Ectopic pregnancy is again on the increase. Recent trends in the incidence of ectopic pregnancies in France (1992–2002)

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BACKGROUND: We aimed to assess the recent incidence trends of ectopic pregnancies (EP) in France (1992–2002). METHODS: A population-based register of all women aged 15–44 years with EP was set up in Auvergne (central France). We calculated rates of EP as a ‘reproductive failure’ or as a ‘contraceptive failure’, frequencies of exposure to the two main risk factors for EP (cigarette smoking and chlamydial infection) and contraceptive methods between 1992 and 2002. RESULTS: The overall EP rate decreased by 2%, from 96.4 per 100 000 women aged 15–44 in 1992 to 95.3 per 100 000 in 2002. However, the rate of ‘reproductive failure’ EP increased by 17%, while the rate of ‘contraceptive failure’ EP, mostly intrauterine device failure, decreased by 29%. CONCLUSION: Appropriate analysis reveals that the rate of EP as reproductive failure is increasing again in France. This result is of interest for many European and North America countries where chlamydial infections or smoking or both are increasing in women of reproductive age. The rates of EP as contraceptive failure and of that as reproductive failure evolve differently in the population and should not be confused in epidemiological studies.

Key words: contraception/ectopic pregnancy/epidemiology/intrauterine device/reproduction failure

Introduction
During the 1970s and early 1980s, the incidence of ectopic pregnancy (EP) doubled or tripled in most industrialized countries to reach annual incidence rates of between 100 and 175 per 100 000 women aged 15–44 (Coste et al., 1994; Centers for Disease Control, 1995; Thorburn, 1995; Makinen, 1996; Storeide et al., 1997). A stabilization or even a decrease in the rates has since been observed in Sweden and Finland (Thorburn, 1995; Makinen, 1996; Egger et al., 1998), Australia (Boufous et al., 2001), France (Coste et al., 2000) and the UK (Rajkhowa et al., 2000; Irvine and Setchell, 2001) giving the reassuring impression that the ‘epidemic is over’ (Thorburn, 1995). This trend has been attributed to a decline of genital infections, and especially to screening programmes for sexually transmitted diseases (STDs) and Chlamydia trachomatis (Egger et al., 1998) [~33% of EPs are due to infectious factors (Bouyer et al., 2003)]. However, it is unclear whether this trend applies elsewhere [the latest US rates indicate continued increase (Centers for Disease Control, 1995)] and whether modifications of sexual activities in the prolonged era of Acquired Immunodeficiency Syndrome (AIDS) are persisting. Moreover, there are several other risk factors for EP including smoking [which may be responsible for more cases of EP than genital infection (Bouyer et al., 2003)], age at conception (Simms et al., 1997; Makinen et al., 1998; Bouyer et al., 2003); and the current use of an intrauterine device (Rossing et al., 1993; Coste et al., 2000).

We previously argued that EP as a reproductive failure and EP as a contraceptive failure should be considered to be two distinct entities because they have different risk factors, location, prognosis and perception by women (Coste et al., 2000). Using comprehensive data from the Auvergne EP register, we report the most recent trends in the incidence of EP in France (1992–2002).

Materials and methods
Study population
The Auvergne EP register was established in January 1992 in two adjacent administrative units (Puy-de-Dôme and Cantal of central France, ~750 000 inhabitants, stable over time). Details of this register have been described previously (Coste et al., 1994).

The number of women of reproductive age (15–44 years) was derived from the national population register. Data are available annually for each unit, and for particular age categories. The annual numbers of livebirths to residents of the two units were also
obtained from official sources and are available by age category (also for each year).

**Case finding and data collection**

The goal of the register is to record every case of EP among the permanently resident women aged 15–44 years, and to follow these women until 45 years of age to study their reproductive outcome. Cases of EP (women whose diagnosis of ectopic pregnancy is confirmed, mainly by coelioscopy, and who are treated either by surgical or medical procedures) are registered at local participating centres of the two departments and adjacent areas. All centres caring for women with EP are participating, and they include public and private, hospital maternities (n = 18) and surgical units (n = 23). EPs that are treated (e.g. by methotrexate) only in an outpatient setting were also identified: there are very few and all attend a single (university) centre. In each centre, a trained investigator (usually a physician or midwife) is in charge of case identification and data collection. The information collected for each woman includes sociodemographic characteristics, gynaecological, reproductive and surgical histories and conditions of conception, including contraception and method used (if any).

**Completeness of the registration**

To evaluate the completeness of the registration, we reviewed the discharge diagnosis files of the hospitals from 1993 onwards and performed a two-source capture–recapture study (Hook and Regal, 1992). Briefly, the capture–recapture technique examines the degree of overlap between two (or more) sources of cases and uses a simple formula to estimate the total size of the population and also the number of cases missed by each source. The validity of the assumption that the captures are independent is essential if the estimation is to be unbiased. The Sekar method (Sekar and Deming, 1949) was used to verify the independence of the captures by the two sources. It is based on the computation of the correlation coefficient between the number of missed cases in each source obtained in repeated observations (here each month of the study period). To confirm the assumption of independence the coefficient should not differ from 0: this was the case for our study (P = 0.48; non significant). Overall the register completeness remained very stable during the 11-year study period, with an estimated ascertainment of ~88%.

**Statistical analysis**

Global annual incidence of EP was calculated by dividing the recorded number of EP by the number of women aged between 15–44 in the register area. We considered EP as ‘contraceptive failure’ (CF) if the woman was using a contraceptive method and as ‘reproductive failure’ (RF) in other cases. Rates of EP-CF and EP-RF were calculated accordingly. Throughout the period, the rate of EP associated with IUD failure (EP-IUD) was ~75% of that of EP-CF. The incidence of EP was also calculated for women aged 15–24, 25–29, 30–34 and 35–44 years for each calendar year. Poisson regression analysis was used to test linear trends over time, adjusting for age group. To test the sensitivity of the results and explore the influence of the level of fertility of the population in the analysis of EP-RF, the annual number of livebirths was added as a covariate in the Poisson regression models.

**Role of the funding source**

The sponsors of the study had no role in study design, data collection, data analysis, writing of the manuscript, or interpretation of results.

**Results**

The overall EP annual incidence rate remained stable over the study period (96.4 per 100 000 women aged 15–44 in 1992 and 95.3 per 100 000 in 2002, -1.9%, P = 0.35 for test of trend in Poisson regression). During this period, the livebirth rate increased significantly (+10.3%) particularly for women aged 30–34 (+27.0%) and women aged 35–44 (+62.6%).

EP-RF and EP-CF annual incidence rates were 56.0 and 40.4, respectively, per 100 000 women aged 15–44 in 1992. Their trends over the 1992–2002 period were very different (Figure 1). The EP-RF rate increased (+17.1%, P = 0.022 for test of trend in Poisson regression, adjusting for age group), but was unaffected by the level of fertility of the population (P = 0.026 for test of trend in Poisson regression, adjusting for both age group and number of livebirths, the change in the estimate was <0.1%). The EP-CF annual incidence rate decreased (−29.0%, P = 0.035 for test of trend in Poisson regression, adjusting for age group).

EP-RF and EP-CF annual incidence rates for each age group are shown in Figure 2. The EP-RF rate increased especially in the 30–34 years group (+53.7% between 1992 and 2002, most between 1997 and 2002) whereas it was variable in the 25–29 years group and stable in the others. Conversely, the EP-CF rate decreased for 25–29 year olds and 30–34 year olds. For all age groups, EP-IUD rates strictly paralleled EP-CF rates (not shown).

**Discussion**

This register-based study documents recent trends in EP incidence in France. Its major strength is that the data allows EP incidence to be analysed according to the use of
a contraceptive method at the time of conception. This analysis reveals that EP as a contraceptive failure and EP as a reproductive failure have evolved differently between 1992 and 2002. EP as a contraceptive failure decreased, especially EP as an IUD failure, whereas EP as a reproductive failure worryingly increased. These results are probably not confounded by variation in the registration completeness rate or by developments in medical care: both remained stable during the study period, and are unlikely to affect the two types of EP differently. Adjustments were also made for changes in the age and fertility of the population, and changes in these variables, similarly, could not explain the observed
variations in EP rates: on the one hand, the estimated trend of EP as a reproductive failure was unaffected by adjustment for the annual number of livebirths in each age category; on the other hand, the proportion of contraceptive women remained stable overall during the study period (Guibert-Lantoine and Leridon, 1998).

The decrease in the rates of EP as a contraceptive failure is explained by a parallel trend toward less use of IUDs, which has been observed in France since 1988 (Guibert-Lantoine and Leridon, 1998). This decrease in IUD use has been mainly explained by the older maternal age at first (and subsequent) conception. IUDs, unlike oral contraceptives, are preferentially prescribed for multiparous women (Guibert-Lantoine and Leridon, 1998) and the age at which women are prescribed IUD has increased. This has led to a decreased proportion of IUD contraception, and an increased proportion of pill contraception in the population of fertile women. Sales data support this observation.

Unmasked by an appropriate analysis, the rate of EP as reproductive failure is shown to be on the increase again in France. This result may be relevant to many other European and North American countries (and Australia). The recent increase in both chlamydial infections and cigarette smoking [two factors which explain ~60% of cases of EP (Bouyer et al., 2003)] in French women of reproductive age [the prevalence of C. trachomatis infection increased (+23%) between 1998 and 2002 after having decreased (~46%) between 1992 and 1997 and the frequency of smoking in women aged 15–44 increased by 8.2% between 1995 and 1999 (Guibert et al., 2001)] led us to suspect this result. It has been shown that trends in the risk of ectopic pregnancy do not necessarily lag behind those of chlamydial infection (Egger et al., 1996). After a decade of decrease, the incidence of C. trachomatis infection has again been increasing in France since 1998. This trend has also been observed since the middle of the 1990s in the Netherlands, Finland and Sweden (van Bergen, 2001; Stenqvist et al., 2002; Hiltunen-Back et al., 2003).

An increase in the prevalence of cigarette smoking in women of reproductive age has been observed in France and in many other countries, including Germany, Switzerland, Spain, Finland, Poland and Russia (Dobson et al., 1998; Molarius et al., 2001). Indeed, despite widespread evidence that smoking adversely impacts pregnancy outcome and the health of the newborn, most young women remain unaware of the health risks specific to women from smoking (Roth and Taylor, 2001). Further efforts to diffuse information about the adverse effects of smoking on reproduction are required (and the marketing strategies used by the tobacco industry in response to regulation policies, e.g. by sponsoring students’ meetings and promoting the freedom of smoking for the young, should also be fought).

In conclusion, the decline of EP in France is over, and the rate of EP as reproductive failure has resumed its increase. This is associated with the exposure of women of reproductive age to cigarette smoking and to chlamydial infections which are both once again increasing. The consequences of this type of EP on women’s fertility are still serious [infertility in 40% and recurrence in 30% of cases at 2 years (Bernoux et al., 2000)], and therefore the implications of this news for prevention should be carefully considered.

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