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Improved fertility following conservative surgical treatment of ectopic pregnancy

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Objective To evaluate fertility after salpingectomy or tubotomy for ectopic pregnancy.

Design Retrospective cohort study.

Setting Clinical University Center, Hvidovre Hospital, Copenhagen.

Population Two hundred and seventy-six women undergoing salpingectomy or tubotomy for their first ectopic pregnancy between January 1992 and January 1999 and who actively attempted to conceive were followed for a minimum of 18 months.

Methods Retrospective cohort study combined with questionnaire to compare reproductive outcome following salpingectomy or tubotomy for ectopic pregnancy. Cummulative probabilities of pregnancy for each group were calculated by the Kaplan–Meier estimator and compared by Cox regression analysis to control for potential confounders.

Main outcome measures Intrauterine pregnancy rates and recurrence rates of ectopic pregnancy after surgery for ectopic pregnancy.

Results The cumulative intrauterine pregnancy rate was significantly higher after tubotomy (88%) than after salpingectomy (66%) (log rank $P < 0.05$) after correction for confounding factors. No difference was found in the recurrence rate of ectopic pregnancy between the treatments (16% *vs* 17%). In patients with contralateral tubal pathology, the chance of pregnancy was poor (hazard ratio 0.463) and the risk of recurrence was high (hazard ratio 2.25), assessed with Cox regression. The rate of persistent ectopic pregnancy was 8%.

Conclusion Conservative surgery is superior to radical surgery at preserving fertility. Conservative surgery is not followed by an increased risk of repeat ectopic pregnancy, but by the risk of persistent ectopic pregnancy, which should be taken into account when deciding on the operative procedure. Management in case of contralateral tubal pathology is disputed and should ideally be addressed in a randomised clinical trial.

INTRODUCTION

The incidence of ectopic pregnancy has increased dramatically worldwide over the past few decades, currently accounting for 2% of all pregnancies. The increased incidence of ectopic pregnancy has occurred simultaneously with an increased incidence of pelvic inflammatory diseases, suggesting a causal relationship. Improvements in the treatment of pelvic inflammatory diseases may partly preserve tubal function in women who earlier were prone to complete infertility. The increased incidence of ectopic pregnancy is also a result of the progress in diagnostic modalities as highly sensitive human chorionic gonadotrophin radio-immunoassay and vaginal ultrasonography allowing early diagnosis of tubal pregnancies, some of which may have been unrecognised in the past. Early diagnosis and treatment of ectopic pregnancy has led to a decreased mortality rate and has changed the management of unruptured tubal pregnancy from an immediate, life-saving intervention to methods directed at preserving fertility. Laparoscopic surgery has become the golden standard for the treatment of ectopic pregnancy and seems to have advantages compared with laparotomy in terms of: duration of surgery, length of hospital stay and reconvalesence, analgesic requirement and hospital cost[1–4]. There is a growing consensus that laparotomy should be performed only in the instances in which the laparoscopic approach is difficult or the patient is haemodynamically unstable. Differences in future fertility between the two surgical approaches have not been firmly established[2–5].

Early diagnosis and the laparoscopic approach have been accompanied by an increased use of tubotomy with removal of the products of conception and preservation of the tube hoping that fertility is preserved. The choice between a conservative tube-preserving operation and a radical salpingectomy requires detailed knowledge of the benefits and risks of each type of surgery. Of special interest are the effects of surgery on future fertility, the risk of persistent trophoblast and the risk of a repeat

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ectopic pregnancy. The aim of this study was to clarify these issues.

METHODS

Between January 1992 and January 1999, 806 surgical interventions for ectopic pregnancy were performed at the Department of Obstetrics and Gynaecology, Hvidovre University Hospital, Denmark. The present study was confined to women who presented with their first spontaneous, histologically verified, tubal ectopic pregnancy during this interval, were treated with either salpingectomy or linear tubotomy, were aged 17 to 38 years, had not previously been sterilised and who actively attempted to conceive post-operatively.

Data were obtained retrospectively from medical files. The following information was collected: age, parity, previous history of ectopic pregnancy, location of the ectopic pregnancy, ruptured tube, operation method, presence of pelvic adhesions, condition of the contralateral salpinx, previous abdominopelvic surgery, treatment of infertility and the use of IUDs.

Subsequent fertility was elucidated using a mailed questionnaire. Questions included desire for pregnancy, treatment for infertility and pregnancy achieved after the operation. The women stated the outcome of the pregnancy as live birth, miscarriage, induced abortion or ectopic pregnancy as well as the time of termination of the pregnancy. For those giving birth, the last menstrual date was calculated assuming delivery at 40 weeks of gestation and for pregnancies resulting in abortion (spontaneous or induced), an average gestational age of eight weeks was used for calculation of last menstrual date. The questionnaire was mailed in June 2000, which resulted in at least 18 months follow up for all women.

Of the 651 women who underwent surgery for their first ectopic pregnancy in the defined period, 46 women were not between 17 and 38 years of age, 11 had previously been sterilised, 9 had a bilateral salpingectomy, 28 had other types of surgery than the two of interest and 48 were not histologically verified. In 39 cases, the ectopic pregnancy was a result of fertility treatment and 31 women were not available for contact (emmigration/death). The remaining 473 women, who satisfied the selection criteria, were identified and sent a questionnaire. Three hundred and fifty-five (75%) women returned the questionnaire. Of these, 79 did not attempt conception, which left 276 women for analysis.

The characteristics of the 118 women lost for follow up did not differ significantly from those available for analysis with respect to surgical intervention.

The women were divided into two groups based on surgical procedure: radical (salpingectomy) and conservative (tubotomy) surgery.

Baseline characteristics of the two groups were compared using Fisher's exact test or Student's t test as appropriate, with $P < 0.05$ as the level of statistical significance.

Cumulative probabilities of spontaneous intrauterine pregnancy over time were calculated for each group by use of the Kaplan–Meier estimator. The starting point for the calculations was the date of operation. The endpoint was the primary outcome measure, the date of accomplished spontaneous intrauterine pregnancy. If pregnancy was obtained by aid of infertility treatment, the woman was censored from the analysis at the date the treatment began (28 in the conservative group and 12 in the radical group). The endpoint for the women who did not become pregnant was the last date of contact. In the same way, cumulative probabilities of repeated ectopic pregnancy were calculated for each group. Cumulative pregnancy curves were generated and compared using the log-rank test.

Cox proportional hazard regression analysis was used to compare the effect of conservative surgery with radical surgery, and to take into account potential confounding factors through multivariate analysis. The covariate factors were tested for time consistency, log linearity and additivity before the analysis was performed. The factors considered to be potential confounders were: age, contralateral tube pathology and previous fertility surgery as a sign of infertility. All statistical analyses were performed by use of SAS system version 8 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline characteristics of the 276 women available for analysis are presented in Table 1. Two hundred and eight (75%) women were treated conservatively and 68 (25%) radically. The women who underwent radical surgery were generally older ($P = 0.06$); they were more likely to have

Table 1. Baseline characteristics in 276 women treated by either conservative (tubotomy) or radical (salpingectomy) surgery for ectopic pregnancy. Values are given as number of patients with percentage in the parentheses.

	Conservative	**Radical**
	$n = 208$ (75%)	$n = 68$ (25%)
Age, mean [SD]	29.0 [3.97]	30.1 [4.45]
Nulliparity	131 (63)*	33 (49)
History of induced abortion	58 (28)	21 (31)
History of miscarriage	58 (28)	13 (19)
History of a abdominopelvic surgery	23 (11)	9 (13)
History of fertility surgery	16 (8)	7 (10)
Per-operative adhesion	64 (31)*	30 (44)
Per-operative contralateral pathology	30 (14)*	17 (25)
Rupture	7 (3)**	19 (28)
IUD—*in situ*	10 (5)	4 (6)
Laparoscopy	193 (93)	52 (76)
Laparotomy	15 (7)	16 (23)

* $P < 0.05$, Student's t test and Fisher's exact test.
** $P < 0.001$, Student's t test and Fisher's exact test.

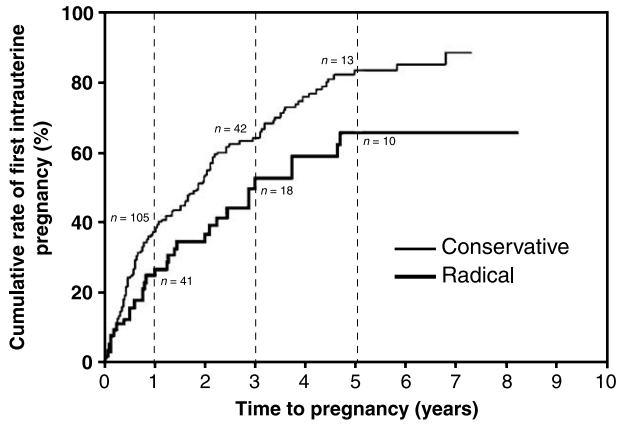

Fig. 1. Cumulative pregnancy rates (Kaplan–Meier estimator) for the first ectopic pregnancy in 276 women (208 conservative and 68 radical) attempting pregnancy. Number of women left for analysis after one, three and five years are stated.

given birth ($P < 0.04$); more had adhesions ($P < 0.04$) and contralateral tube pathology ($P < 0.04$). The women treated with radical surgery presented more frequently with tubal rupture ($P < 0.0001$).

Two hundred (72%) women obtained a spontaneous intrauterine pregnancy during follow up, 161 after conservative surgery and 39 after radical surgery. Among the 161 women with an intrauterine pregnancy after conservative surgery, 88 had a full-term birth, 36 a miscarriage, 5 an induced abortion and 4 were still pregnant at the time of the analysis. Among the 39 women with intrauterine pregnancy after radical surgery, 21 had a full-term birth, 9 a miscarriage and 1 an induced abortion.

The cumulative rates of spontaneous intrauterine pregnancies for both groups are shown in Fig. 1. Women treated with conservative surgery were more likely to conceive ($P < 0.006$, log-rank test). The seven year cumulative spontaneous intrauterine pregnancy rate was 89% after conservative surgery and 66% after radical surgery. In the group treated radically, the women stopped conceiving after five years follow up, whereas the women in the conservative group continued to conceive. In the group treated with conservative surgery, a 50% conception rate was reached after the first 22 months follow up (95% CI 16–26). In the radical group, a 50% conception rate was not reached until 36 months after surgery (95% CI 25–56). The effect of conservative surgery is given in Table 2. With conservative treatment as the reference, the hazard ratio for radical treatment in the univariate analysis is 0.582 (i.e. if given radical treatment, the chance of conceiving was only 58% of the chance of conceiving if given conservative treatment). When adjusting for confounders, the difference between the treatments was reduced to 0.630 (95% CI 0.421–0.940; $P < 0.024$).

Disregarding the type of surgery, the chances of conceiving were better if the contralateral tube was normal (hazard ratio: 0.463; 95% CI 0.262–0.820; $P < 0.008$).

Thirty-six (13%) women had a repeat ectopic pregnancy during follow up, 28 after conservative surgery and 8 after radical surgery.

The cumulative rates of repeat ectopic pregnancies were generated for both groups (data not shown). There was no difference in the risk of repeat ectopic pregnancy between the two groups ($P = 0.55$, log-rank test). The two year cumulative repeat ectopic pregnancy rate was 16% after radical surgery and 17% after conservative surgery. In the radical group, there were no repeat ectopic pregnancies beyond the first two years. In the conservative group, three women had a repeat ectopic pregnancy after two years, giving a 3.5 year cumulative repeat ectopic pregnancy rate at 23% in this group.

Cox regression multivariate analysis showed no significant difference in the risk of repeat ectopic pregnancy after the two surgical methods (Table 3). However, other factors were found to be correlated with an increased risk of repeat ectopic pregnancy, including contralateral tubal pathology with a hazard ratio of 2.25 (95% CI 1.116–4.531; $P < 0.02$) and previous fertility operation with a hazard ratio of 2.514 (95% CI 1.002–6.308; $P < 0.05$).

Seventeen women treated with conservative surgery experienced a persistent ectopic pregnancy after the index

Table 2. Hazard ratios for the occurrence of spontaneous intrauterine pregnancy using Cox regression analysis.

	Univariate analysis hazard ratio (95% CI)	Multivariate analysis hazard ratio (95% CI)*
Radical surgery	0.582** (0.393–0.861)	0.630** (0.421–0.940)
Conservative surgery	1	1
Age		
<22	1.834 (0.875–3.843)	1.762 (0.837–3.71)
22–25	1.088 (0.705–1.680)	1.034 (0.668–1.600)
26–29	1	1
30–33	0.994 (0.673–1.469)	1.004 (0.679–1.486)
>33	0.690 (0.420–1.134)	0.795 (0,478–1,322)
Contralateral tube pathology	0.421** (0.239–0.742)	0.463** (0.262–0.820)
Previous fertility operation	0.598 (0.280–1.276)	0.739 (0.342–1.596)

* Adjusted for the factors in the table.

** $P < 0.05$.

Table 3. Hazard ratios for the occurrence of repeat ectopic pregnancy using Cox regression analysis.

	Univariate analysis hazard ratio (95% CI)	Multivariate analysis hazard ratio (95% CI)*
Radical surgery	0.785 (0.358–1.724)	0.782 (0.348–1.755)
Conservative surgery	1	1
Age		
<22	0	0
22–25	0.378 (0.112–1.281)	0.401 (0.118–1.362)
26–29	1	1
30–33	0.679 (0.307–1.502)	0.621 (0.275–1.399)
>33	0.563 (0.210–1.509)	0.469 (0.167–1.315)
Contralateral tube pathology	2.291** (1.145–4.853)	2.248** (1.116–4.531)
Previous fertility operation	2.546** (1.057–6.134)	2.514** (1.002–6.308)

* Adjusted for the factors in the table.
** $P < 0.05$.

ectopic pregnancy, diagnosed as a lack of decline in serum hCG or clinical symptoms. Nine were treated initially with methotrexate (7 successfully, 2 needed salpingectomy), 7 with salpingectomy and 1 with repeated salpingotomy. Thirteen of these women had a spontaneous intrauterine pregnancy during follow up.

DISCUSSION

This study supports the notion that conservative surgery is superior to radical surgery at preserving fertility following ectopic pregnancy.

An ectopic pregnancy with a ruptured or severely damaged tube renders little choice but salpingectomy. In many cases, early diagnosis allows a conservative approach resulting in a tube with normal macroscopic appearance and thereby hopefully preserved tubal patency and function. However, leaving the affected tube infers a risk of persistent trophoblast disease. A conservative procedure can therefore only be recommended if the method is associated with other advantages, most importantly, an increased possibility of intrauterine pregnancy, and a risk of repeat ectopic pregnancy comparable to that of salpingectomy.

The observed cumulative pregnancy rates of 89% for conservative and 66% for radical surgery are fairly high[6–10]. The pregnancy rate is highly influenced by baseline characteristics, which vary from study to study. Compared with other studies, the present population of the present study is generally younger, with a lower frequency of women with a history of infertility and contralateral tubal pathology, which are all factors known to influence pregnancy rate. It is possible that our pregnancy rates are over-estimated due to selection bias. The women not responding were identical to the responders in basic characteristics, but women hoping for, but not achieving, pregnancy may be less likely to report their negative outcomes. The response rate of 75 is, however, comparable to that in most retrospective studies addressing fertility after treatment of ectopic pregnancy[7,8]. All women included in the analysis had a desire for pregnancy, which gives the most accurate fertility result, and avoids a skewed result if they are not evenly distributed in the two groups. The wish for pregnancy may vary depending on different life circumstances and, as in most other studies, we could not control for such factors. Obtaining a more accurate measurement of fertility rates requires knowledge of the women's continued wish to become pregnant, an active attempt and a fertile partner. Selection biases and difficulties in obtaining accurate assessments are problems of retrospective studies, and could only be overcome with the use of a prospective study with close surveillance of the cohort.

Direct comparison of cumulative pregnancy rates with other studies requires the use of identical methodology, including survival analysis, taking into account the differences in duration of follow up. Some studies report absolute intrauterine pregnancy rates and do not perform survival analysis[11–13]. Others perform survival analysis, but do not adjust for confounding factors[7,8,14]. Some do not report whether or not the women desired pregnancy, and fail to report how subsequent pregnancies were achieved[13,15].

Using survival analysis, cumulative pregnancy rates of 38–62% have been found in a retrospective study[16] and rates of 57–73% in an 18 month prospective study[9]. Both these studies included women with their second or third ectopic pregnancy. Several studies have shown that fertility is reduced by one-third for each additional ectopic pregnancy between the first and the third ectopic pregnancies[17,18]. Our study only included patients with their first ectopic pregnancies and had a longer follow up. These differences may account partly for the high cumulative pregnancy rates.

The strength of the present study is the large study group that is highly selected to avoid major biases. Only histologically confirmed cases were included, because inclusion of non-verified pregnancies could over-estimate the pregnancy rate and under-estimate the rate of persistent ectopic pregnancy and repeat ectopic pregnancy. Survival analysis was performed, taking into account differences in duration of follow up. Women who obtained an IVF pregnancy were

included, but were censored at the start of the IVF treatment, at which point their ability to conceive spontaneously could no longer be measured. Women referred to IVF are likely to have a low fertility prognosis, but censoring these women completely would lead to an over-estimation of the pregnancy rate.

In the present study, conservative surgery was significantly better than radical surgery in preserving fertility. Because our study was not randomised, it was important to make sure that the two treatment groups were comparable. Multivariate analysis was performed to take into account potential confounding factors that could affect the choice of surgery. The factors chosen in this study — age, contralateral tubal pathology and history of infertility — have all been associated with subsequent infertility in numerous studies[6–8,18]. The fact that more women in the radical group had given birth infers a better fertility in the radical group. It is therefore unlikely that differences in response rates or selection bias can explain the differences between the two groups.

Earlier studies have not been able to show a significant difference in fertility after different types of tubal surgery for ectopic gestation. Mol *et al.*[16] found a difference between the two surgical methods in 135 women but the cumulative pregnancy rates of 38% radical surgery and 62% for conservative surgery were not significant after adjusting for confounders (hazard ratio 1.9; 95% CI 0.91–3.8). In a prospective study, Bouyer *et al.*[9] found no significant differences between an 18 month cumulative pregnancy rate of 73% after conservative surgery and 57% after radical surgery (hazard ratio 0.72; 95% CI 0.45–1.1). Accurate measures of the women's desire for pregnancy were obtained prospectively by telephone interviews and with an impressive response rate of 90%, the risk of selection bias is small. A comparative non-significant difference with pregnancy rates of 56% and 72% was described in a prospective study with a follow up of one year (hazard ratio 1.56; 95% CI 0.96–2.65)[6]. Similarly, Ego *et al.*[18] found that the fertility was unrelated to the type of surgical treatment as assessed by Cox multivariate analysis (hazard ratio 1.33; 95% CI 0.97–1.81).

In our study, the cumulative pregnancy rates continued to increase during the full length of the follow up period and increased more rapidly after conservative surgery than after radical surgery. Compared with other studies, our population was larger and had a longer duration of follow up. The conclusion of a better fertility prognosis after the conservative approach is therefore substantiated by other recent studies showing a trend in favour of the conservative approach.

We found an overall risk of repeat ectopic pregnancy of 16%, which is comparable to that obtained in other studies[6,11]. Some report higher rates of repeat ectopic pregnancy around 25%[9,16], but these studies have included women with their second and third ectopic pregnancies (i.e. women with a confirmed higher risk of repeat ectopic pregnancy). In the present study, the risk of repeat ectopic pregnancy was independent of the type of surgery. This is consistent with several studies[8,10,19]. It can therefore be concluded that a conservative operation does not seem to increase this risk of repeat ectopic pregnancy.

The occurrence of persistent ectopic pregnancy was 8% and all incidents followed conservative surgery. The risk of persistent trophoblast varies from study to study and both lower[8,10], and higher[15,20] incidences are reported. It is very likely that the discrepancy depends on different definitions of persistent ectopic pregnancy, although factors such as patient selection and differences in operative skill could play a role. Treatment of persistent ectopic pregnancy does not seem to affect the fertility prognosis adversely, although the number of cases in the present study is too small to draw firm conclusions.

In concordance with many investigators, we found that contralateral tubal pathology is highly related to a poor fertility prognosis and an increased risk of repeat ectopic pregnancy, disregarding the type of surgery. Handling of these cases is controversial. Should both damaged tubes be removed and IVF offered or should the surgeon try to preserve both tubes? Some investigators have demonstrated that conservative surgery is especially effective compared with radical surgery in preserving fertility when the contralateral tube is diseased[16,19]. It would be of great value to investigate the crude pregnancy rates after conservative surgery compared with bilateral salpingectomy plus IVF treatment, as this is another alternative to conservative treatment especially relevant for older women.

CONCLUSION

In conclusion, we have found conservative surgery to be superior to radical surgery at preserving fertility. Conservative surgery is not followed by an increased risk of repeat ectopic pregnancy, but the risk of persistent ectopic pregnancy should be taken into account when deciding on operative procedure. Management in case of contralateral tubal pathology is disputed and should ideally be addressed in a randomised clinical trial.

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