

# BMJ Open Fertility outcome analysis after surgical management of tubal ectopic pregnancy: a retrospective cohort study

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## ABSTRACT

**Objectives:** To compare the subsequent fertility and risk of recurrence of an ectopic pregnancy (EP) in women who had had an EP, according to the type of surgical treatment they received—that is, salpingectomy, salpingostomy or tubal anastomosis.

**Methods:** A retrospective cohort study was carried out between January 2003 and September 2011 of 618 patients admitted to hospital with tubal EP and who had received surgical treatment (salpingectomy, n=434; salpingostomy, n=112; and tube anastomosis, n=72). Main outcomes included the first intrauterine pregnancy (IUP) and recurrent EP.

**Results:** The crude IUP rates up to 24 months after surgery were 55.5% for salpingectomy, 50.9% for salpingostomy and 40.3% for tubal anastomosis treatments. In the multivariate-adjusted model, with the patients receiving salpingectomy as the reference group, HR for patients after salpingostomy and tubal anastomosis treatments for IUP were 0.912 (95% CI 0.762 to 2.017) and 0.619 (95% CI 0.328 to 0.927), respectively. The 2-year cumulative recurrent EP rates were found to be 8.1% for salpingectomy, 6.3% for salpingostomy and 16.7% for tubal anastomosis treatments. Taking the patients receiving salpingectomy as the reference group, the patients who received tubal anastomosis had a positively higher risk of recurrent EP (HR=2.280; 95% CI 1.121 to 4.636) in univariate analysis. Adjustment for other potential confounders only slightly attenuated the HR.

**Conclusions:** The patients with an EP receiving tubal anastomosis treatments appeared to have a lower 2-year rate of IUP and a higher risk of recurrent EP after adjustment for other potential risk factors.

## INTRODUCTION

The incidence of ectopic pregnancy (EP) has increased to a level of 2% in developed countries and may seriously affect women's health and future fertility.<sup>1 2</sup> During recent decades, the diagnosis and efficacy of treatment of EP has progressed significantly.<sup>3–5</sup> Surgical intervention has long been the 'gold standard' for treatment of EP, although the medical management of unruptured EP is a safe and effective alternative.<sup>3</sup> Whichever

## Strengths and limitations of this study

- Controversy still exists about the role of surgical treatment in optimising subsequent fertility for patients with ectopic pregnancy (EP). This study evaluated the difference between tubal anastomosis and other types of surgical treatment for EP in China.
- Patients with EP were recruited from one hospital, which might have led to selection bias and limited external validity of the findings.
- This was a retrospective observational study and a randomised clinical trial is required to validate our findings.

treatment is used, in addition to its effectiveness, must preserve patients' fertility, and limit the risk of recurrence.

Surgical treatment for EP includes salpingectomy, salpingostomy and tubal anastomosis. However, controversy still exists about the role of surgical treatment in optimising subsequent fertility, which has been examined by previous studies.<sup>6 7</sup> Fertility after salpingectomy has been compared with salpingostomy in many retrospective studies or reviews.<sup>7</sup> In a population-based study, the crude cumulative rates of intrauterine pregnancy (IUP) differed according to the treatment method in univariable analysis ( $p=0.0079$ ), with a lower fertility after radical treatment compared with conservative treatments. However, the results were not statistically significant after adjustment for confounders.<sup>8</sup> In addition, the risk of recurrence according to the surgical techniques is still uncertain, with some retrospective studies showing higher recurrence rates after laparoscopic salpingostomy,<sup>9</sup> and others showing no difference.<sup>8 10 11</sup>

Tubal anastomosis restores patency of the fallopian tubes after sterilisation, in patients who wish to become pregnant. Pregnancy rates are between 54% and 88% for laparotomy and 31–85% for laparoscopy.<sup>12</sup>

Tubal anastomosis is also used as a method of surgical treatment for EP. However, there are few data evaluating the difference between tubal anastomosis and other types of surgical treatment.

This study aimed to compare the subsequent fertility and risk of recurrence of an EP in women who had had an EP, according to the type of surgical treatment they received—that is, salpingectomy, salpingostomy and tubal anastomosis.

## PATIENTS AND METHODS

### Patients recruited

We retrospectively reviewed patients with a tubal EP who were admitted to hospital for surgical treatment in the department of obstetrics and gynecology in Shengjing Hospital between January 2003 and September 2011. Three choices of surgical approach were available for EP: salpingectomy (removal of the fallopian tube), salpingostomy (incising the tube to remove the tubal gestation but leaving the remainder of the tube intact) and tubal anastomosis (removing abnormal tissue and reapproximating the healthy tubal segments with as little adhesion formation as possible). Indications for surgery included haemodynamic instability; suspicion of, or risk factors for, rupture; contraindications to methotrexate or failed medical treatment. The decision to choose salpingectomy, salpingostomy or tubal anastomosis was based on the pretherapeutic score proposed by Pouly *et al.*<sup>13</sup>

Before surgery, women underwent evaluation for EP and routine preoperative evaluation and preparation. During surgery, methylene blue was given to check whether or not the contralateral tube was open at operation. All interventions were carried out in accordance with the procedural standards of the participating hospital. All patients seen for EP are admitted to hospital for close follow-up. Patients excluded from this study were those with a prior history of EP, patients who did not report seeking pregnancy during follow-up and were using a contraceptive method, patients who had not wanted a baby or had not attempted to conceive, those who had received bilateral salpingectomy or hysterectomy, patients who had received medical treatment with methotrexate and patients receiving in vitro fertilisation; 767 patients met our inclusion criteria. Of these, 149 patients were not included in the study because they were lost to follow-up (n=114; 14.9%) or because they were aged  $\geq 45$  years. Finally, reproductive outcome was analysed for 618 patients (salpingectomy, n=434; salpingostomy, n=112; and tubal anastomosis, n=72). The study was approved by the ethical committee of Shengjing Hospital of China Medical University and all patients gave their written consent to participate in the study.

### Data collection

A standard case report form at baseline was developed to assess related information for each woman and included: sociodemographic characteristics; sexual,

gynaecological, reproductive and surgical histories; smoking habits; condition of conception (eg, contraception, ovulation induction); characteristics of the EP and treatment procedures used.

To identify persistent trophoblast, serum human chorionic gonadotrophin (human chorionic gonadotropin (hCG), expressed in IU/L) was measured postoperatively until undetectable concentrations were reached in all study groups. Persistent trophoblast is defined as postoperative rising or plateauing of serum hCG concentrations.<sup>14</sup> Patients were contacted and asked whether they had a new pregnancy up to 24 months, were pregnant again, the outcome of subsequent pregnancies and the use of contraceptives and medical measures related to infertility. All IUPs were taken into account regardless of the outcome. For the fertility study, any recurrence was ignored and the follow-up continued and conversely for the recurrence study. Only the first IUP or the first recurrence was used for this analysis.

### Statistical analysis

Continuous variables are presented as the means and SD and categorical variables are expressed as percentages. We compared patients' baseline characteristics according to surgical treatment by  $\chi^2$  tests for categorical variables and one-way analysis of variance for continuous variables. The persistent trophoblast and future fertility outcomes (the 2-year cumulative rates of recurrent EP and spontaneous IUP) were calculated for each of the three surgical treatments. Cox proportional hazards models were used to calculate HRs with 95% CIs for the associations between surgical treatments and fertility outcomes, with the patients receiving salpingectomy as reference group. Univariate and multivariate analysis were used to evaluate the association between the types of surgical treatment and first IUP or the first recurrence.

In the multivariate model, we adjusted for age, surgical treatment, marital status, smoking habits, previous spontaneous abortion and induced abortion, history of live birth, tubal disease and normal contralateral tube. Next, we repeated the multivariate analysis for a subgroup of patients after exclusion of those with an abnormal tube in the salpingectomy group. The proportionality assumption was evaluated by scaled Schoenfeld residuals and the global fit of the models was evaluated by graphically examining the cumulative hazards function relative to the Cox–Snell residuals. All analyses were performed with SPSS statistical software V.13.0 (SPSS Inc, Chicago, Illinois, USA). A p value  $< 0.05$  was accepted as indicating statistical significance.

## RESULTS

Treatments were salpingectomy for 434 women, salpingostomy for 112 and tubal anastomosis for 72. The mean $\pm$ SD ages of patients receiving salpingectomy, salpingostomy and tubal anastomosis were 29.4 $\pm$ 5.1 years, 28.8 $\pm$ 4.9 years and 28.1 $\pm$ 6.0 years (p=0.116),

respectively. Characteristics of the patients in this study are shown in [table 1](#). The 114 patients who were lost to follow-up had a baseline age (median: 30.2 vs 29.1 years;  $p>0.05$ ) similar to that of the patients included in the study ( $n=618$ ). There was no significant difference in the proportion of patients receiving salpingectomy, salpingostomy or tubal anastomosis between the patients who completed the study and those who were lost to follow-up (434:112:72 vs 76:23:15,  $p>0.05$ ).

The crude IUP rates up to 24 months after operation were 55.5% ( $n=241$ ) for salpingectomy, 50.9% ( $n=57$ ) for salpingostomy and 40.3% ( $n=29$ ) for tubal anastomosis treatments. The cumulative IUP rates differed according to the surgical treatment methods in univariate analysis ( $p=0.049$ ), with a lower fertility after tubal anastomosis than after salpingectomy treatment (HR=0.469, 95% CI 0.285 to 0.772). No statistically significant difference was found in the IUP rates between the salpingectomy and salpingostomy groups ( $p=0.276$ ). Adjustment for other potential confounders only slightly attenuated the HR ([table 2](#)). In the multivariate-adjusted model, HR for patients with salpingostomy and tubal anastomosis treatments for IUP were 0.912 (95% CI 0.762 to 2.017) and 0.619 (95% CI 0.328 to 0.927), compared with the patients receiving salpingectomy as the reference group ([table 2](#)).

[Table 3](#) shows the risk of persistent trophoblast and recurrent EP after different surgical treatments. Persistent trophoblast occurred significantly more often in the salpingostomy (9.8%) and tubal anastomosis (8.3%) group than in the salpingectomy group (1.8%) ([table 3](#)). The 2-year cumulative recurrent EP rates were found to be 8.1% for salpingectomy, 6.3% for salpingostomy and 16.7% for tubal anastomosis treatments. With the patients receiving salpingectomy as the reference group, the patients who received tubal anastomosis had a higher risk of recurrent EP (HR=2.280, 95% CI 1.121 to 4.636) in univariate analysis. Adjustment for other potential confounders only slightly attenuated the HR ([table 3](#)). There was no significant difference for the risk of recurrent EP between salpingectomy and salpingostomy treatments.

In the next subgroup analysis, 327 patients in salpingectomy group with a normal tube had an increased crude IUP rate ( $n=190$ , 58.1%) and a similar recurrent EP rate ( $n=26$ , 8.0%). With the patients receiving salpingectomy with a normal tube as the reference group, the multivariate-adjusted HR for patients with tubal anastomosis for IUP and recurrent EP were 0.584 (95% CI 0.308 to 0.891) and 1.653 (95% CI 1.079 to 4.637), respectively. There was no significant difference for the IUP and risk of recurrent EP between salpingectomy and salpingostomy treatments and the multivariate adjusted HRs were 0.947 (95% CI 0.771 to 2.109) and 0.984 (95% CI 0.629 to 1.985), respectively.

## DISCUSSION

EP is one of the important reasons for maternal morbidity and mortality in the first trimester, accounting for a 13% mortality rate.<sup>15</sup> The effect of different surgical management strategies on subsequent fertility after tubal EP is still controversial.<sup>16 17</sup> Major findings of our study were that patients with an EP receiving tubal anastomosis treatment seemed to have a lower 2-year rate of IUP and a higher risk of recurrent EP after adjustment for other potential risk factors.

Many retrospective studies compared subsequent fertility after salpingectomy versus salpingostomy. According to some studies, there was no statistical difference in subsequent fertility.<sup>18 19</sup> However, with the development of the laparoscopic technique, a trend in favour of conservative surgical treatment was noted by some retrospective studies.<sup>9</sup> Turan showed that there is no significant difference in IUP rates up to 24 months between salpingectomy (65.2%) and salpingostomy (60.1%) groups in younger Turkish women.<sup>11</sup> One retrospective cohort study found that the 7-year cumulative IUP rate was lower in women who had undergone salpingectomy than in those who had undergone salpingostomy.<sup>10</sup> In our study, patients receiving salpingostomy seem to have a lower rate of IUP (50.9%) than patients receiving salpingectomy (55.5%). However, consistent with other studies,<sup>20 21</sup> there was no statistically significant difference.

**Table 1** Clinical characteristics of women with an ectopic pregnancy according to surgical treatment\*

Characteristics	Salpingectomy	Salpingostomy	Tubal anastomosis	p Value
Number	434	112	72	
Age (years), mean±SD	29.4±5.1	28.8±4.9	28.1±6.0	0.116
Unmarried, n (%)	98 (22.6)	20 (17.9)	22 (30.6)	0.133
Smoking habits, n (%)	39 (9.0)	9 (8.0)	7 (9.7)	0.920
Previous spontaneous abortion, n (%)	26 (6.0)	4 (4.2)*	5 (11.1)#	0.271
Previous induced abortion, n (%)	184 (42.4)	30 (26.8)	25 (34.7)	0.008
History of live birth, n (%)	164 (37.8)	28 (29.2)*	22 (48.9)#	0.030
Tubal disease, n (%)	49 (11.3)	14 (12.5)	11 (15.3)	0.616
Normal contralateral tube, n (%)	327 (75.3)	72 (64.3)	32 (44.4)	<0.001

\*Data based on 95 women.

#Data based on 45 women.

**Table 2** Univariate and multivariate analysis factors influencing intrauterine pregnancy

Treatment	Intrauterine pregnancy, n (%)	HR and 95%CI			
		Univariate	p Value	Multivariate*	p Value
Salpingectomy (n=434)	241 (55.5)	1.000 (reference)			
Salpingostomy (n=112)	57 (50.9)	0.831 (0.602 to 1.156)	0.276	0.912 (0.762 to 2.017)	0.308
Tubal anastomosis (n=72)	29 (40.3)	0.469 (0.285 to 0.772)	0.003	0.619 (0.328 to 0.927)	0.039

\*Adjusted by age, marital status, smoking habits, previous spontaneous abortion and induced abortion, history of live birth, tubal disease and normal contralateral tube.

Laparotomy microsurgical tubal reanastomosis after tubal sterilisation has been performed for more than 30 years, with recently reported pregnancy rates of 60–91%.<sup>22</sup> Koh and Janik<sup>23</sup> reported a 71% pregnancy rate during a follow-up of 12 months after laparoscopic microsurgical tubal anastomosis. Tan and Loh<sup>24</sup> also reported that the pregnancy rates with this same surgery were 47.4% (<6 months), 57.9% (6–12 months), 68.4% (12–48 months) and 73.7% (>48 months). The IUP rate of our study was 40.3%, which is lower than the results of other studies. Different population characteristics may partly explain the disparity. In addition, there are few studies that compare the fertility outcomes among tubal anastomosis and salpingectomy or salpingostomy in a similar study. In our study, with the patients with an EP undergoing salpingectomy as reference, those receiving tubal anastomosis had a lower risk of IUP.

In addition, recurrent EP was associated with mortality and morbidity, but the risk of recurrence according to the surgical technique used is still under discussion, with conclusions divided. Some found a higher risk of recurrence after laparoscopic salpingostomy.<sup>9</sup> For others, the rate of recurrence was similar after salpingectomy and salpingostomy.<sup>10–25</sup> In our study, the highest recurrent

EP rates were found in the tubal anastomosis group (16.7%) and the patients receiving this treatment had a higher rate of recurrent EP after adjustment for other potential risk factors. In addition, EP recurrence rates for surgical treatment with salpingectomy (8.1%) and salpingostomy (6.3%) were similar.

There are two possible explanations for the lower IUP rate and higher EP recurrence after tubal anastomosis. First, a tubal surgery scar after tubal anastomosis can easily cause stenosis and tubal blockage, which interferes with sperm fertilisation of eggs in the fallopian tube, resulting in blastocyst formation in the fallopian tube. Thus, there would be a lower IUP rate and higher recurrence of EP after tubal anastomosis. Second, other potential risk factors may produce these results. In summary, the mechanisms of lower IUP rate and higher EP recurrence after tubal anastomosis are still unclear and further study is needed.

Some limitations of the study should be considered. First, the patients with an EP were recruited from one hospital, which might have led to selection bias and limited external validity of the findings. The results were further examined in a population-based study. Second, this is a retrospective observational study and additional randomised clinical trials are needed to validate our

**Table 3** Univariate and multivariate analysis for persistent trophoblast and recurrent ectopic pregnancy (EP) according to surgical treatment

Treatment	n (%)	HR and 95% CI			
		Univariate	p Value	Multivariate*	p Value
Salpingectomy (n=434)					
Persistent trophoblast	8 (1.8)	1.000 (reference)		1.000 (reference)	
Recurrent EP	35 (8.1)	1.000 (reference)		1.000 (reference)	
Ipsilateral tube	16 (3.7)	1.000 (reference)		1.000 (reference)	
Contralateral tube	19 (4.4)	1.000 (reference)		1.000 (reference)	
Salpingostomy (n=112)					
Persistent trophoblast	11 (9.8)	4.613 (2.942 to 7.285)	<0.001	4.078 (2.113 to 6.959)	<0.001
Recurrent EP	7 (6.3)	0.760 (0.328 to 1.760)	0.522	0.983 (0.629 to 1.982)	0.767
Ipsilateral tube	5 (4.5)	1.179 (0.653 to 1.621)	0.358	1.054 (0.359 to 1.747)	0.524
Contralateral tube	2 (1.8)	0.697 (0.231 to 1.125)	0.078	0.703 (0.307 to 1.351)	0.219
Tubal anastomosis (n=72)					
Persistent trophoblast	6 (8.3)	3.094 (1.782 to 4.801)	<0.001	2.981 (1.653 to 4.478)	<0.001
Recurrent EP	12 (16.7)	2.280 (1.121 to 4.636)	0.023	1.654 (1.080 to 3.718)	0.047
Ipsilateral tube	9 (12.5)	3.782 (1.829 to 4.612)	0.017	3.214 (1.507 to 4.731)	0.038
Contralateral tube	3 (4.2)	0.961 (0.457 to 1.501)	0.814	0.980 (0.421 to 1.593)	0.769

\*Adjusted by age, marital status, smoking habits, previous spontaneous abortion and induced abortion, history of live birth, tubal disease and normal contralateral tube.

findings. Third, we measured the outcomes of IUP and recurrence of EP up to 24 months, but a longer follow-up is needed.

In conclusion, the results of this study suggest that the tubal anastomosis group had a lower rate of IUP and a higher rate of recurrent EP. The choice of surgical treatment should be comprehensively evaluated in clinical practice.

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**Competing interests** None.

**Patient consent** Obtained.

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**Data sharing statement** No additional data are available.

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