

Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France.

Jean Bouyer, Joël Coste, Taraneh Shojaei, Jean-Luc Pouly, Hervé Fernandez, Laurent Gerbaud, Nadine Job-Spira

▶ **To cite this version:**

Jean Bouyer, Joël Coste, Taraneh Shojaei, Jean-Luc Pouly, Hervé Fernandez, et al.. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France.. American Journal of Epidemiology, 2003, 157 (3), pp.185-94. inserm-00086499

HAL Id: inserm-00086499
https://inserm.hal.science/inserm-00086499

Submitted on 27 Feb 2007

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

HAL author manuscript

Am J Epidemiol 01/02/2003; 157(3): 185-94

Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control population-based study in France

Word counts

text: 3083

abstract: 198

Jean Bouyer [1]

Joël Coste [1]

Taraneh Shojaei [1]

Jean-Luc Pouly [3]

Hervé Fernandez [1,2]

Laurent Gerbaud [4]

Nadine Job-Spira [1]

This is a pre-copy-editing, author-produced PDF of an article accepted for publication in American journal of epidemiology following peer review.
The definitive publisher-authenticated version 2003 Feb 1;157(3):185-94 is available online at: http://aje.oxfordjournals.org/

HAL author manuscript inserm-00086499, version 1

HAL author manuscript inserm-00086499, version 1

Abbreviations

AR: attributable risk
CI: confidence interval
EP: ectopic pregnancy
IUD: intrauterine device
OR: odds ratio
PID: pelvic inflammatory disease
STD: sexually transmitted disease

Authors' affiliation

[1] INSERM U569, IFR69 (The French Institute of Health and Medical Research) Le Kremlin-Bicêtre. France

[2] Hôpital Antoine Béclère, Service de Gynécologie-Obstétrique, Clamart, France

[3] Centre Hospitalier Hôtel-Dieu, Service de Gynécologie-Obstétrique, Clermont-Ferrand, France

[4] Service d'Epidémiologie et de Santé Publique, Clermont-Ferrand, France

Reprint requests:
J. Bouyer, INSERM U569 - Hôpital de Bicêtre - 82 rue du Général Leclerc - 94276 Le Kremlin-Bicêtre Cedex. France
(Fax: 33 1 45 21 20 75; e-mail: Bouyer@vjf.inserm.fr)

Running head: Risk factors for ectopic pregnancy

Short title: Risk factors for ectopic pregnancy

Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control population-based study in France

HAL author manuscript inserm-00086499, version 1

HAL author manuscript inserm-00086499, version 1

ABSTRACT

This case-control study was associated with a regional register of ectopic pregnancy (EP) in France. It included 803 cases of EP and 1683 deliveries, and was powerful enough to investigate all EP risk factors. The main risk factors were infectious history (adjusted attributable risk AR_a = 0.33 and adjusted odds ratio for previous pelvic infectious disease OR_a= 3.4 (95%CI: 2.4, 5.0)), and smoking (AR_a = 0.35; OR_a= 3.9 (95% CI: 2.6, 5.9) for more than 20 cigarettes/day versus women who had never smoked. The other risk factors were age (associated *per se* with a risk of EP), prior spontaneous abortions, history of infertility, and previous use of an intrauterine device. Prior medical induced abortion was associated with a risk of EP: OR_a= 2.8 (95% CI: 1.1; 7.2); no such association was observed for surgical abortion (OR_a = 1.1 (95% CI: 0.8, 1.6)). The total AR of all the factors investigated was 0.76. As tight associations were found between EP and infertility and between EP and spontaneous abortion, further research into EP should focus on risk factors common to these conditions. In terms of public health, increasing awareness of the effects of smoking may be useful for EP prevention.

HAL author manuscript inserm-00086499, version 1

During the 1980s and 1990s, the incidence of ectopic pregnancy (EP) in developed countries increased by a factor of three to four (1-5), reaching 100 to 175 per 1,000,000 women aged 15-44.

Several risk factors for EP have been identified (3, 6-8) including pelvic inflammatory disease (PID), smoking and, previous EP. Other factors, such as age, surgical and obstetric history are also thought to be involved. However, the role played by these factors remains unclear due to problems with the sample size or design of previous studies. Published meta-analyses on EP risk factors (9-11) only partly answered the questions addressed, mainly because their ability to adjust for confounders was limited (12, 13). This problem is particularly severe in analyses of EP, which has a large number of highly correlated risk factors. The selection of studies to be included in the meta-analysis, and assessment of their quality, may also cause difficulties. Strikingly, in the two most recent meta-analyses on this subject, two different sets of studies were selected (9, 10).

The EP register of Auvergne (France) (14), and associated case-control studies, provide an opportunity to analyze the risk factors for EP in a large sample, representative of a geographically defined population. Results concerning women using contraception at the time of conception have already being published (15). This study focuses on women not using contraception at the time of conception and aimed to provide a comprehensive analysis of the EP risk factors in these women.

MATERIALS AND METHODS

Study population

The methodology of the register has been described elsewhere (14). The register was established in January 1992 in the Auvergne region in central France (around 1.1 million inhabitants). All the women between 15 and 44 years of age living in the target area who were treated for ectopic pregnancy were registered. At each center (15 maternity hospitals and 12 surgical units, either public or private), a trained investigator — a midwife or a physician — was responsible of case identification and data collection and this investigator checked the completeness of case recording at the end of each year. The information collected for each woman (from interview and medical records) included socio-demographic characteristics, gynecological, reproductive and surgical

HAL author manuscript inserm-00086499, version 1

history, conditions at conception (use of contraception, ovulation induction), smoking habits, results of serological tests for *Chlamydia trachomatis*, characteristics of the EP, and the treatment procedures used.

Each case of EP in a woman not using contraception was associated with two controls: women who gave birth at the center at which the case was treated, and whose delivery occurred very shortly after treatment of the case. For some cases, only one control was interviewed, and no control was associated with cases retrieved at the end of the year when checking the completeness of the register. The same questionnaire was used for cases and controls, except for items directly relating to the diagnosis and treatment of EP. Between September 1993 (beginning of controls recruitment) and December 2000, 1065 cases and 1881 controls were collected.

Women who underwent induced abortion were not included in the control group because, in France, these women are referred to specialist centers unconnected with maternity hospitals. However, a certain proportion of cases might have undergone induced abortion had their pregnancy been intrauterine. We attempted to take this into account by the method recommended by Weiss *et al.* (16), which involves restricting the analysis to women married (or living in a couple) and not using contraception at the time of conception (803 cases and 1683 controls). As stated by Weiss *et al*., this restriction should make cases and controls more comparable, reducing the magnitude of the bias present when evaluating variables associated with induced abortion.

Statistical analysis

We carried out a two-stage analysis as a large number of potential risk factors were investigated. We first assigned the risk factors to four groups: 1) socio-demographic characteristics, 2) surgical, gynecological and obstetric history, 3) potential exposure to infectious factors, 4) contraceptive history and fertility markers. Univariate analyses were performed to generate crude odds ratios (OR). Logistic regressions were then performed within each group, including variables with p values ≤ 0.2 in univariate analysis (17). Finally, variables with p values ≤ 0.2 in these four partial

HAL author manuscript inserm-00086499, version 1

analyses were included in a global logistic regression analysis. The assignment of a factor to a particular group was a matter of debate in some instances. We checked that the assignment of such factors to particular groups had no influence on the final logistic regression analysis.

For quantitative variables, such as age or time since the previous pregnancy, the association with EP risk was plotted using fractional polynomials (18), a simple and powerful way of modeling non-linear relationships.

Finally, attributable risks (AR) were calculated for each risk factor. AR provide an additional dimension to risk factors that is useful for public health purposes. The OR gives the individual increase in risk of EP for a woman exposed to that risk, whereas the AR indicates the burden of this risk factor at the population level. AR were adjusted for the other risk factors as described by Bruzzi *et al.* (19). For age, the category 25-29 years was taken as the reference because this corresponds to the mean age for delivery in France at the time of the study. Thus, OR and AR were calculated with this category considered as "non-exposed".

A woman experiencing several EPs during the study period generated multiple case entries, one for each EP. In this study, 43 women experienced 2 EPs and 4 women experienced 3 EPs, i.e. 12% of all EPs. Although this proportion was relatively small, the potential non-independence of data induced was taken into account using random effects model (17) in the multivariate analysis (incidentally, we observed that the results were quite similar to those obtained with a usual logistic model).

Statistical analyses were performed with STATA software (20).

RESULTS

The results of univariate analysis are shown in Tables 1 to 4. Table 5 gives the results of the multivariate analysis (final logistic regression), and Table 6, the adjusted ARs.

Socio-demographic characteristics and cigarette smoking

The crude risk of ectopic pregnancy increased with age (Table 1). Although the trend was less

HAL author manuscript inserm-00086499, version 1

marked after adjustment, it remained statistically significant (Figure 1 and Table 5). The slope of the association appeared to be steeper after 35-40 years. There was no association between ectopic pregnancy and other socio-demographic characteristics (not shown).

The risk associated with smoking increased in a dose-dependent manner (Table 5). Among past smokers, the time since smoking cessation was not associated with EP risk (not shown). The prevalence of past or current smoking in our population was particularly high (41 percent among controls), resulting in an adjusted attributable risk of smoking as high as 35 percent (Table 6).

Surgical and obstetric history

Most of the items recorded in the patients' obstetric histories were associated with EP (Table 2). However, the age of the woman and previous IUD use accounted for the crude association with prior delivery. We therefore did not include the variable "prior deliveries" in the final multivariate analysis to avoid over-adjustment. Although the association with prior ectopic pregnancies was very strong, this variable was not included in the final multivariate analysis. Instead, we included a broader variable, "tubal surgery", which covered all indications for tubal surgery, not only EP treatment.

Prior spontaneous abortions increased the risk of EP, especially for women with three or more spontaneous abortions (Tables 2 and 5).

The risk of EP was higher in women who had had induced abortions. However, the OR differed according to the method used for abortion (Table 2). The results were similar after adjustment (Table 5): with prior surgical abortion only OR = 1.1 (95 percent CI: 0.8; 1.6), whereas the OR in women with prior medical abortion only (Mifepristone and Misoprostol) was 2.8 (1.1; 7.2).

Infectious history

Infectious history was studied through direct items such as prior sexually transmitted diseases (STDs), or indirect items such as age at first intercourse, and the number of sexual partners, which were considered to be markers of potential risk of STD.

HAL author manuscript inserm-00086499, version 1

The indirect factors were associated with a risk of EP in univariate analysis (Table 3), but not in multivariate analysis. Prior STDs were associated with a risk of EP, with an adjusted OR of 3.4 (95 percent CI: 2.4; 5.0) for prior confirmed pelvic infectious disease (Table 5). If infectious history and prior tubal surgery (frequently performed due to infection) were considered together, their adjusted attributable risk was 0.33 (Table 6).

Contraceptive history and fertility markers

Previous use of oral contraception was associated with a decreased risk of EP. In contrast, previous use of an intrauterine device was associated with an increased risk of EP. The induction of ovulation with clomiphene citrate was associated with a risk of EP in univariate analysis, but this association disappeared after adjustment for prior infertility. A history of infertility was strongly associated with the risk of EP, with a dose-response relationship and an adjusted OR for more than two years of infertility of 2.7 (95 percent CI: 1.8; 4.2).

The crude relationship between time since the previous pregnancy and risk of EP gave a J-shaped curve (Table 4). However, time since the previous pregnancy was closely associated with the woman's age, infertility and previous use of an intrauterine device. We did not include this variable in the multivariate analysis, to avoid over-adjustment.

DISCUSSION

This study was restricted to women without contraception at the time of conception because the epidemiology of EP is different for these women and for women using contraception at the time of EP. These two groups differ in time trends of incidence (21), risk factors (3, 15), subsequent fertility (22-24), and psychological stress (25).

Almost all the women living in the Auvergne region who were treated for ectopic pregnancy during the studied period were included in this study, with the completeness of the Auvergne EP register estimated at about 90 percent (26, 21). Controls were selected from the same geographical population as cases.

HAL author manuscript inserm-00086499, version 1

Multicolinearity, due to the large number of highly correlated EP risk factors, was dealt with in several ways including adjustment for confounders in multivariate analyses, the building of synthetic variables (for instance prior STDs), the removal of certain variables corresponding to possible intermediate factors from subsequent analysis (for instance time since the last pregnancy) and the choice of variables closer to possible causal factors (for instance age of the woman and previous IUD use rather than prior delivery). This careful consideration of all potential factors and the large sample in this study resulted in a comprehensive study of the risk factors for EP, whether previously known or only suspected.

Prior genital infections and tubal surgery

Tubal surgery may be a direct consequence of prior tubal infection and may therefore be considered with infectious factors. The importance of infectious factors in ectopic pregnancy is well documented (27, 3, 6, 28). There is probably a causal link: in Sweden, declining rates of chlamydial infections, attributed to preventive policies, have been accompanied by a fall in the risk of ectopic pregnancy (29). The other variables suggestive of a higher probability of exposure to STDs (age at first intercourse and number of sexual partners) were associated with a risk of EP in univariate analysis. However, this association was not significant after adjustment for diagnosed prior STDs. This indicates both that these factors are not risk factors per se and that they are good markers of exposure to STDs.

Finally, the adjusted attributable risk of EP for both infectious factors and tubal surgery was 0.33 (Table 6), making these the most important risk factors for EP.

Smoking

A strong association between tobacco consumption and EP has been demonstrated by several studies (3, 30, 31, 8, 28). Our study confirmed this association, demonstrating a dose-effect relationship. This is probably a causal relationship (32) and tobacco consumption may play a role at various stages in reproduction: ovulation, fertilization, viability and implantation (33-36). Smoking

HAL author manuscript inserm-00086499, version 1

cessation reduces the risk of EP to a level intermediate between current smokers and women who have never smoked. However, no trend was observed for time since cessation.

Although the magnitude of the effect of smoking on EP risk is sometimes poorly appreciated, it is striking to note the parallelism between smoking and infectious factors. The odds ratios, trends and attributable risks are of similar magnitude (Tables 5 and 6). Therefore, smoking is a risk factor for EP that is almost as important as infectious factors.

Age

Age has long been suspected to play a role in EP risk, but studies have provided conflicting results (1, 37-39, 6, 8, 29). In our study, after careful adjustment, we found a significant relationship between age and EP. Therefore, unlike certain other authors (38, 39), we conclude that it is unlikely that the higher probability of exposure to most risk factors in older women accounts for the higher risk of EP. The physiological effect on EP risk of an advanced maternal age at conception remains unclear. It is unlikely to involve an increase in chromosomal abnormalities in the trophoblastic tissue (40, 41). Age-related changes in tubal function may delay ovum transport and result in tubal implantation. However, these hypotheses remain to be tested (42).

Prior spontaneous abortions

The results concerning prior spontaneous abortion differ between studies (3, 43, 11, 44). We found a "dose"-response relationship with prior spontaneous abortions, the adjusted risk of EP being particularly high in women with three or more previous spontaneous abortions. Spontaneous abortions may have a causal effect, possibly mediated by infection (43). However, there may also be common risk factors for EP and spontaneous abortions, such as chromosomal abnormalities (40, 45) or hormonal factors (46, 47). The available evidence suggests that the chromosomal abnormalities may be ruled out (41), but hormonal factors require further study, together with other factors including immunological factors.

HAL author manuscript inserm-00086499, version 1

Previous use of an IUD

In previous studies, OR greater than one were obtained for current IUD use, but OR were generally not significant for previous IUD use (48, 6, 49, 50). A meta-analysis produced an OR slightly greater than 1, but adjustment for confounders is necessarily imperfect. In this study, the significant adjusted OR for previous IUD use (Table 5) confirms that previous IUD use has an etiological role in EP *per se*, not only through an association with infection as previously suggested (51, 52). We did not know the duration of past IUD use, and we could not study the type of IUD used because all but four of the women had used copper devices.

Infertility

We found that the adjusted risk of EP increased with the duration of infertility, and this relationship persisted if the analysis was restricted to women whose pregnancy was not induced. It is therefore likely that a history of infertility *per se* (independently of infertility drug use) is associated with EP risk. However, as EP is known to be a risk factor for subsequent infertility (53, 54, 24), the links between EP and infertility, which seem to be mutual risk factors, are likely to be complex. Common risk factors for both conditions should be sought.

Previous induced abortions

Conflicting results have been reported in previous studies on this issue (55). This study, including a larger number of cases and controls, found an association between previous induced abortions and EP, with an adjusted OR of 1.9 (95 percent CI: 1.0; 3.8) for women with two or more prior induced abortions. The main source of bias may derive from ascertainment of the number of previous induced abortions, which may be underreported by the subject herself (56). In France, estimates of the number of induced abortions for the year 1988 range from 22 to 30 per 100 births (57, 58). If we took into account the number of induced abortions for each woman, we noted a slightly lower ratio in our control sample (15 declared induced abortions for 100 births). Similar results were obtained by Daling *et al*. in the USA (59). Misclassification bias could account for the observed relationship

HAL author manuscript inserm-00086499, version 1

only if it was differential and concerned mainly controls but not cases (or to a lesser extent). Holt *et al*. found such a differential bias but in the reverse direction (60). Although a differential misclassification bias cannot be excluded, we think it unlikely that its magnitude or direction could account for our results.

In a previous study on another French population, we found an association between induced abortion and EP (55). We interpreted the association as the consequence of uterine injuries or infections following abortion because most, if not all, of the abortions in this previous study were surgical. This interpretation was not confirmed by the study presented here: the risk of EP was higher only for women who underwent medical abortions. However, the hypothesis that induced abortion leads to a higher risk of EP as a result of infection cannot be rejected. The association with medical abortion may be accounted for by the absence of systematic antibiotic prophylaxis in this group of women, whereas such prophylaxis is more routinely given in cases of surgical abortion.

Research perspectives

The total attributable risk of EP for the known risk factors is around 70 percent. This figure should be interpreted with caution (61, 62), but they are clearly other factors that may cause ectopic pregnancy. The search has turned towards possible common risk factors for EP and spontaneous abortion or infertility. It has been suggested that EP is linked to chromosomal abnormalities (63, 45) or exposure to antineoplastic drugs (64). Specific studies were conducted, which did not support these hypotheses (40, 65, 41). Hormonal factors have also been suspected (46) and immunological factors may be involved.

CONCLUSION

Although several risk factors for EP are known, the cause of a large proportion of EPs remains unknown. Our new findings on the association between previous medical induced abortion and EP should be confirmed by further results. On the other hand, as EP and infertility or spontaneous abortion have been found to be tightly linked, further research may concern both EP epidemiology

and the wider field of infertility. Increasing our knowledge of risk factors for EP may improve our understanding of the causes of infertility.

In terms of public health, increasing awareness of the role of smoking may be useful in the formulation of EP prevention policies. It would also be interesting to evaluate the effects on the incidence of EP (and other infertility parameters) of the increase in STD incidence observed in recent months or years (66, 67).

HAL author manuscript inserm-00086499, version 1

Acknowledgements: This study was supported by National Register Committee (Comité National des Registres - INSERM - InVS), France. We thank Julie Sappa for her careful review of the English version of this paper.

HAL author manuscript inserm-00086499, version 1

HAL author manuscript inserm-00086499, version 1

REFERENCES

1. Weström L, Bengtsson LPH, Mardh P-A. Incidence, trends and risks of ectopic pregnancy in a population of women. British Medical Journal 1981;282:15-18.

2. Atrash HK, Hughes J, Hogue CJR. Ectopic pregnancy in the United States, 1970-1983. CDC Surveillance summaries. Morbidity and Mortality Weekly Report 1986;35:29-37.

3. Chow WH, Daling JR, Cates W, Greenberg RS. Epidemiology of ectopic pregnancy. Epidemiologic Review 1987;9:70-94.

4. Mäkinen JI. Ectopic pregnancy in Finland 1967-83: a massive increase. British Medical Journal 1987;294:740-741.

5. MMWR. Ectopic pregnacy - United States, 1970-1992. Morbidity and Mortality Weekly Report 1995;44:46-48.

6. Coste J, Job-Spira N, Fernandez H, Papiernik E, Spira A. Risk factors for ectopic pregnancy: a case-control study in France, with special focus on infectious factors. American Journal of Epidemiology 1991;133:839-849.

7. Fernandez H, Coste J, Job-Spira N. Controlled ovarian hyperstimulation as a risk factor for ectopic pregnancy. Obstetrics and Gynecology 1991;78:656-659.

8. Job-Spira N, Collet P, Coste J, Brémond A, Laumon B. Facteurs de risque de la grossesse extra-utérine. Résultats d'une enquête cas-témoins dans la région Rhône-Alpes [Risk factors for ectopic pregnancy. Results of a case control study in the Rhone-Alpes region]. Contraception Fertilité Sexualité 1993;21:307-312.

9. Mol BWJ, Ankum WM, Bossuyt PMM, van der Veen F. Contraception and the risk of ectopic pregnancy: a meta-analysis. Contraception 1995;52:337-341.

10. Xiong X, Buekens P, Wollast E. IUD use and the risk of ectopic pregnancy: a meta-analysis of case-control studies. Contraception 1995;52:23-34.

11. Ankum WM, Mol BWJ, van der Veen F, Bossuyt PMM. Risk factors for ectopic pregnancy: a meta analysis. Fertility and Sterility 1996;65:1093-1099.

12. Coste J, Bouyer J, Job-Spira N. Meta-analysis - "Does one bad apple spoil the barrel?" Fertility and Sterility 1997;67:791-792.

13. Rothman KJ, Greenland S. Modern epidemiology. Boston: Little, Brown and Company, 1998.

14. Coste J, Job-Spira N, Aublet-Cuvelier B*, et al.* Incidence of ectopic pregnancy. First results of a population-based register in France. Human Reproduction 1994;9:742-745.

15. Bouyer J, Rachou E, Germain E*, et al.* Risk factors for extrauterine pregnancy in women using an intrauterine device. Fertility and Sterility 2000;74:899-908.

16. Weiss NS, Daling JR, Chow WH. Control definition in case-control studies of ectopic pregnancy. American Journal of Public Health 1985;75:67-68.

HAL author manuscript inserm-00086499, version 1

17. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons, 2000.

18. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. International Journal of Epidemiology 1999;28:964-974.

19. Bruzzi P, Green SB, Byar DP, Brinton LA, Schaire C. Estimating the population attributable risk for multiple risk factors using case-control data. American Journal of Epidemiology 1985;122:904-914.

20. StataCorp. Stata Statistical Software. Release 7.0. College Station (TX): Stata Corporation, 2001.

21. Coste J, Bouyer J, Germain E, Ughetto S, Pouly JL, Job-Spira N. Recent declining trend in ectopic pregnancy in France: evidence of two clinicoepidemiologic entities. Fertility and Sterility 2000;74:881-886.

22. Mäkinen JI, Salmi TA, Nikkanen VPJ, Koskinen EYJ. Encouraging rates of fertility after ectopic pregnancy. International Journal of Fertility 1989;34:46-51.

23. Pouly JL, Chapron C, Canis M*, et al.* Subsequent fertility for patients presenting with an ectopic pregnancy and having an intra-uterine device in situ. Human Reproduction 1991;6:999-1001.

24. Bernoux A, Job-Spira N, Germain E, Coste J, Bouyer J. Fertility outcome after ectopic pregnancy and use of an intrauterine device at the time of the index ectopic pregnancy. Human Reproduction 2000;15:1173-1177.

25. Bachelot A, Fernandez H, Job-Spira N. Vécu de la grossesse extra-utérine [Experience of ectopic pregnancy]. Contraception Fertilité Sexualité 1994;1994:478-484.

26. Coste J, Aublet-Cuvelier B, Bouyer J, Germain E, Job-Spira N. Evaluation de l'exhaustivité du registre des grossesses extra-utérines d'Auvergne par la méthode capture-recapture [Evaluation of the completeness of the Auvergne register of ectopic pregnancy with the capture-recapture method]. Revue d'Epidémiologie et de Santé Publique 1995;43(S1):10.

27. Weström L. Influence of acute pelvic inflammatory disease on fertility. American Journal of Obstetrics and Gynecology 1975;121:707-713.

28. Tay JI, Moore J, Walker JJ. Ectopic pregnancy. British Medical Journal 2000;320:916-919.

29. Egger M, Low N, Smith GD, Linblom B, Herrmann R. Screening for chlamydial infections and the risk of ectopic pregnancy in a county in Sweden: ecological analysis. British Medical Journal 1998;316:1776-1780.

30. Handler A, Davis F, Ferre C, Yeko T. The relationship of smoking and ectopic pregnancy. American Journal of Public Health 1989;79:1239-1242.

31. Coste J, Job-Spira N, Fernandez H. Increased risk of ectopic pregnancy with maternal cigarette smoking. American Journal of Public Health 1991;81:199-201.

32. Bouyer J, Coste J, Fernandez H, Job-Spira N. Tabac et grossesse extra-utérine. Arguments en faveur d'une relation causale [Smoking and ectopic pregnancy. Arguments for a causal relationship]. Revue d'Epidémiologie et de Santé Publique 1998;46:93-99.

33. Neri A, Eckerling B. Influence of smoking and adrenaline (epinephrine) on the utero-tubal insufflation test (Rubin Test). Fertility and Sterility 1969;20:818-828.

HAL author manuscript inserm-00086499, version 1

34. Fuentealba B, Nieto M, Croxato HB. Progesterone abbreviates the nuclear retention of estrogen receptor in the rat oviduct and conteracts estrogens action on egg transport. Biology of Reproduction 1988;38:63-69.

35. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. American Journal of Obstetrics and Gynecology 1990;162:502-514.

36. Van Voorhis BJ, Dawson JD, Stovall DW, Sparks AET, Syrop CH. The effects of smoking on ovarian function and fertility during assisted reproduction cycles. Obstetrics and Gynecology 1996;88:785-791.

37. Atrash HK, Hughes JM, Hogue CJR. Ectopic pregnancy in the United States, 1970-1983, CDC surveillance summaries. Morbidity and Mortality Weekly Report 1986;35:29-37.

38. Thorburn J, Philipson M, Lindblom B. Background factors of ectopic pregnancy: II. Risk estimation by means of a logistic model. European Journal of Obstetrics, Gynecology, and Reproductive Biology 1986;23:333-340.

39. Mäkinen JI. Increase of ectopic pregnancies in Finland. Combination of time and cohort effect. Obstetrics and Gynecology 1989;73:21-24.

40. Goddijn M, van der Veen F, Schuring-Blom GH, Ankum WM, Leschot NJ. Cytogenetic characteristics of ectopic pregnancy. Human Reproduction 1996;11:2769-2771.

41. Coste J, Fernandez H, Joye N*, et al.* Role of chromosome abnormalities in ectopic pregnancy. Fertility and Sterility 2000;74:1259-60.

42. Yeko TR, Handler A. The effect of aging on tubal function and ectopic pregnancy. Seminars in Reproductive Endocrinology 1991;9:215-220.

43. Doyle MB, Decherney AH, Diamond MP. Epidemiology and etiology of ectopic pregnancy. Obstetrics and Gynecology Clinics of North America 1991;18:1-152.

44. Saada M, Job-Spira N, Bouyer J*, et al.* La récidive de GEU : rôle des antécédents gynéco-obstétricaux, contraceptifs et du tabagisme [Ectopic pregnancy recurrence: role of gynecologic, obstetric, contraceptive and smoking history]. Contraception Fertilité Sexualité 1997;25:457-462.

45. Job-Spira N, Coste J, Bouyer J, Tharaux-Deneux C, Fernandez H. Chromosomal abnormalities and ectopic pregnancy? New directions for aetiological research. Human Reproduction 1996;11:239-242.

46. Fernandez H, Bouyer J, Coste J, Job-Spira N. The hidden side of ectopic pregnancy: the hormonal factor. Human Reproduction 1996;11:243-244.

47. Neugebauer R, Kline J, Stein Z, Shrout P, Warburton D, Susser M. Association of stressful life events with chromosomally normal spontaneous abortion. American Journal of Epidemiology 1996;143:588-596.

48. Marchbanks P, Annegers J, Coulam C, Strathy J, Kurland L. Risk factors for ectopic pregnancy. A population based-study. JAMA 1988;259:1823-1827.

49. Fernandez H, Coste J, Job-Spira N, Spira A, Papiernik E. Facteurs de risque de la grossesse extra-utérine. Etude cas-témoins dans 7 maternités de la région parisienne [Risk factors for ectopic pregnancy. A case-control study at 7 maternity units in the Paris area]. Journal de

HAL author manuscript inserm-00086499, version 1

Gynécologie Obstétrique et Biologie de la Reproduction 1991;20:73-79.

50. Kalandidi A, Doulgerakis M, Tzonou A, Hsieh CC, Aravandinos D, Trichopoulos D. Induced abortions, contraceptive practices, and tobacco smoking as risk factors for ectopic pregnancy in Athens, Greece. British Journal of Obstetrics and Gynaecology 1991;98:207-213.

51. Weström L, Bengtsson LPH, Mardh P-A. The risk of pelvic inflammatory disease in women using intrauterine contraceptive devices compared to nonusers. Lancet 1976;II.

52. Vessey MP, Yeates D, Flavel R, Mc Pherson K. Pelvic inflammatory disease and the intrauterine device: findings of a large cohort study. British Medical Journal 1981;282:855-857.

53. Ory SJ, Nnadi E, Herrmann R, O'Brien PS, Melton LJ. Fertility after ectopic pregnancy. Fertility and Sterility 1993;60:231-235.

54. Job-Spira N, Bouyer J, Pouly JL*, et al.* Fertility after ectopic pregnancy: first results of a population-based cohort study in France. Human Reproduction 1996;11:99-104.

55. Tharaux-Deneux C, Bouyer J, Job-Spira N, Coste J, Spira A. Risk of ectopic pregnancy and previous induced abortion. American Journal of Public Health 1998;88:401-405.

56. Houzard S, Bajos N, Warszawski J*, et al.* Analysis of the underestimation of induced abortions in a survey of the general population in France. European Journal of Contraception and Reproductive Health Care 2000;5:52-60.

57. INED. Statistiques de l'avortment en France - Annuaire 1988 [Induced abortion in France 1988]. Paris, 1993.

58. Blayo C. L'évolution du recours à l'avortement en France depuis 1976. Population 1995;50:779-810.

59. Daling JR, Chow WH, Weiss NS. Ectopic pregnancy in relation to previous induced abortion. JAMA 1985;253:1005-1008.

60. Holt VL, Daling JR, Voigt LF*, et al.* Induced abortion and the risk of subsequent ectopic pregnancy. American Journal of Public Health 1989;79:1234-1238.

61. Rockhill B, Weinberg CR, Newman B. Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability. American Journal of Epidemiology 1998;147:826-33.

62. Madigan P, Ziegler RG, Benichou J, Byrne C, Hoover RN. Re: "Population attributable fraction estimation for established breast cancer risk factors: considering the issues of high prevalence and unmodifiability". American Journal of Epidemiology 1999;150:543-4.

63. Bouyer J, Tharaux-Deneux C, Coste J, Job-Spira N. Grossesses extra-utérines : des facteurs liés à l'anomalie de l'oeuf [Ectopic pregnancy: risk factors related to egg abnormalities ?]. Revue d'Epidémiologie et de Santé Publique 1996;44:101-110.

64. Saurel-Cubizolles MJ, Job-Spira N, Estryn-Behar M. Ectopic pregnancy and occupational exposure to antineoplastic drugs. Lancet 1993;341:1169-1171.

65. Bouyer J, Saurel-Cubizolles MJ, Grenier C, Aussel L, Job-Spira N. Ectopic pregnancy and occupational exposure of hospital personnel. Scandinavian Journal of Work, Environment and Health 1998;24:98-103.

66. MMWR. Increases in unsafe sex and rectal gonorrhea among men who have sex with men - San Francisco. California,1994-97. Morbidity and Mortality Weekly Report 1999:45-48.

67. Goulet V, Sednaoui P, Massari V. Confirmation de la recrudescence des gonococcies en France depuis 1998. Bulletin Epidémiologique Hebdomadaire 2001;14.

HAL author manuscript inserm-00086499, version 1

HAL author manuscript inserm-00086499, version 1

Table 1: Ectopic pregnancy and socio-demographic characteristics: crude odds ratios (OR) and 95 percent confidence intervals (CI). Register of the Auvergne region, France, 1993-2000

Variables	Controls (n = 1683)		Cases (n = 803)				
	n	%	n	%	OR	CI	p*
Woman's age (years)							
< 20	19	1.1	5	0.6	0.7	0.3, 1.9	
20-24	288	17.2	91	11.3	0.9	0.6, 1.1	
25-29	686	40.9	253	31.5	1		< 0.001
30-34	487	29.0	273	34.0	1.5	1.2, 1.9	
35-39	178	10.6	141	17.6	2.1	1.6, 2.8	
≥ 40	19	1.3	40	5.0	5.7	3.2, 10.2	
Smoking							
never	990	59.1	299	38.9	1		< 0.001
past smoker	176	10.5	81	10.5	1.5	1.1, 2.0	
1-9 cig/day	215	12.8	106	13.8	1.6	1.2, 2.1	
10-19 cig/day	185	11.1	161	20.9	2.9	2.2, 3.7	
≥ 20 cig/day	108	6.5	122	15.9	3.7	2.8, 5.0	
Educational level							
primary	130	7.8	55	7.2	1		0.8
secondary	1125	67.5	530	69.5	1.1	0.9, 1.4	
higher	411	24.7	178	23.3	1.0	0.7, 1.5	

* p-value (for variables with more than two categories, the p-value of the test for trend is given)

HAL author manuscript inserm-00086499, version 1

Table 2: Ectopic pregnancy and surgical, gynecological and obstetric history: crude odds ratios (OR) and 95 percent confidence intervals (CI). Register of the Auvergne region, France, 1993-2000

Variables	Controls (n = 1683)		Cases (n = 803)				
	n	%	n	%	OR	CI	p*
Prior deliveries							
none	784	46.6	317	39.5	1		<0.001
1	616	36.6	286	35.6	1.1	0.9, 1.4	
2	214	12.7	136	16.9	1.6	1.2, 2.0	
≥ 3	69	4.1	64	8.0	2.3	1.6, 3.3	
Prior ectopic pregnancies							
none	1661	98.8	672	84.1	1		<0.001
1	19	1.1	96	12.0	12.5	7.5, 20.9	
≥ 2	1	0.06	31	3.9	76.6	10.1, 580	
Prior spontaneous abortions							
none	1365	81.1	566	70.5	1		<0.001
1	255	15.2	171	21.3	1.6	1.3, 2.0	
2	48	2.9	37	4.6	1.9	1.2, 2.9	
≥ 3	15	0.9	29	3.6	4.7	2.5, 8.8	
Prior induced abortions							
none	1463	86.9	660	82.2	1		0.001
1	199	11.8	115	14.3	1.3	1.0, 1.6	
≥ 2	21	1.3	28	3.5	3.0	1.7, 5.3	
Type of prior induced abortion							
none	1463	88.3	660	83.3	1		0.001
surgical only	182	11.0	115	14.5	1.4	1.1, 1.8	
medical only	11	0.7	13	1.6	2.6	1.2, 5.9	
both	1	0.1	4	0.5	8.9	1.0, 79	
Appendectomy							
no, or unruptured appendix	1630	96.9	756	94.6	1		0.006
yes, ruptured appendix	52	3.1	43	5.4	1.8	1.2, 2.7	
Prior tubal surgery							
no	1626	96.6	613	76.3	1		<0.001
yes	57	3.4	190	23.7	8.8	6.4, 12.3	

* p-value (for variables with more than two categories, the p-value of the test for trend is given)

HAL author manuscript inserm-00086499, version 1

Table 3: Ectopic pregnancy and sexual and infectious history: crude odds ratios (OR) and 95 percent confidence intervals (CI). Register of the Auvergne region, France, 1993-2000

Variables	Controls (n = 1683)		Cases (n = 803)				
	n	%	n	%	OR	CI	p*
Age at first intercourse (years)							
< 14	109	6.8	70	9.6	1		0.002
15-17	621	38.4	302	41.5	0.8	0.5, 1.1	
18-20	756	46.8	311	42.7	0.6	0.5, 0.9	
> 20	130	8.0	45	6.2	0.5	0.3, 0.9	
Life-long number of sexual partners							
1	433	27.4	176	25.0	1		0.003
2-5	935	59.1	386	54.9	1.0	0.8, 1.3	
> 5	213	13.5	141	20.1	1.6	1.2, 2.1	
Prior STDs							
no	1154	69.0	411	52.7	1		<0.001
yes without salpingitis	407	24.3	157	20.1	1.1	0.9, 1.3	
yes with probable PID†	12	0.7	19	2.4	4.4	2.1, 9.3	
yes with confirmed PID‡	100	6.0	193	24.7	5.4	4.1, 7.2	

*p-value (for variables with more than two categories, the p-value of the test for trend is given)
†probable pelvic inflammatory disease (PID), association of fever, abdominal pain and vaginal discharge
‡PID confirmed by laparoscopy, and/or positive serological tests for *Chlamydia trachomatis*

HAL author manuscript inserm-00086499, version 1

Table 4: Ectopic pregnancy, contraceptive history and fertility markers: crude odds ratios (OR) and 95 percent confidence intervals (CI). Register of the Auvergne region, France, 1993-2000

Variables	Controls (n = 1683)		Cases (n = 803)				
	n	%	n	%	OR	CI	p*
Previous use of oral contraceptive							
no	298	17.8	209	26.5	1		<0.001
yes	1377	82.2	581	73.5	0.6	0.5, 0.7	
Previous use of intrauterine device							
no	1460	87.2	637	80.6	1		<0.001
yes	215	12.8	153	19.4	1.6	1.3, 2.0	
Ovulation induced with clomiphene citrate							
no	1632	97.4	762	95.1	1		0.003
yes	43	2.6	39	4.9	1.9	1.2, 3.0	
History of infertility							
no	1475	89.0	543	69.2	1		<0.001
<1 year	47	2.8	35	4.5	2.0	1.3, 3.2	
1-2 years	58	3.5	64	8.2	3.0	2.1, 4.3	
>2 years	77	4.7	143	18.2	5.0	3.7, 6.8	
Time since previous pregnancy†							
≤ 6 months	128	13.5	77	14.4	1.3	0.9, 1.9	0.11
6 months, 1 year	96	10.1	54	10.1	1.2	0.8, 1.9	(0.02)‡
1-2 years	165	17.3	82	15.4	1.1	0.8, 1.6	
2-3 years	201	21.1	92	17.2	1		
3-4 years	107	11.2	51	9.6	1.0	0.7, 1.6	
4-5 years	77	8.1	38	7.1	1.1	0.7, 1.7	
> 5 years	178	18.7	140	26.2	1.7	1.2, 2.4	

*p-value (for variables with more than two categories, the p-value of the test for trend is given)
†Time from the end of the previous pregnancy to the beginning of the index pregnancy
‡p-value of the global test

HAL author manuscript inserm-00086499, version 1

Table 5: Main risk factors for ectopic pregnancy. Final logistic regression analysis (random effects model): adjusted odds-ratios (OR_a) and 95 percent confidence intervals (CI). Register of the Auvergne region, France, 1993-2000.

Variables	OR_a	CI	p*
Woman's age (years)			
< 20	0.6	0.2, 2.1	
20-24	0.9	0.7, 1.3	
25-29	1		0.01
30-34	1.3	1.0, 1.7	
35-39	1.4	1.0, 2.0	
≥ 40	2.9	1.4, 6.1	
Smoking			
never	1		<0.001
past smoker	1.5	1.1, 2.2	
1-9 cig/day	1.7	1.2, 2.4	
10-19 cig/day	3.1	2.2, 4.3	
≥ 20 cig/day	3.9	2.6, 5.9	
Prior spontaneous abortions			
none	1		0.02
1-2	1.2	0.9, 1.6	
≥ 3	3.0	1.3, 6.9	
Prior induced abortions			
none	1		0.05
surgical only	1.1	0.8, 1.6	
medical (or medical and surgical)	2.8	1.1, 7.2	
Appendectomy			
no, or unruptured appendix	1		0.20
yes, ruptured appendix	1.4	0.8, 2.4	
Prior STDs			
none	1		<0.001
yes without salpingitis	1.0	0.8, 1.3	
yes with probable PID†	2.1	0.8, 5.4	
yes with confirmed PID‡	3.4	2.4, 5.0	
Prior tubal surgery			
no	1		<0.001
yes	4.0	2.6, 6.1	
Previous use of oral contraceptive			
no	1		0.03
yes	0.7	0.5, 1.0	
Previous use of intrauterine device			
no	1		0.10
yes	1.3	1.0, 1.8	
History of infertility			
no	1		<0.001
<1 year	2.1	1.2, 3.6	
1-2 years	2.6	1.6, 4.2	
>2 years	2.7	1.8, 4.2	

*p-value (for variables with more than two categories, the p-value of the test for trend is given)
†probable pelvic inflammatory disease (PID), association of fever, abdominal pain and vaginal discharge
‡PID confirmed by laparoscopy, and/or positive serological tests for *Chlamydia trachomatis*

HAL author manuscript inserm-00086499, version 1

Table 6: Adjusted attributable risk (AR_a) of the main risk factors for ectopic pregnancy. Register of the Auvergne region, France, 1993-2000.

Variables	AR_a	
Woman's age	0.14	
Past or current smoking	0.35	
Prior spontaneous abortions	0.07	
Prior induced abortions	0.03	
Appendectomy	0.02	
Prior STDs	0.18	0.33
Prior tubal surgery	0.18	
Previous use of oral contraceptive*	0.08	
Previous use of intrauterine device	0.05	
History of infertility	0.18	
Total	0.76	

* AR_a for not using oral contraceptive

HAL author manuscript inserm-00086499, version 1

Figure 1: Crude and adjusted association between age and ectopic pregnancy (EP) risk. Register of the Auvergne region, France, 1993-2000. The figure provides the values of the risk of EP. As this is a case-control study, these values cannot be interpreted directly and thus the y-axis is not scaled. However, the shape of the curves does correspond to the variation in EP risk according to age. The observed values (circles) were calculated for 1-year age classes.

HAL author manuscript inserm-00086499, version 1

