



The Effect of Therapy for Tubal Ectopic Pregnancy on Subsequent Reproductive Capacity and the Frequency of Recurrence

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Abstract

Objectives: Ectopic pregnancy (EP), which is defined as the implantation of an embryo outside the uterine cavity, occurs with notable frequency in the first trimester (especially between the sixth and ninth weeks of gestation) and can cause severe intra-abdominal bleeding and death. Treatment options include salpingotomy with tubal preservation, transampullar expression of the EP ("milking" of the tube), wedge excision with the chance for tubal reconstruction in a subsequent surgery and partial or complete salpingectomy. Drug treatment with Methotrexate (MTX) is also an option.

Materials and Methods: In this retrospective study, we analysed the data of patients who had been treated for an EP in the gynaecological department of Hanover Medical School, Germany, between 2006 and 2013.

Results: We observed a pregnancy rate of 73.1% in those who wanted to have children following EP treatment, and 33 women (28.2%) became pregnant a second time. The birth rate after EP increased from 67.1% in the first subsequent pregnancy to more than 80% in the second. The frequency of recurrent EP was 6.6% in the first pregnancy after surgery and 3% in the second.

Conclusions: These data are encouraging for EP patients, who have a good chance to conceive, whether spontaneously, after tubal reconstructive surgery or using in vitro fertilisation (IVF).

Keywords: Ectopic tubal pregnancy, Sterility, Reproductive capacity, Recurrence rate, Frequency of recurrence

Introduction

Ectopic pregnancy (EP), defined as the implantation of an embryo outside the uterine cavity, is a notable complication in the first trimester (especially between the sixth and ninth weeks of gestation) and can cause severe intra-abdominal bleeding and death.

In the United States, from 2013–2017, there were 0.36 EP deaths per 100 000 live births. In addition, from 1998–2007, excessive haemorrhage, shock or renal failure accompanied 67.4% of the EP deaths of hospitalized women (1). Clinical symptoms of EP are pain in the lower abdomen and vaginal bleeding in combination with a positive pregnancy test. In the case of rupture of a fallopian tube, patients may show signs of haemorrhagic shock, including dyspnoea, hypotonia and tachycardia (2). A prior EP may also negatively affect female fertility due to damage or loss of the fallopian tube.

More than 95% of all EPs are tubal pregnancies, 1%–2% are located in the intramural part of the uterus and a small number are ovarian, cervical or abdominal pregnancies. The very rare case of a combination intrauterine and EP, called a heterotopic pregnancy, occurs in 1 of every 3000 EPs (3). The aetiology of EP is multifactorial, including anatomic obstruction of the fallopian tube, malfunction of

the tubal mobility and molecular factors (4).

The main risk factors for the occurrence of EP are pelvic inflammatory diseases (chlamydia trachomatis, and gonorrhoea), previous sterilisation, application of an intrauterine device (IUD), previous tubal or intrauterine surgeries, previous EP, endometriosis, smoking and assisted reproductive techniques (ART) such as in vitro fertilisation (IVF) when performed in women with tubal pathologies (5–8). The prevalence of EP has increased worldwide due to improved diagnostic capabilities, increasing use of ART and tubal surgery and increased maternal age (2).

The rate of EP following natural conception is approximately 2%, whereas the rates following ART are from 2.1%–11% (9). In Germany, following IVF, the highest EP rate is 4.5%, which is in smokers under age 30 who have tubal pathology (8). Tubal surgeries also can cause EP, with an incidence rate of up to 40%, depending on the location, type and severity of the tubal pathology and the surgical procedure performed (10).

Often, verifying an EP is difficult. The diagnosis is made using a combination of the clinical symptoms, vaginal ultrasound and serum biochemistry, although there is no existing human chorionic gonadotropin (hCG) value



that defines a particular location of the EP. Differential diagnoses are pregnancies of unknown localisation, very early intrauterine pregnancies and early abortions (11).

The most common therapy for EP is surgical intervention by laparoscopy or in severe cases laparotomy. Treatment options include salpingotomy with tubal preservation, transampullar expression of the EP ("milking" of the tube), wedge excision with the chance for tubal reconstruction in a subsequent surgery and partial or complete salpingectomy (12). Drug treatment options include Methotrexate (MTX) to treat persistent trophoblastic tissue or persistently elevated hCG levels after surgery and in pregnancies of unknown localisation (13).

It must be noted that the organ-preserving procedure salpingotomy includes an increased risk for persistence of trophoblastic tissue in 4%-15% (3). Another risk of salpingotomy is the recurrence of EP in a subsequent pregnancy, which is important, considering that a high percentage of patients want to become pregnant. The literature describes the recurrence rate up to 15% (2,3,14,15).

The present study investigated the effects of various EP treatments on both subsequent fertility capacity (including pregnancy and birth rates) and the frequency of recurrent EP in subsequent pregnancies.

Materials and Methods

This retrospective study analysed the data of patients who had been treated for an EP in the gynaecological department of Hanover Medical School, Germany, between 2006 and 2013.

Inclusion and Exclusion Criteria

The study included all patients who had been treated for an EP in the department by surgery or medical therapy. Therefore, there were no exclusion criteria.

Primary outcome parameters included the following.

- The post-treatment pregnancy rate depending on the type of EP treatment.
- The post-treatment frequency of EP recurrence, both in total and depending on the type of EP treatment used.

Secondary outcome parameters included the following.

- The post-treatment pregnancy rates depending on the age of the woman.
- The post-treatment pregnancy rates depending on the method of conception (ART or natural conception).
- The post-treatment birth rate.

Data Collection

The following data were collected from the patients' charts: age; body mass index (BMI); hCG level at the beginning of EP treatment; method of surgical treatment (partial or total salpingectomy, wedge excision, salpingotomy, milking of the tube, retrieval of tubal abortion); drug treatment with MTX; intraoperative blood loss; duration

of hospital stay; and previous surgeries on the fallopian tubes or uterus.

The patients were surveyed by a questionnaire regarding the following items: number and side of previous EPs; previous surgeries; adnexitis or pelvi-peritonitis; previous surgical procedures/reconstruction of the tubes; nicotine consumption; number of pregnancies before and after the present EP; the method of conception (natural fertilization or ART); and the outcome of post-therapeutic pregnancies (full birth, abortion, another EP recurrence).

Statistical Analysis

The statistical analysis was conducted in collaboration with the Institute of Statistics of the Leibniz University of Hanover, Germany. Depending on the variables, statistical analysis was performed using correlation analysis, and the significance of the correlations was tested using the corrected contingency coefficient. In addition, linear regression analysis or logistic regression analysis was performed using the statistics software R (<http://www.cran.r-project.org>). Statistical significance was achieved if $P < 0.05$.

Results

Types of Therapy

The questionnaire was sent to 384 patients who had been treated for an EP, and 62 letters were returned as undeliverable, so 322 questionnaires were received. Of these, 124 were returned (a 38.5% response rate). In 7 cases, the patient's file or the questionnaire was largely incomplete, so the data could not be used. Therefore, the data of 117 patients were analysed. As Table 1 shows, 7 therapies used for EP were identified. More than 50% of the patients had undergone some type of salpingectomy, with 33% having been treated by total salpingectomy and 22% by partial salpingectomy. In addition, salpingotomy as an organ-saving surgery had been performed in 25% of cases and a wedge excision in 10%. Milking of the fallopian tube or MTX administration had been performed only in very rare cases. Finally, 5.1% of patients had experienced a tubal abortion.

The median age of the patients was 32.6 years (20-42 years), and the median BMI was 24.1 (19-40). The patients had 1.4 pregnancies (range: 0-9) before the EP occurred, and 92 (78.6%) had given birth to at least one child previously. Of the 117 patients, 20 (17.1%) had at least one previous EP: 16 patients had 1, 3 had 2 and 1 had 3 previous EPs. Of the 117 patients, 18 (15.4%) smoked from 3-20 cigarettes per day. The average hospital stay had been 3.5 days (range: 0-9). There was a statistically significant relationship between the type of therapy and the duration of hospital stay, with the longest duration being for total salpingectomy, followed by salpingotomy and partial salpingectomy. The shortest durations had been for milking and conservative therapy with MTX. These differences were highly statistically significant,

Table 1. Absolute and Relative Rates of Various Ectopic Pregnancy Therapies

	Total Salpingectomy	Salpingotomy	Partial Salpingectomy	Wedge Excision	Tubal Abortion	Milking	Methotrexate	Total
Number of patients	39	28	26	11	6	5	2	117
Percentage	33.33	23.93	22.22	9.40	5.13	4.27	1.71	100

with a corrected coefficient of contingency of 0.7078 ($P=0.0023$).

The median loss of blood had been 1.03 pints (± 0.49) on the haemoglobin scale (preoperative value [12.86] minus postoperative haemoglobin value [11.83]). Only 2 patients with ruptures of the fallopian tubes had needed transfusions of 2 and 4 erythrocyte concentrates, respectively, due to the threat of haemorrhagic shock and preoperative haemoglobin values of 5.8 and 7.7 g/dL, respectively.

Post-treatment Pregnancy Rates

Of the 117 patients, 79 became pregnant at least once after surgical intervention or MTX therapy, for a post-treatment pregnancy rate of 67.5%. In addition, 33 women (28.2%) became pregnant a second time.

Of the 117 patients, 79 were age 34 or younger (67.5%), and 38 were age 35 or older (32.5%). Those age 34 or younger had a pregnancy rate of 77.2% ($n=61$), and those 35 or older had a pregnancy rate of 47.4% ($n=18$).

The subgroup analysis investigated the pregnancy rate depending on the desire to become pregnant. Of the 117 patients, 108 wanted to become pregnant again after EP treatment, while 9 had no plans for more children. The pregnancy rate in this subgroup wanting children was 73.1% (79/108). Table 2 shows the rates depending on type of EP therapy. The corrected coefficient of contingency shows a very high correlation between the desire to have children and the pregnancy rate after an EP (0.5434) ($P<0.001$). There was no statistical significance between the type of therapy and the post-treatment pregnancy rate. The rate of those who became pregnant at least once following salpingotomy was remarkably high, 85.7%, and the rates after partial or total salpingectomy were 70.8% and 61.8%, respectively.

Another subgroup analysis addressed the method of conception, natural or IVF/ART, following EP treatment. It may be necessary to undergo ART if both fallopian tubes are damaged or removed or if surgical tubal reconstruction could not be attempted or was

unsuccessful. Other indications for ART include male infertility, ovarian diseases or endometriosis. The study analysed 76 pregnancies, as data on conception method were unavailable in 3 cases. Of the 76 cases, 22.4% of the patients became pregnant following ART, and 77.6% became pregnant spontaneously.

Post-treatment Birth Rates and Pregnancy Complications Including EP Recurrence

The birth rate in the first pregnancy following the EP treatment was 67.1%, and in the second pregnancy 81.8%. Regarding the rate of complications in the first pregnancy after EP therapy, we found abortions in 26.3% of the pregnancies, a recurrent EP in the same tube in 2.6%, EP in the contralateral tube in 2.6% and intramural pregnancies in 1.38%. In summary, the EP recurrence rate was 6.58% in the first post-therapeutic pregnancy, and in the second post-therapeutic pregnancy, there were abortions in 15.2% and recurrent EPs in 3.0%. Therefore, the EP recurrence rate in the second post-therapeutic pregnancy was markedly lower than that in the first.

For the second pregnancy after EP, the corrected coefficient of contingency had a value of 0.4966, indicating a statistically significant relationship between the EP recurrence rate and the conception method with a lower EP recurrence rate after natural conception ($P=0.0312$). However, the study found no statistically significant relationship between the EP recurrence rate and the conception method for the first pregnancy after EP therapy. Table 3 shows the absolute rate and the percentage of recurrent EPs after EP therapy for both conception methods (natural conception or ART).

Regarding the relationship between EP recurrence rates and surgical treatment, the study found the following results for first pregnancies by spontaneous conception: following a total salpingectomy, recurrent EP occurred in 2 out of 14 cases (14.3%) and after partial salpingectomy, in 2 out of 16 cases (12.5%). After all other therapies, including salpingotomy, the study found no recurrent EPs in spontaneous conceptions (Table 4). Regarding the

Table 2. Pregnancy Rates After Various Ectopic Pregnancy Treatments in Patients Wanting Children (Without Statistical Significances)

Ectopic pregnancy therapy, number of treated patients	Total Salpingectomy n = 34	Partial Salpingectomy n = 24	Wedge Excision n = 10	Salpingotomy n = 28	Milking of the Tube n = 5	Methotrexate n = 2	Tubal abortion n = 5
No. of pregnant patients (%)	21 (61.8)	17 (70.8)	7 (70)	24 (85.7)	4 (80)	2 (100)	4 (80%)

Table 3. Absolute and Percentage Rates of Recurrent Ectopic Pregnancy by Conception Method

	Repeated Ectopic Pregnancy	Absolute No. of Pregnancies, Conception Method			Percentage of Pregnancies, Conception Method			P Value
		Natural	ART	Total	Natural	ART	Total	
First Pregnancy	No	55	16	71	93.22 (55/59)	94.12 (16/17)	93.42	>0.05
	Yes	4	1	5	6.78 (4/59)	5.88 (1/17)	6.58	>0.05
	Total	59	17	76	77.63	22.37	100.00	
Second Pregnancy	No	27	5	32	100.00 (27/27)	83.33 (5/6)	96.97	>0.05
	Yes	0	1	1	0.00	16.67 (1/6)	3.03	0.031
	Total	27	6	33	81.82	18.18	100.00	

Table 4. Number of Recurrent Ectopic Pregnancies by Treatment Type (Without Statistical Significances)

	Recurrent Ectopic Pregnancy: No		Recurrent Ectopic pregnancy: Yes		% of Ectopic Pregnancy	
	Natural Conception/ART (Total)		Natural Conception/ART (Total)		Natural Conception/ART	
Total salpingectomy	12/5 (17)		2/0 (2)		14.28/0	
Partial salpingectomy	14/1 (15)		2/0 (2)		12.5/0	
Wedge excision	6/1 (7)		0/0 (0)		0/0	
Salpingotomy	16/7 (23)		0/1 (1)		0/12.5	
Milking	3/1 (4)		0/0 (0)		0/0	
Methotrexate	2/0 (2)		0/0 (0)		0/0	
Tubal abortion	2/1 (3)		0/0 (0)		0/0	
Total number	55/16 (71)		4/1 (5)		6.78/5.88	

EP recurrence rate in first pregnancies by IVF, the study found only 1 recurrent EP out of 8 cases, which occurred after a salpingostomy. In summary, we found no statistical significances between the different types of surgical intervention and the rates of EP recurrence even if divided by the way of conception.

Another subgroup analysis addressed the pregnancy rates following EP treatment in the group of 28 patients (23.9%) who had previous tubal surgeries, including tubal reconstruction, EPs or adhesiolysis. After these surgeries, 57.1% of the patients became pregnant, whereas in the group who had no prior tubal surgeries, 70.8% became pregnant at least once. There was no statistically significant difference between these groups. Furthermore, the analysis showed no effect of previous adnexitis or appendicitis on the pregnancy or FP recurrence rates.

To identify any correlation between the hCG values and the EP treatment type, hCG values were categorised into low (up to 799 U/L), middle (800 to 1999 U/L) and

high (more than 2000 U/L) ranges, with, 39 patients having a low hCG value, 30 patients a middle one and 46 patients a high value. Table 5 shows the various therapies and the corresponding hCG values. In 2 patients, hCG had not been measured before treatment. The corrected coefficient of contingency (0.457) showed a statistically significant correlation between the hCG value and a subsequent invasive therapy, including salpingectomy, wedge excision and salpingotomy. However, a high number of patients who had low hCG values (up to 799 U/L) needed a surgical therapy. The study also examined the effect of hCG values on the subsequent pregnancy rates. A low hCG value appeared to be related to a higher rate of subsequent pregnancies, but the relationship was not statistically significant.

Discussion

EP still plays an important role in first trimester pathology. Patients may show signs of haemorrhagic shock after tubal

Table 5. Types of Ectopic Pregnancy Therapy and Corresponding hCG Values (Without Statistical Significances)

Ectopic Pregnancy Therapy	hCG Value			Total Number
	Low (<800 U/L)	Middle (800–1999 U/L)	High (≥2000 U/L)	
Total salpingectomy	12	8	18	38
Partial salpingectomy	8	8	10	26
Wedge excision	2	2	10	10
Salpingotomy	7	10	11	28
Milking	3	2	0	5
Methotrexate	2	0	0	2
Tubal abortion	5	0	1	6
Total number	39	30	46	115

rupture, which can be life-threatening. In addition, having had an EP previous may negatively affect female fertility due to damage or loss of fallopian tubes. After an EP, patients who want to give birth often fear their chances of conceiving are reduced or that they must undergo IVF treatments, which cannot be guaranteed to be successful.

The goals of the present study were to investigate the pregnancy rate after an EP and the EP recurrence rate, both in total and depending on the EP treatment used.

Overall, the study found a pregnancy rate of 67.5% after an EP, with a higher pregnancy rate of 73.1% in the subgroup of patients desiring a pregnancy. In addition, 33 patients (28.2%) had a second post-EP pregnancy. The birth rate after an EP increased from 67.1% in the first subsequent pregnancy to more than 80% in the second.

These data show that in everyday clinical practice, physicians may encourage EP patients that they have a very good chance of conceiving, whether spontaneously, after tubal reconstructive surgery or using IVF.

Surgical tubal reconstruction still plays an important role in infertility treatment, with pregnancy rates of up to 80% following reversal of sterilization and rates of from 65%-70% after salpingostomy or adhesiolysis (16-18). In a study of 1118 cases of microsurgical re sterilization, the overall pregnancy rate was 54.8%, with a delivery rate of 72.5% of all pregnant women. The risk of EP following re sterilization was less than 10% (19).

In our own previous study, the rate of EP following re sterilization was 6.7% (8). In the presence of acquired tubal disease, the EP rate following adhesiolysis, salpingostomy, salpingoneostomy, fimbrioplasty and anastomosis of the fallopian tubes was 7.9% (8). Data from the German IVF Register demonstrate a significantly increased incidence of EP following ART in the presence of tubal pathology (8). The highest EP rate related to all clinical pregnancies was 4.5% (95% CI: 3.0-6.0), which was in smoking women under age 30 with tubal pathology and IVF conception (8).

In the present study, it was remarkable that 17.1% of the women had already at least one previous EP. It is possible that the study had a higher than usual sample of patients positive for EP, because prior to the EP involved in the study, 78.6% had given birth to at least one child.

The correlation between the pregnancy rate and each type of EP treatment was high, and there were no statistically significant differences among treatment groups. The study's results were consistent with those of 2 multicentre, prospective randomized studies from 2013 and 2014 (20,21), which reported pregnancy rates of 61%-70% after organ-preserving surgery and of 56%-64% after salpingectomy and found no statistically significant differences between these 2 groups.

It remains unclear whether salpingectomy or salpingotomy has more negative effects on future long-term fertility rates. Mol et al found a rate of recurrent EP of from 5%-10% after surgery (21). The present study found

that regardless of the type of EP therapy and regardless of the method of conception, recurrent EP occurred in very few cases (6.6% in the first pregnancy after surgery and 3% in the second). Lee found an eight-fold risk of recurrent EP in women with a history of EP but a very low risk after ipsilateral partial salpingectomy (22), whereas Abraham and Seethappan reported a spontaneous live recurrence of EP after ipsilateral salpingectomy that led to a tubal rupture with 1.5 L of hemoperitoneum (23). Although the mechanisms of recurrent EP after partial salpingectomy remain unclear, physicians must be aware that this severe pathology could arise (23). D'Hooghe and Tomassetti proposed salpingotomy in cases where the contralateral tube is damaged or in cases of past sterility. In these situations, the cumulative rate of pregnancy might be higher than after salpingectomy (24).

Bachman and Barnhart concluded that sufficient clinical practice and good surgical expertise are essential to a well-performed management of EP (13). However, both these factors are difficult to analyse in clinical studies. Although ours is a maximum-care university hospital with at least 3 gynaecologists and anaesthesiologists (including a Senior Consultant) on duty at all times, the surgeries included in the study were performed by various surgeons with differing experiences and skills, which may have influenced the outcomes.

A drug treatment like MTX is indicated only for a small group of patients who have very good compliance. In Germany, in contrast to the English-speaking countries, MTX therapy for EP is not common (25). Studies have found inconsistent results regarding the response to treatment, with rates of from 63%-97% (20). The present study included only 2 patients treated with MTX, so we cannot make recommendations concerning the medical treatment of an EP. Only one prospective randomized study has compared observant management with MTX treatment, and its authors found no significant differences between those 2 therapies (26).

In the subgroup of patients age 34 and younger, 77.2% became pregnant after EP treatment, whereas only 47.4% of the patients age 35 or older became pregnant, a difference that highlights the well-known fact that fecundity decreases with age.

The present study found a statistically significant relationship between the type of therapy and the duration of hospital stay, with those who underwent total salpingectomy having the longest stays (3.9 days), followed by those who underwent partial salpingectomy (3.8 days) and those who underwent salpingostomy (3.5 days). Those who underwent milking of the tube had the shortest stays (2.4 days), except for those who underwent drug therapy with MTX (0.5 days). This correlation has not yet been discussed in the literature. Although in the present study, transampullar milking of the tube was correlated with a significantly shorter hospital stay, this technique is possible only when the EP is located in an

ampullar location, enabling the use of nontraumatic instruments without force (12).

Laparoscopy is generally accepted as the preferred surgical approach for treating EP. Its advantages over laparotomy include faster surgical access to the abdomen, shorter duration of operation and hospital stay, less loss of blood, fewer adhesions and faster convalescence (27).

The present study found a statistically significant correlation between the hCG value and subsequent invasive therapies, including salpingectomy, wedge excision and salpingotomy. However, physicians must be aware of the possibility that even with a low hCG value, tubal rupture may occur.

We are aware of some limitations of the present study, foremost among them that the rate of response to the questionnaire was 38.5%. We can only speculate about the reasons for this. Perhaps patients did not have time to fill out the two-sided questionnaire or to post it, although it was already stamped. It is also likely that the questionnaire could have triggered negative memories, especially in women who wanted to become pregnant but did not. Finally, it is possible that women who did not want more children were not motivated to respond to the survey.

In the literature, the response rates for surveys differ a greatly. A study by Watt et al found an overall response rate for online surveys of 32.6% and for paper-based surveys of 33.3% (28). However, Baruch and Holtom analysed 1607 studies having 400 000 respondents and published in 17 academic journals between 2000 and 2005, finding an average response rate for surveys that collected data from individuals of 52.7%, with a standard deviation of 20.4, and an average response rate for studies that collected data from organizations of 35.7%, with a standard deviation of 18.8 (29). They also found that electronic data collections efforts, including email, phone and web, resulted in response rates that were as high as or higher than traditional mail collection efforts (29).

Conclusions

The present study found a pregnancy rate of 73.1% following EP treatment in those patients who wanted children, with 33 (28.2%) becoming pregnant a second time. The birth rate after EP increased from 67.1% in the first subsequent pregnancy to more than 80% in the second subsequent pregnancy. The frequency of recurrent EP was 6.6% in the first pregnancy after surgery and 3% in the second. These data are encouraging for EP patients, who have a good chance to conceive, whether spontaneously, after tubal reconstructive surgery or using IVF.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Hanover Medical School (no. 2751-2015) prior to study

procedure.

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