

# Fertility after tubal ectopic pregnancy: results of a population-based study

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**Objective:** To assess the reproductive outcome after an ectopic pregnancy (EP) based on the type of treatment used, and to identify predictive factors of spontaneous fertility.

**Design:** Observational population based-study.

**Setting:** Regional sistry.

**Patient(s):** One thousand sixty-four women registered from 1992 to 2008.

**Intervention(s):** Laparoscopic (radical or conservative), or medical treatment.

**Main Outcome Measure(s):** Epidemiologic characteristics, clinical presentation, treatments performed, reproductive outcome, recurrence.

**Result(s):** The 24-month cumulative rate of intrauterine pregnancy (IUP) was 67% after salpingectomy, 76% after salpingostomy, and 76% after medical treatment. IUP rate was lower after radical treatment compared with conservative treatments in univariable analysis. In multivariate analysis, IUP rate was significantly lower for patients >35 years old or with history of infertility or tubal disease. For them, IUP rate was significantly higher after conservative treatment compared with salpingectomy. The 2-year cumulative rate of recurrences was 18.5% after salpingostomy or salpingectomy and 25.5% after medical treatment. History of infertility or of previous live birth would be protective, in contrast to history of voluntary termination of pregnancy.

**Conclusion(s):** Conservative strategy seems to be preferred, whenever possible, to preserve patients' fertility without increasing the risk of recurrence. The choice between conservative treatments does not rely on subsequent fertility, but more likely on their own indications and therapeutic effectiveness. Risk factors of recurrence could be considered for secondary prevention. (*Fertil Steril*® 2012;98:1271–6. ©2012 by American Society for Reproductive Medicine.)

**Key Words:** Fertility, ectopic pregnancy, recurrence, risk factor, treatment method, laparoscopy, methotrexate

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Ectopic pregnancies (EPs) occur among 2% of pregnant women in developed countries (1) and may seriously compromise women's health and future fertility (2). The management of EPs has made significant

progress in diagnostic and therapeutic efficiency (3, 4). Over the past 40 years, laparoscopy has emerged as the criterion standard technique for the surgical management of EP (5), and in the meantime medical treatment with

methotrexate has been widely developed (5, 6). Whatever the treatment, in addition to its effectiveness, the current issue is the preservation of patients' fertility, including limiting the risk of recurrence. The role of treatment in optimizing subsequent fertility is a controversial subject, which has not been settled by previous studies (7). Fertility after laparoscopic salpingectomy has been compared with laparoscopic salpingostomy in many retrospective studies or reviews. Some

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didn't seem to show a difference between the two techniques (8–10), whereas others showed higher rates of intrauterine pregnancy (IUP) after conservative-surgical treatment (11–13). However, the results of these studies were not statistically significant after adjustment for confounders. Similarly, the risk of recurrence according to the surgical techniques is still discussed, with some retrospective studies showing higher recurrence rates after laparoscopic salpingostomy (11), and others no difference (8, 13, 14). More recently, the question arose of the existence of a variation of future fertility based on the conservative treatment chosen: laparoscopic salpingostomy or medical treatment with methotrexate. Few prospective randomized studies have been published, and their results do not support a conclusion on this issue (15, 16).

The present study aimed to compare the subsequent fertility of women who had experienced EP according to the type of treatment they received—radical, conservative-surgical or medical—and to find risk factors of repeated ectopic pregnancy. It was based on population-based data of the Auvergne (France) Ectopic Pregnancy Registry.

## METHODS

The Auvergne Ectopic Pregnancy Registry data were analyzed from 1992 to 2008. The methodology of the registry has been described previously (1, 17). All of the women from 15 to 44 years old, who resided permanently in the Auvergne region, treated for an EP in one of the 20 health center areas were registered. They were prospectively followed until the age of 45 years to study their reproductive outcome. The information collected for each woman included: sociodemographic characteristics; sexual, gynecologic, reproductive, and surgical histories; smoking habits; condition of conception (e.g., contraception, ovulation induction); results of *Chlamydia trachomatis* serologic tests; characteristics of the EP; and treatment procedures used. Women followed were interviewed on the phone every 6 months during the first 2 years and every year after. The questions focused on the quest for a new pregnancy, getting pregnant again, the outcome of subsequent pregnancies, and the use of contraceptives and medical measures related to infertility.

To evaluate the accuracy of the registry, the discharge diagnosis files of the different centers from 1993 onward were reviewed (two-source capture-recapture method). The completeness of the register was estimated to be 90%.

The registry was granted and qualified by Comité National des Registres (CNR). Data collected were treated confidentially according to Commission Nationale de l'Informatique et Liberté (CNIL) statements. Institutional Review Board approvals from CNR and CNIL were obtained. Data were then centralized at the Department of Medical Information of the Centre Hospitalier Universitaire in Clermont-Ferrand.

After excluding patients with prior history of an EP, patients who did not report seeking pregnancy during follow-up, those who benefited from a second-line treatment, those treated with RU-486 or laparotomy, and patients supported with in vitro fertilization (IVF), 1,622 patients met our inclu-

sion criteria. Among them, 558 patients were not retained in the study because they were lost in follow-up ( $n = 314$ ; 12.3%) or because they were 45 years old or were minor or received bilateral salpingectomy with no desire of IVF. Finally, reproductive outcome were studied for 1,064 patients (Supplemental Fig. 1, available online at [www.fertstert.org](http://www.fertstert.org)).

Patients received conservative medical, conservative laparoscopic, or radical laparoscopic treatment. Medical treatment was chosen for asymptomatic patients with no evidence of tubal rupture and  $\beta$ -hCG  $< 5,000$  UI/L. The protocol consisted of an intramuscular injection of a single dose of methotrexate ( $50 \text{ mg/m}^2$ ). In case of history of methotrexate failure, surgical treatment was chosen. The decision between salpingostomy and salpingectomy was based on the pretherapeutic score proposed by Pouly et al. (18).

All IUPs were taken into account regardless of the outcome. For fertility study, if a recurrence occurred, it was ignored and the follow-up continued, and conversely for the recurrence study. Only the first IUP or the first recurrence was registered. In both cases, survival analysis methods were used, with a calculation of the time needed to conceive, which is the cumulative period of time during which a woman is trying to become pregnant until she gets pregnant or is censored. Because only spontaneous fertility was studied, the follow-up was censored if a woman began an IVF program.

For subsequent spontaneous IUP, we first analyzed the whole sample. According to the results of our previous studies, women with history of infertility or tubal disease at the time of the first EP and those  $> 35$  years old were studied separately from the others (19). The group of patients with a history of tubal disease included women who, at the time of inclusion in the register, said that they have had a history of tubal surgery or microsurgery, pelvic inflammatory disease, and/or *Chlamydia trachomatis* infection.

Cumulative rates of recurrent EP and spontaneous IUP were calculated by the Kaplan-Meier estimator with confidence interval for each of the three treatments. The curves obtained were compared by log rank tests for single-variable analysis and by Cox regression to take into account confounding variables, such as sociodemographic and clinical characteristics of women, that may influence the choice of treatment. Regarding recurrences, risk factors were also searched by single-variable and multivariable analysis. Statistical analysis was performed with the use of SAS statistical software v8.02 (SAS Institute). Statistical significance was established at  $P < .05$ .

## RESULTS

### Fertility Outcome

The treatment given was radical for 299 women (28%), conservative-surgical for 646 (61%), and conservative-medical for 119 (11%). Some sociodemographic and clinical characteristics of the women differed according to the treatment they had received (Supplemental Table 1).

Among the 1,064 women who attempted to conceive again, 744 were pregnant spontaneously. The outcome of these pregnancies was 82% for a vaginal delivery or cesarean section, 17% for miscarriage, and 1% for a voluntary

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