

Endometriosis and Beta-hCG > 775 IU/l Increase the Risk of Non-tube-preserving Surgery for Tubal Pregnancy

Endometriose und Beta-hCG > 775 IU/l erhöhen das Risiko für nicht tubenerhaltende Chirurgie bei Tubargravidität



Authors

Kristin Nicolaus¹, Jorge Jimenez-Cruz², Dominik Michael Bräuer¹, Thomas Lehmann³, Anke Regina Mothes¹, Ingo B. Runnebaum¹

Affiliations

- 1 Klinik und Poliklinik für Frauenheilkunde und Fortpflanzungsmedizin, Universitätsklinikum Jena, Friedrich-Schiller-Universität Jena, Jena, Germany
- 2 Abteilung für Geburtshilfe und Pränatalmedizin, Universitätsklinikum Bonn, Bonn, Germany
- 3 Institut für Medizinische Statistik, Informatik und Dokumentation, Universitätsklinikum Jena, Jena, Germany

Key words

endometriosis, tubal pregnancy, beta-hCG, salpingotomy, salpingectomy

Schlüsselwörter

Endometriose, Tubargravidität, Beta-hCG, Salpingotomie, Salpingektomie

received 29.1.2018

revised 23.4.2018

accepted 28.5.2018

Bibliography

DOI <https://doi.org/10.1055/a-0635-8453>

Geburtsh Frauenheilk 2018; 78: 690–696 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0016-5751

Correspondence

Prof. Ingo B. Runnebaum
Klinik und Poliklinik für Frauenheilkunde
und Fortpflanzungsmedizin, Universitätsklinikum Jena,
Friedrich-Schiller-Universität Jena
Am Klinikum 1, 07747 Jena, Germany
Direktion-gyn@med.uni-jena.de

Deutsche Version unter:
<https://doi.org/10.1055/a-0635-8453>

ABSTRACT

Introduction Tubal pregnancy is the most clinically relevant form of ectopic pregnancy. Surgery consisting of laparoscopic salpingotomy is the therapeutic gold standard. This study looked at risk factors for non-tube-preserving surgery. The aim was to determine a cut-off value for beta-hCG levels, which could be used to predict the extent of tubal surgery.

Materials and Method 97 patients with tubal pregnancy who underwent primary salpingotomy in the Department of Gynecology and Obstetrics of Jena University Hospital between 2010 and 2016 were retrospectively analyzed. A prior medical history of risk factors such as adnexitis, ectopic pregnancy, tubal surgery, treatment for infertility and intrauterine pessary was included in the analysis. The study population was divided into two subgroups: (1) a group which underwent laparoscopic linear salpingotomy, and (2) a group which had laparoscopic partial tubal resection or salpingectomy. Risk factors for salpingectomy were determined using binary logistic regression analysis. Statistical analysis was done using SPSS, version 24.0, to identify risk factors for non-tube-preserving surgery.

Results 68 patients (70.1%) underwent laparoscopic salpingotomy and 29 patients (29.9%) had laparoscopic salpingectomy. The two groups differed with regard to age ($p = 0.01$) but not with regard to the parameters ‘gestational age’, ‘viability and rupture status of the ectopic pregnancy’ or ‘symptoms at presentation’. Patients who were known to have endometriosis prior to surgery or who were diagnosed with endometriosis intraoperatively were more likely to undergo salpingectomy (OR: 3.28; 95% CI: 0.9–10.8; $p = 0.05$). Calculated mean beta-hCG levels were higher in the salpingectomy group compared to the group who had tube-preserving salpingotomy (3277.8 IU/l vs. 9338.3 IU/l, $p = 0.01$). A cut-off beta-hCG value of 775 IU/l prior to surgery was predictive for salpingectomy with a true positive rate of 86.2% and increased the probability that salpingectomy would be necessary (OR: 5.23; 95% CI: 0.229–0.471; $p = 0.005$).

Conclusion Endometriosis and a beta-hCG value of more than 775 IU/l significantly increased the risk for non-tube-preserving surgery in women with tubal pregnancy.

ZUSAMMENFASSUNG

Einleitung Die Tubargravidität stellt klinisch die relevanteste Form der ektopen Schwangerschaft dar. Therapeutischer Goldstandard in der operativen Therapie ist die laparoskopische Salpingotomie. Risikofaktoren für ein nicht tubenerhaltendes operatives Vorgehen sollten untersucht werden. Ein Beta-hCG-Cut-off-Wert sollte ermittelt werden, anhand dessen das operative Ausmaß der erforderlichen Tubenchirurgie möglicherweise vorherzusagen ist.

Material und Methode 97 Patientinnen mit Tubargravidität zur primär angestrebten Salpingotomie in der Universitätsfrauenklinik Jena von 2010 bis 2016 wurden retrospektiv erfasst. Anamnestiche Risikofaktoren wie Adnexitis, Extrauterinravidität, Tubenchirurgie, Sterilitätstherapie und liegendes Intrauterinmissar wurden aufgenommen. Das Untersuchungskollektiv wurde in 2 Subgruppen eingeteilt: (1) laparoskopische lineare Salpingotomie oder (2) laparoskopische Tubenteilresektion respektive Salpingektomie. Risikofaktoren für die Salpingektomie wurden über eine binäre logistische Regression erhoben. Die statistische Analyse erfolgte über SPSS, Version 24.0, um Risikofaktoren für die nicht tubenerhaltende Chirurgie zu ermitteln.

Ergebnisse Eine laparoskopische Salpingotomie erhielten $n = 68$ Patientinnen (70,1 %) und $n = 29$ Patientinnen (29,9 %) eine laparoskopische Salpingektomie. Beide Gruppen unterschieden sich im Alter ($p = 0,01$), jedoch nicht bei den Parametern Gestationsalter, Vitalitäts- und Rupturstatus der Extrauterinravidität, Symptome bei Vorstellung. Patientinnen mit einer präoperativ bekannten Endometriose oder intraoperativ neu diagnostizierten Endometriose erhielten häufiger eine Salpingektomie (OR: 3,28, 95 %-KI 0,9–10,8, $p = 0,05$). Für die Gruppe der Salpingektomie errechnete sich ein höherer Mittelwert des Beta-hCG als in der Gruppe der tubenerhaltenden Salpingotomie (3277,8 IU/l vs. 9338,3 IU/l, $p = 0,01$). Ein Cut-off-Wert des Beta-hCGs von 775 IU/l sagte eine Salpingektomie mit einer Richtig-positiv-Rate von 86,2 % vorher und zeigte eine Risikoerhöhung für die Wahrscheinlichkeit einer notwendigen Salpingektomie (OR: 5,23; 95 %-KI 0,229–0,471, $p = 0,005$).

Schlussfolgerung Das Vorhandensein einer Endometriose sowie ein Beta-hCG-Wert ab 775 IU/l erhöhen signifikant das Risiko für eine nicht tubenerhaltende Chirurgie bei Tubargravidität.

Introduction

Ectopic pregnancy (EP) is the cause of up to 6 % of cases of pregnancy-related maternal morbidity; in the first trimester of pregnancy EP is the leading gestational cause of death [1,2]. The incidence of EP is increasing because of the improved diagnosis of ectopic pregnancies, the increased maternal age, an increase in surgical procedures in the tubal area, and the increased use of assisted reproductive technologies [2]. Tubal pregnancy is the most common form of ectopic pregnancy (95.5 %), while ovarian (3.2 %) and abdominal (1.3 %) implantation sites are far less common [3–5].

Diagnosis may be delayed due to the heterogeneity of symptoms. Clinically, presentation can range from asymptomatic with an intact pregnancy to acute abdomen or hemorrhagic shock following tubal rupture or miscarriage. The diagnosis is usually made between the 6th and the 9th week of pregnancy [2]. Depending on the time of examination, the differential diagnosis can include intact intrauterine early pregnancy not yet visible on ultrasound or early miscarriage [6,7].

As minimally invasive surgery is becoming more widely available in clinical practice, potential ectopic pregnancies are being investigated and detected at early stages, and treatment is more likely to be organ-sparing. Tubal ruptures are decreasing. The gold standard of care consists of surgical laparoscopy with organ-sparing treatment or ablation; expectant management or medication are less commonly used. The procedure generally consists of linear salpingotomy performed in the antimesenteric area of the tube with a monopolar needle or monopolar scissors using a low setting. Aquadissection is subsequently used to make it easier to remove the ectopic pregnancy. Tubal closure using an endo-suturing device has not been shown to offer any benefits for fertility compared to leaving the tube wall open [8,9].

A meta-analysis [10] has associated the organ-sparing procedure with a risk of persistent trophoblastic tissue and a 2.3-times higher risk for recurrent tubal pregnancy, which must be set against the benefit of improved fertility following preservation of the tube. Both surgical options and the risk of residual ectopic pregnancy tissue and recurrence when the tube is preserved must all be discussed with the patient before the operation.

Known risk factors for non-tube-preserving surgery are the size of the ectopic pregnancy (> 33.5 mm) and an isthmic or fimbrial site of pregnancy [11]. The aim of this study was to identify further risk factors for non-tube-sparing surgery with the aim of using them in the future when informing and discussing possible options with patients preoperatively. The presence of endometriosis was of particular interest, because of a reported prevalence of about 50 % in affected patients who wished to conceive and the risk it represents for tubal infertility and for ectopic pregnancy [12].

Beta-hCG values are usually determined preoperatively and can be used to make the diagnosis and decide on the indications for surgery during surgical exploration of an ectopic pregnancy. The aim was to investigate whether this marker could also be used to estimate the risk of potentially losing the affected fallopian tube.

Method

Study design

A retrospective analysis was done of all patients who underwent laparoscopic surgical exploration for tubal ectopic pregnancy in the period from 2010 to 2016 in the Department of Gynecology and Obstetrics of Jena University Hospital ($n = 105$). The proposed

study was submitted to the Ethics Commission of Friedrich Schiller University Jena for approval prior to the start of the study.

Five patients were excluded from the study because they did not want any more children and had been referred for salpingectomy. Preoperative diagnostic procedures used to make the diagnosis included transvaginal ultrasound and serum beta-hCG determination (given in IU/l).

In 3 cases, patients were treated immediately without awaiting the information on beta-hCG levels because these patients presented with hemodynamic instability due to tubal rupture and hemoperitoneum; these 3 patients were also excluded from the study.

Recorded parameters included age, week of pregnancy (from the last menstrual period), ultrasound findings and risk factors such as status post (s/p) adnexitis, ectopic pregnancy, tubal surgery, infertility treatment or the presence of an intrauterine pessary.

Method

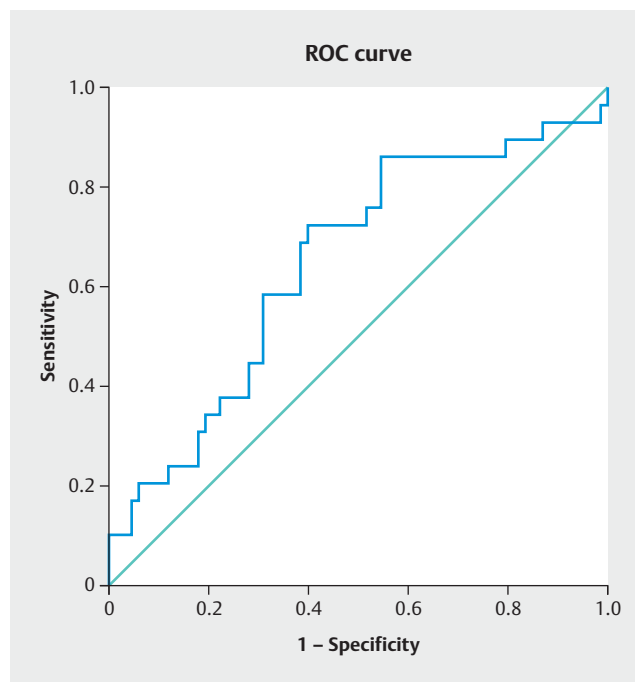
Serum beta-hCG levels were also measured as part of diagnostic procedures. Levels (given as IU/l) were determined in-house preoperatively in the 24-hour period immediately prior to the procedure.

During the above-mentioned study period, a total of 97 patients were treated for ectopic tubal pregnancy in the Department of Gynecology and Obstetrics of Jena University Hospital, with primary treatment consisting of laparoscopy in the majority of patients. All 97 patients were treated after previously undergoing a complete preoperative workup resulting in a working diagnosis of ectopic tubal pregnancy. All of the patients wanted organ-preserving surgery. The abdomen and lesser pelvis were explored using a laparoscopic approach, the diagnosis of tubal pregnancy was confirmed, and extirpation was done by longitudinal excision of the affected fallopian tube and removal of the tissue, followed by careful and sparing hemostasis. According to the surgical reports, indications to carry out salpingectomy based on intraoperative findings included persistent bleeding from the trophoblastic bed following extirpation which required extensive coagulation. Based on the retrospectively analyzed reports, salpingectomy was also necessary following ipsilateral recurrence and pregnancy in a previously operated fallopian tube. Prior to statistical analysis, the study cohort was subdivided into two groups based on the chosen surgical procedure – laparoscopic linear salpingotomy and laparoscopic partial tubal resection or salpingectomy – and the risk factors for the respective surgical procedure were then determined.

Thirteen patients either had a prior history of endometriosis or endometriosis was diagnosed intraoperatively as an ancillary finding. Tissue was sampled during surgery and the diagnosis of endometriosis was subsequently confirmed histologically.

Statistical analysis

Mean values and standard deviations or frequencies were calculated for continuous and categorical variables. Differences between mean values of metric variables such as patient age and gestational age were determined using Student's t-test or Mann-Whitney U-test for categorical variables. Parameters such as vital



► **Fig. 1** ROC curve for the probability prediction of an intraoperative decision for salpingectomy based on serum beta-hCG levels. Sensitivity = true positive rate, specificity = false positive rate.

ity and rupture status were calculated using Pearson's chi-square test. Receiver operating characteristics (ROC) curve analysis was done to determine a cut-off value for serum beta-hCG concentrations which could be used to predict salpingectomy. The sensitivity, specificity, and the positive and negative predictive values were determined for the respective beta-hCG levels. A beta-hCG level of 775 IU/l had a true positive rate of 86.2% and a false positive rate of 45.6% for salpingectomy being required and was therefore defined as the cut-off value.

Binary logistic regression analysis was also done to determine the predictors for salpingectomy. Analysis was done using the SPSS program, version 24.0. Statistical significance was defined as $p \leq 0.05$.

Results

During the study period, a total of 97 patients underwent primary surgery based on a working diagnosis of ectopic pregnancy and the wish for organ-preserving surgery. It was possible to preserve the fallopian tube in 68 patients (70.1%). It was not possible to preserve the tube in 29 patients (29.9%), and salpingectomy was performed in these patients.

Serum beta-hCG levels

The mean patient age was higher for patients who subsequently had non-tube-sparing treatment, and the mean beta-hCG level prior to making the final diagnosis was also higher in these patients ($p = 0.01$).

The ROC curve in ► **Fig. 1** shows that beta-hCG levels can be used to predict non-tube-sparing procedures. The optimal selec-

► **Table 1** Clinical parameters of patients who underwent salpingotomy or salpingectomy for tubal pregnancy. Results are shown as mean ± standard deviation or as percentages.

	Salpingotomy (n = 68)	Salpingectomy (n = 29)	p-value
Age (years), mean ± SD	29.9 ± 4.87	32.9 ± 5.44	0.01
Gestational age (GW), mean ± SD	6.2 ± 1.30	6.3 ± 1.79	0.99
Viability	3 (4.41%)	1 (3.44%)	1
Rupture	10 (14.70%)	4 (11.60%)	1
Symptoms			0.11
▪ none	3 (4.41%)	3 (10.34%)	
▪ lower abdominal pain	22 (32.35%)	15 (51.72%)	
▪ vaginal bleeding	12 (17.65%)	2 (6.89%)	
▪ lower abdominal pain and vaginal bleeding	31 (45.59%)	9 (31.03%)	
Beta-hCG level (IU/l), mean	3277.8	9338.3	0.01

► **Table 2** Risk factors based on previous medical conditions of patients who had salpingotomy or salpingectomy for tubal pregnancy. Results are shown as percentages and in absolute numbers.

	Salpingotomy (n = 68)	Salpingectomy (n = 29)	p-value
Known to have endometriosis	6 (8.82%)	7 (24.14%)	0.05
s/p miscarriage	16 (23.53%)	4 (13.79%)	0.21
s/p EP	4 (5.88%)	5 (17.24%)	0.12
s/p chlamydia infection	4 (5.88%)	2 (6.89%)	1
s/p IVF treatment	5 (7.35%)	3 (10.34%)	0.69
IUD	1 (1.47%)	2 (6.89%)	0.21

tivity was reflected by a serum beta-hCG level of 775 IU/l; this value was correlated with tubal loss and had a sensitivity of 86.2% and a specificity of 45.6%. A clinically relevant cut-off value of 1546 IU/l already had a higher false-positive rate of 60.3% for salpingectomy being required. After carrying out binary regression analysis, the risk probability for a non-tube-sparing procedure was higher for a cut-off value of beta-hCG of 775 IU/l (OR: 5.24; 95% CI: 1.64–16.68; $p = 0.005$).

Endometriosis

Ablation to treat tubal pregnancy was more commonly associated with a preoperative history or intraoperative diagnosis of endometriosis ($n = 13$), compared to the group who underwent organ-sparing procedures ($p = 0.05$). After carrying out binary regression analysis, the risk probability for salpingectomy being required was higher for patients with endometriosis (OR: 3.28; 95% CI: 0.9–10.8; $p = 0.05$).

Additional risk factors

► **Table 1** summarizes the clinical parameters of patients with tubal pregnancy according to the surgical method used to treat them. Distribution of gestational age, viability and rupture status of the ectopic pregnancy and the symptoms at presentation did not differ between groups. When the risk factors based on previous medical conditions recorded during the preoperative analysis were summarized in ► **Table 2**, there was no difference be-

tween ablation and salpingotomy with regard to previous ectopic pregnancy, previous chlamydia infection, infertility treatment, miscarriage or current utilization of an intrauterine pessary. Our study shows that it is not possible to calculate the risk probability that salpingectomy will be required based on any of the above-listed factors. ► **Table 3** summarizes the results of univariate analysis, using salpingectomy as the independent variable.

Complications

All 97 cases in this study cohort underwent primary laparoscopic treatment. One case required conversion to laparotomy due to hemorrhagic aspiration during introduction of a Verres needle. Postoperative complications, such as packed red blood cell transfusions for anemia, methotrexate administration for ectopic pregnancy tissue residue, and bleeding requiring re-intervention, were rare. Overall, fewer complications occurred in women who had non-tube-preserving procedures ($p = 0.05$). ► **Table 4** shows the distribution of complications requiring re-intervention.

Discussion

Surgical laparoscopy followed by linear salpingotomy is the gold standard to treat tubal pregnancy. In 29.9% of cases, intraoperative findings will indicate the need for ablative treatment.

The intraoperative choice between the two surgical procedures depends on the extent of tubal tissue damage determined

► **Table 3** Univariate analysis of parameters, including the regression coefficient, standard error, p-value, odds ratio and the upper and lower confidence intervals, with salpingectomy as the dependent variable.

	Regression coefficient B	Standard error	p-value	Odds ratio	Lower CI	Upper CI
Known to have endometriosis yes vs. no	1.19	0.609	0.05	3.28	0.996	10.851
Beta-hCG > 775 vs. < 775 beta-hCG > 1546 (IU/l)	1.656 1.383	0.591 0.484	0.005 0.004	5.236 3.986	1.644 1.544	16.676 10.288
Viability yes vs. no	- 0.256	1.177	0.827	0.774	0.077	7.766
Rupture yes vs. no	- 0.075	0.638	0.90	0.92	0.266	3.242
s/p IVF treatment yes vs. no	0.374	0.767	0.625	1.454	0.324	6.532
IUD in place yes vs. no	1.602	1.246	0.198	4.963	0.432	57.036
s/p tubal pregnancy yes vs. no	1.204	0.712	0.091	3.33	0.825	13.463
s/p miscarriage yes vs. no	- 0.654	0.61	0.283	0.52	0.157	1.718
s/p chlamydia infection yes vs. no	0.154	0.896	0.863	1.167	0.201	6.756

► **Table 4** Comparison of intraoperative and postoperative complications in absolute and relative numbers for both procedures, salpingotomy and salpingectomy.

	Salpingotomy (n = 68)	Salpingectomy (n = 29)	p-value
Conversion to laparotomy	0 (0%)	1 (3.44%)	0.29
Postoperative complications			0.05
Bleeding requiring transfusion	5 (7.35%)	1 (3.44%)	
Ectopic pregnancy tissue residue (MTX administration)	3 (4.41%)	0 (0%)	
Surgical re-intervention for postoperative bleeding	3 (4.41%)	1 (3.44%)	

intraoperatively, the condition of the contralateral fallopian tube, and whether the patient wishes to conceive [13]. The availability of reproductive medical technologies and the surgeon's experience in performing laparoscopic procedures also play a role [8].

Known risk factors for non-tube-preserving surgery are a product of conception larger than 33.5 mm and an isthmic or fimbrial site of pregnancy [33].

The aim of this study was to investigate risk factors for non-conservative surgical procedures.

Non-tube-sparing surgical procedures were associated with significantly higher mean serum beta-hCG levels of 9338.3 IU/l compared to salpingotomy procedures which had mean beta-hCG levels of 3277.8 IU/l ($p = 0.01$).

In itself, the serum marker beta-hCG is not sufficient to make a diagnosis. In every fifth ectopic pregnancy, the hCG levels correspond to those of a viable intact pregnancy. In clinical practice, it is not always possible to wait and monitor the dynamic changes in hCG concentration over 48 hours [14]. When hCG levels are < 1000 IU/l and there are no symptoms, laparoscopic detection of the ectopic pregnancy can be difficult. With the help of modern

transvaginal ultrasound technology, the differential diagnosis of ectopic pregnancy can already be made when serum beta-hCG concentrations are between 1000 and 2000 IU/l [15]. hCG values of more than 1500 IU/l and the lack of any intrauterine signs of pregnancy suggest the presence of an ectopic pregnancy with a sensitivity of 92% and a specificity of 84% [16, 17].

The diagnostic importance of beta-hCG is undisputed. The innovative approach of this study is raising the question whether this parameter can also be used to predict the surgical decision. In our study, non-tube-sparing procedures were associated with significantly higher serum beta-hCG levels at the time of making the diagnosis. A cut-off value could be used to predict the loss of a fallopian tube. A beta-hCG value of 775 IU/l correctly positively predicted 86.2% of required salpingectomy procedures. After this cut-off value, patients had a 5.24 times higher risk of non-tube-sparing surgery.

In addition to significantly higher mean serum beta-hCG levels at the time of diagnosis, our study also found a significantly higher rate of endometriosis in the salpingectomy group, whereby patients either had a known history of endometriosis or endometrio-

sis was detected intraoperatively by macroscopic examination and subsequently verified by histological analysis of the excised tissue samples (8.82 vs. 24.14%, $p = 0.05$).

A recent German study of > 100 000 women found that endometriosis was a risk factor for EP (OR = 1.51) [12] as did a recent Scottish study of 5375 patients with verified endometriosis and 30 years of follow-up (OR = 2.70) compared to women without endometriosis [18]. Endometriosis can lead to tubal sterility and facilitate the development of tubal pregnancies. Endometriosis may be detected in patients wishing to conceive during surgical procedures to diagnose the cause of infertility [19]. There are no prospective data on any correlation with an increased risk of losing the tube due to endometriosis in patients treated for tubal pregnancy. In our study, the presence of endometriosis was associated with a 3.28 times higher risk of it being impossible to preserve the fallopian tube intraoperatively.

Higher maternal age is also included as a risk factor; from the age of 35, the risk of ectopic pregnancy increases significantly [1, 20]. As reported in other published patient cohorts, the mean patient age of the group who underwent laparoscopic salpingotomy was significantly lower at the time of surgery (29.9 vs. 32.9 years, $p = 0.01$). It is not possible to do a risk assessment about the required surgical method based on patient age.

Our data reflect the known risk factors for the occurrence of ectopic pregnancy. None of these risk factors looked at in our study was found to be associated with surgical outcome in terms of organ preservation or organ removal. Ruptured tubal pregnancies ($p = 1$) and viable ectopic pregnancies ($p = 1$) occurred both in the salpingotomy group and in the salpingectomy group ($p = 1$). Advances in transvaginal ultrasound and in the capacity to determine highly sensitive beta-hCG levels in serum mean that more than 80% of ectopic pregnancies are diagnosed before rupture occurs [8].

The percentage of women previously treated for infertility who subsequently experienced an ectopic pregnancy was the same for both groups (7.35 vs. 10.34%, $p = 0.69$). The use of assisted reproductive methods has led to an increase of ectopic pregnancies to 2–5% [1, 21]. Risk factors for ectopic pregnancy include tubal factor infertility, transfer of blastocysts, higher numbers of embryos at transfer, decreased endometrial thickness and, above all, a medical history of endometriosis [22–26].

The benefits of conservative management must be weighed up against risks such as the presence of tissue residues, recurrent tubal pregnancy, and postoperative bleeding [1]. In the patient cohort investigated in this study, the percentages for postoperative complications were in single figures for both groups. However, there were significantly more postoperative complications in the salpingotomy group ($p = 0.05$); complications included the need for packed red blood cell transfusions for higher intraoperative blood loss (7.35 vs. 3.44%), postoperative bleeding requiring surgical revision (4.41 vs. 3.44%), and the administration of methotrexate for residual ectopic pregnancy tissue after preservation of the tube (4.41 vs. 0%). In the ESEP trial, 20% of patients in the salpingotomy group required intraoperative conversion to salpingectomy because of persistent bleeding from the trophoblastic bed; the salpingotomy group also had a higher rate of postoperative complications requiring transfusion (7 vs. 3%), and a

higher rate of surgical revisions for subsequent bleeding in 1% of cases and for ectopic pregnancy tissue residues in 2% of cases [27]. The presence of ectopic pregnancy tissue residue is diagnosed when no decrease in beta-hCG levels occurs during follow-up. Beta-hCG levels should drop to under 50% of the initial level within the first four days after surgery [8, 28]. Risk factors for ectopic pregnancy tissue residues are ectopic pregnancies with diameters of less than 2 cm and beta-hCG concentrations of more than 3000 IU/l [29]. Between 12.5–28% of women who were previously treated for tubal pregnancy go on to experience a repeat tubal pregnancy [30]. There is a higher risk of a subsequent ectopic pregnancy occurring in the region of the surgically treated, preserved tube [10, 27]. Because of the retrospective study design, it was not possible to obtain data on the prevalence of recurrence.

In recent years, organ-preserving procedures and the associated risk of persistent trophoblastic tissue and of repeat tubal pregnancy must be set against the increasingly doubtful benefit of improved chances of spontaneous fertility. 93% of women wishing to conceive become pregnant again in the 18 months following surgical treatment for EP [31]. A survey of patients showed that they are prepared to bear the risk if organ preservation is associated with a minimal benefit for spontaneous conception [32]. The ESEP trial reported a cumulative pregnancy rate after spontaneous conception of 60.7% after salpingotomy and 56.2% after salpingectomy. There was no significant difference in pregnancy rates between the two groups ($p = 0.678$). There was also no significant difference in the 2-year rate of intrauterine pregnancies (70–61% in the organ preservation group vs. 64–56% in the salpingectomy group). If the contralateral tube is healthy, conservative management will not improve the cumulative pregnancy rate after spontaneous conception. Preserving the tube increases the risk of the presence of ectopic pregnancy tissue residues and the necessity of subsequent interventions. The limitations of this study were a lack of information about the surgeon's level of surgical experience with salpingotomy, and the fact that no tubal patency examinations were carried out, and that there were no explanations for the causes of repeat ectopic pregnancy following salpingectomy [27]. In contrast, a French study reported a cumulative pregnancy rate after 24 months of 76% after salpingotomy and 67% after salpingectomy; multivariate analysis showed a significant difference in favor of organ preservation for women aged more than 35 years and for patients with a medical history of infertility [33]. Ödesjö et al. investigated IVF outcomes after salpingectomy and salpingotomy for ectopic pregnancy [13]. The number of retrieved oocytes was the same for both groups (11.69 vs. 11.80) as was the subsequent pregnancy rate. It would appear that the surgical method had no impact on ovarian reserve and response. The availability of assisted reproductive techniques can influence the surgeon's decision about the preferred method of surgery [2]. Despite the availability of reproductive medical treatment in the Clinic and Policlinic for Gynecology and Reproductive Medicine of Jena University Hospital, the majority of procedures to treat EP consisted of non-ablative salpingotomies, not least because of the expectations of the referring gynecological practices.

Because of the retrospective study design, it was not possible to collect data on fertility.

The limitations of our study were the low number of cases and the retrospective study design. A prospective recording of the specific ultrasound findings and the actual intraoperative size of the tubal pregnancy could help identify additional risk factors for non-tube-preserving procedures.

Conclusion

Laparoscopic salpingotomy is currently the procedure of choice for the surgical treatment of tubal pregnancy.

In our study, when treatment options were being considered, higher serum beta-hCG levels were a risk factor for non-tube-preserving surgery (3277.8 IU/l vs. 9338.3 IU/l). A serum level of 775 IU/l allowed salpingectomies to be predicted with a true positive rate of 86.2%. Above this cut-off value, there was a 5.23 times higher probability risk for salpingectomy ($p = 0.005$).

A further risk factor was the presence of endometriosis; in our study cohort, endometriosis was associated with a 3.34 times higher probability risk of requiring ablation, a significantly higher risk ($p = 0.048$).

Conflict of Interest

The authors state that they have no conflict of interest.

References

- Farquhar CM. Ectopic pregnancy. *Lancet* 2005; 366: 583–591
- Barnhart KT. Clinical practice. Ectopic pregnancy. *N Engl J Med* 2009; 361: 379–387
- Bouyer J, Coste J, Fernandez H et al. Sites of ectopic pregnancy: a 10 year population-based study of 1800 cases. *Hum Reprod* 2002; 17: 3224–3230
- Sivalingam VN, Duncan WC, Kirk E et al. Diagnosis and management of ectopic pregnancy. *J Fam Plann Reprod Health Care* 2011; 37: 231–240
- Walker JJ. Ectopic pregnancy. *Clin Obstet Gynecol* 2007; 50: 89–99
- Kirk E, Bottomley C, Bourne T. Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location. *Hum Reprod Update* 2014; 20: 250–261
- Pisarska MD, Carson SA, Buster JE. Ectopic pregnancy. *Lancet* 1998; 351: 1115–1120
- Mueller M. Gynäkologische Notfälle: Chirurgische Therapie der Extrauterin-gravidität. *Frauenheilkunde Aktuell* 2013; 22: 30–36
- Wallwiener D, Becker S. Atlas of gynecologic Surgery. 4th ed. Stuttgart, New York: Thieme; 2013
- Cheng X, Tian X, Yan Z et al. Comparison of the Fertility Outcome of Salpingotomy and Salpingectomy in Women with Tubal Pregnancy: A Systematic Review and Meta-Analysis. *PLoS One* 2016; 11: e0152343
- Kayatas S, Demirci O, Kumru P et al. Predictive factors for failure of salpingostomy in ectopic pregnancy. *J Obstet Gynaecol Res* 2014; 40: 453–458
- Jacob L, Kalder M, Kostev K. Risk factors for ectopic pregnancy in Germany: a retrospective study of 100,197 patients. *Ger Med Sci* 2017; 15: Doc19
- Odesjo E, Bergh C, Strandell A. Surgical methods for tubal pregnancy – effects on ovarian response to controlled stimulation during IVF. *Acta Obstet Gynecol Scand* 2015; 94: 1322–1326
- van Mello NM, Mol F, Opmeer BC et al. Diagnostic value of serum hCG on the outcome of pregnancy of unknown location: a systematic review and meta-analysis. *Hum Reprod Update* 2012; 18: 603–617
- Mehta TS, Levine D, Beckwith B. Treatment of ectopic pregnancy: is a human chorionic gonadotropin level of 2,000 mIU/mL a reasonable threshold? *Radiology* 1997; 205: 569–573
- Condous G, Kirk E, Van Calster B et al. Failing pregnancies of unknown location: a prospective evaluation of the human chorionic gonadotrophin ratio. *BJOG* 2006; 113: 521–527
- Kirk E, Condous G, Van Calster B et al. Rationalizing the follow-up of pregnancies of unknown location. *Hum Reprod* 2007; 22: 1744–1750
- Saraswat L, Ayansina DT, Cooper KG et al. Pregnancy outcomes in women with endometriosis: a national record linkage study. *BJOG* 2017; 124: 444–452
- Nawroth F, Römer T. Diagnostik und Therapie der weiblichen Sterilität. Berlin, München, Boston: Walter de Gruyter GmbH; 2015
- Marion LL, Meeks GR. Ectopic pregnancy: History, incidence, epidemiology, and risk factors. *Clin Obstet Gynecol* 2012; 55: 376–386
- Strandell A, Thorburn J, Hamberger L. Risk factors for ectopic pregnancy in assisted reproduction. *Fertil Steril* 1999; 71: 282–286
- Decler W, Osmanagaoglu K, Meganck G et al. Slightly lower incidence of ectopic pregnancies in frozen embryo transfer cycles versus fresh in vitro fertilization-embryo transfer cycles: a retrospective cohort study. *Fertil Steril* 2014; 101: 162–165
- Huang B, Hu D, Qian K et al. Is frozen embryo transfer cycle associated with a significantly lower incidence of ectopic pregnancy? An analysis of more than 30,000 cycles. *Fertil Steril* 2014; 102: 1345–1349
- Refaat B, Dalton E, Ledger WL. Ectopic pregnancy secondary to in vitro fertilisation-embryo transfer: pathogenic mechanisms and management strategies. *Reprod Biol Endocrinol* 2015; 13: 30
- Rombauts L, McMaster R, Motteram C et al. Risk of ectopic pregnancy is linked to endometrial thickness in a retrospective cohort study of 8120 assisted reproduction technology cycles. *Hum Reprod* 2015; 30: 2846–2852
- Zhang YL, Sun J, Su YC et al. [Study on the incidence and influences on ectopic pregnancy from embryo transfer of fresh cycles and frozen-thawed cycles]. *Zhonghua Fu Chan Ke Za Zhi* 2012; 47: 655–658
- Mol F, van Mello NM, Strandell A et al. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. *Lancet* 2014; 383: 1483–1489
- Spandorfer SD, Sawin SW, Benjamin I et al. Postoperative day 1 serum human chorionic gonadotropin level as a predictor of persistent ectopic pregnancy after conservative surgical management. *Fertil Steril* 1997; 68: 430–434
- Seifer DB. Persistent ectopic pregnancy: an argument for heightened vigilance and patient compliance. *Fertil Steril* 1997; 68: 402–404
- Patil M. Ectopic pregnancy after infertility treatment. *J Hum Reprod Sci* 2012; 5: 154–165
- Dubuisson JB, Aubriot FX, Foulot H et al. Reproductive outcome after laparoscopic salpingectomy for tubal pregnancy. *Fertil Steril* 1990; 53: 1004–1007
- van Mello NM, Mol F, Opmeer BC et al. Salpingotomy or salpingectomy in tubal ectopic pregnancy: what do women prefer? *Reprod Biomed Online* 2010; 21: 687–693
- de Bennetot M, Rabischong B, Aublet-Cuvelier B et al. Fertility after tubal ectopic pregnancy: results of a population-based study. *Fertil Steril* 2012; 98: 1271-6.e1–1271-6.e3