomes following MTX treatment should be evaluated not only from the point of view of successful management by MTX treatment, but also as to the quality of the next pregnancy. MTX treatment reportedly provides 80-90 % successful management [4, 6-10] and also gives good prognoses for next pregnancies [4, 5, 11-13]. However, in those reports, the next pregnancy may have arisen through the healthy contra-lateral tube. Hence, we examined the fecundity of the affected tube by focusing on patients whose tube(s) was/were disordered by ectopic pregnancy and saved by MTX treatment and are now without a remaining healthy tube. While the overall prognosis of pregnancy did not significantly differ between the affected tube group and the total ectopic group, we clearly demonstrated that many intra-uterine pregnancies develop via “affected, or treated tubes”. This finding suggests that MTX treatment is a good procedure for preserving tube function.

Excluding the IVF-ET cases, approximately 50 % of cases conceived, and the repeat rate of ectopic pregnancy was about 20 % per patient, and 30 % per pregnancy. Although the repeat rate of ectopic pregnancy may appear high at 30 %, this conversely means that 70 % were intrauterine pregnancies. Taking into account the approximately 20% re-ectopic gestation risk even in IVF-ET cases, which indicates the cases with higher risk for ectopic gestation [14], we may consider MTX treatment good at preserving tubal function.

In addition to MTX treatment being available, ultrasonography and hCG measurement have also been developed and enable early precise diagnosis of tubal pregnancy [15-17]. Furthermore, in our reproductive unit, all patients hoped for a child and recorded their basal body temperature diligently, which enabled examination of the pregnancy early in the 5th gestational week. For suspicious ectopic pregnancies, we followed up frequently by ultrasonography with hCG testing. Using this protocol, we were able to diagnose approximately 90 % of ectopic gestations without diagnostic laparoscopy, hence indicating those requiring MTX treatment. A hCG titer of reportedly less than 3,000-5,000 IU/L is one of the most important indicators of MTX treatment [18-21]. The existence of fetal heart movement, suggesting a high hCG titer, may be a contraindication for MTX treatment. A visualized yolk sac was recently reported as an additional indicator for failure of MTX treatment [22].

When a diagnosis was uncertain, laparoscopy was performed and the therapeutic indication decided. However, once an ectopic pregnancy was diagnosed by laparoscopy, it was easily treated surgically whilst under laparoscopy. We sometimes experienced difficulty identifying the implantation site, even with an ultrasonographically diagnosed ectopic pregnancy; such cases clearly demonstrate the accuracy of ultrasonographical diagnosis. The outcome of MTX treatment is reportedly independent of laparoscopy or ultrasonography [23].

In past years, a multiple dose regimen (20-25 mg/body/day for 3 to 5 days) was the standard regimen for tubal pregnancy at our department. Recently, a single dose regimen has become popular, since it is convenient

and has less side effects. However, a multiple dose regimen was reported to be better than a single dose according to a meta-analysis [24]. In our department, we conducted more than 2 sets of a multiple dose regimen before 1993, after which we conducted only one set of the regimen. Nowadays, with established indication, we usually decide to perform surgery if one set produces unsatisfactory results.

In recent years, surgical laparoscopy has become a widely accepted conservative procedure. In fact, in cases of tubal pregnancy, we usually make a 1.5 cm vertical incision in the tube and remove the hematoma without further suture. This procedure, if successful, allows short hospitalization, is only a mildly invasive surgical procedure, and has rapid efficacy. In spite of the risk of retained chorionic tissue and surgical damage to the fallopian tube, we have been using surgical laparoscopy since 1992, and on second-look laparoscopy we found more cases of peritubal adhesion compared with MTX treated patients. This tendency seemed independent of suture closure of the tubal incision.

A comparison of conservative procedures, namely MTX treatment and conservative laparoscopy, by Hajenius *et al.* [5] suggested no difference in the rates of success and tubal patency in their randomized study, while Sowter *et al.* [25] found more cases required additional treatment following MTX treatment than conservative laparoscopy, even where hCG titers works as a pivotal indicator to select either therapy. There have been a few reports regarding the prognosis of pregnancy that compared the two procedures; Fernandez *et al.* [26] suggested a higher intra-uterine pregnancy rate with MTX treatment than conservative laparoscopy. As that report included local injection of MTX cases, we analyzed the prognosis of pregnancy between the conservative procedures in the present study (Table 4). In our cases, no difference in the next pregnancy rate and repetitive ectopic pregnancy rate was found between the two procedures. As conservative laparoscopy has not been shown to be superior to MTX treatment, we believe MTX treatment is the treatment of choice for cases with indications for MTX treatment.

Some recent reports have suggested the "wait and see" approach to treatment of cases with low hCG titer, i.e. indicated MTX treatment [27, 28]. Despite the merits of "no treatment", the success rates were 47.7 % [27] and 73.0 % [28], which seem unacceptably low to define as "successful" treatment. In our experience of the observation method, the presence of the hematoma tends to be prolonged, which suggests the possibility of adhesion after treatment. Thus, at present, when the site of the ectopic pregnancy is identified by ultrasonography with sustained hCG titer, even if low, we recommend MTX as the first treatment of choice.

In conclusion, MTX treatment for ectopic pregnancy appears good at preserving tubal function, and is comparable to the results from most conservative surgical procedures.

[revision was made as noted after the each comment]

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