

# Long-term reproductive outcomes in women whose first pregnancy is ectopic: a national controlled follow-up study

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**STUDY QUESTION:** How does long-term reproductive prognosis among women whose first pregnancy is ectopic differ from prognosis in women with other initial pregnancy outcomes?

**SUMMARY ANSWER:** Women with a first recorded ectopic pregnancy (EP) have a significantly lower long-term delivery rate and a manifold increased risk of further EPs.

**WHAT IS KNOWN ALREADY:** Women with a first EP have an increased risk of further EPs. Few studies have assessed long-term reproductive outcomes after an EP, and none was controlled.

**STUDY DESIGN:** The study was designed as a historical controlled cohort study.

**MATERIALS AND METHODS:** Data were collected from four Danish registries covering the period 1977–2009. Women with an EP as their first recorded pregnancy during the period 1977–1982 were age matched with women whose first recorded pregnancy was a miscarriage, an induced abortion, a delivery, or women with no recorded pregnancies, respectively. The cohorts were followed until the end of 2009 or on average through 30 years.

**MAIN RESULTS:** When compared with women with a first miscarriage, women with a first EP had a relative risk of deliveries of 0.55 [95% confidence interval (CI) 0.52–0.58], miscarriages of 0.46 (0.41–0.52) and induced abortions of 0.72 (0.65–0.80) and a 4.7 (3.8–5.8)-fold increased risk of further EPs. The relative delivery rate when compared with women with a first induced abortion was 0.89 (0.84–0.95) and with women with no pregnancy 0.69 (0.65–0.72).

**LIMITATIONS:** We had no information about the attempts to become pregnant in the different cohorts. New fertility techniques may have improved the prognosis among women with a first EP.

**WIDER IMPLICATIONS OF THE FINDINGS:** These results indicate that fertility is compromised in women whose first pregnancy is ectopic. It is possible that better assisted reproductive techniques that have been developed in recent years could improve the long-term delivery rates for women with EP.

**STUDY FUNDING:** All the expenses were covered by Gynaecological Clinic, Rigshospitalet. Ø.L. has within the last 3 years received honoraria for speeches in pharmacoepidemiological issues. L.L.K., P.E. and C.W.S. had no conflict of interest to declare.

**Key words:** ectopic pregnancy / reproduction / prognosis / miscarriage / delivery

## Introduction

About 1% of all pregnancies are ectopic pregnancies (EPs) ([www.tigrab.dk](http://www.tigrab.dk)). EP is an important cause of reproductive morbidity and : may influence long-term reproductive success rate (Lundorff *et al.*, 1992; Ory *et al.*, 1993; Fernandez *et al.*, 1998a,b; Mol *et al.*, 1998; Bernoux *et al.*, 2000; Bouyer *et al.*, 2000; Ego *et al.*, 2001; Bangsgaard

et al., 2003; Gervaise et al., 2004; Buster and Krotz, 2007; Hajenius et al., 2007; Banz et al., 2010).

Previous tubal damage from infection or surgery, previous EP, IVF, high age and smoking are all known risk factors for EP (Ankum et al., 1996; Saraiya et al., 1998; Bernoux et al., 2000; Farquhar, 2005).

While short-term consequences of EP are well described, few studies have followed women throughout their reproductive life (Buster and Krotz, 2007; Hajenius et al., 2007). Studies assessing fertility after EP have focused on the effect of different treatments (medical versus surgical treatment or salpingectomy versus tubotomy) and found no major differences in terms of the primary treatment modality (Mol et al., 1998; Bouyer et al., 2000; Buster and Krotz, 2007; Krag Moeller et al., 2009).

The existing studies have relatively few patients and short follow-up (Lundorff et al., 1992; Ory et al., 1993; Fernandez et al., 1998a,b; Mol et al., 1998; Bernoux et al., 2000; Bouyer et al., 2000; Ego et al., 2001; Bangsgaard et al., 2003; Gervaise et al., 2004; Banz et al., 2010). We found no controlled study assessing long-term reproductive prognosis in women whose first pregnancy is ectopic.

## Objectives

The aim of this study was to assess long-term reproductive outcomes in women whose first recorded pregnancy was an EP and to compare these outcomes with the outcomes among women whose first recorded pregnancy was a miscarriage, an induced abortion, a delivery or no pregnancy, respectively.

## Materials and Methods

The study was designed as a historical controlled cohort study. Since 1968, all Danish citizens have had a personal identification number (PIN), and since 1977, all discharge diagnoses from public and private hospitals have by law been recorded in the National Registry of Patients together with their identification number. This made it possible to follow women over the three decades for reproductive outcomes.

Information was merged from four National registries: Statistics of Denmark provided the PIN of all Danish women 15–49 years old through the period from 1 January 1977 to 31 December 2009, and time of eventual emigration or death in these women during the follow-up period, both causing censoring.

The National Registry of Patients, the National Birth Registry and the National Registry of Induced Abortions identified women with EPs and other reproductive outcomes during the follow-up period. The specific diagnosis codes used for identification of each reproductive outcome are displayed in Table 1.

First all women recorded with the discharge diagnosis EP during the period from 1 January 1977 to 31 December 2009 were identified. Women who had an EP as their first recorded pregnancy during the period 1977–1982 were considered the 'exposed' group. Every succeeding pregnancy outcome among the exposed women during the follow-up period until the end of 2009 was noted, including new EPs, clinically detectable miscarriages (including blighted ovum), induced abortion, deliveries and hydatidiform mole. Relevant restriction periods were applied in order not to count the same event several times in case such an event had several contacts. In order to optimize the validity of the diagnoses, only diagnosis codes with a simultaneous and relevant gestational age indication were included.

Four control populations were established. The first three of these were characterized by their first recorded pregnancy outcome as a miscarriage, an induced abortion or a delivery, respectively. Randomly selected women were matched 1:1 to the exposed women by age and year (within 1 year) of their first pregnancy for each of these three control cohorts. The last control group included women who had no recorded pregnancy until the year of matching, and were therefore matched only on age. In this case, there was sufficient number of women to realize a 1:4 matching. All pregnancy outcomes among women in the four control cohorts were noted during the follow-up period.

## Data analysis

The reproductive prognosis was expressed as incidence rates of the different recorded pregnancy outcomes during the follow-up period. Rate ratios (RRs) with 95% confidence intervals (CIs) were calculated for each reproductive outcome and with each of the four control cohorts as the comparison group. The reproductive prognosis was also expressed as the proportion of women who had at least one pregnancy outcome after the first pregnancy. The proportion of censored women and time from entering the cohort to time of censoring were calculated for all cohorts. Thus, we ensured not only a close age matching between the different cohorts but also an approximately equal follow-up time in the different cohorts.

Differences were tested by z-test, and *P*-values under 0.05 were considered significant.

Sensitivity tests were made for different age groups for the delivery outcome in order to assess the influence of age at first EP for future

**Table 1** Included diagnosis codes and number of dead and emigrated women during follow-up in the different cohorts of women according to their first pregnancy outcome.

	Delivery	Miscarriage	Induced abortion	Ectopic pregnancy	No pregnancy
ICD 8 codes <sup>a</sup>	650–666	643 + 645.1	640–642	631.09–99	—
ICD 10 codes <sup>b</sup>	DO600–849	DO021, 030–039	DO040–059	DO000–009	—
Cohort size ( <i>n</i> )	2917	2917	2917	2917	11 668
Dead ( <i>n</i> )	57	97	86	102	354
Emigrated ( <i>n</i> )	59	72	123	72	1 167
Follow-up time (years)	23.3	23.2	22.8	23.2	21.1

<sup>a</sup>Used 1977–1993.

<sup>b</sup>Used 1994–2010.

deliveries. In these analyses, the miscarriage and induced abortion cohorts were the comparison cohorts.

The study was approved by The National Board of Health (j. no. 7-201-03-08/1) and The Danish Data Protection Agency (j. no. 2006-41-6907).

## Results

We identified 40 101 women with at least one EP during the period from 1 January 1977 to 31 December 2009. Of these, 2917 had a first EP during the period 1977–1982.

Of the 2917 index women, 72 (3.5%) emigrated during the follow-up period, and 102 (2.5%) died. The corresponding numbers in the other cohorts are indicated in Table 1. The average follow-up time after these censoring was 23.2 years, approximately the same as for

the other cohorts (22.8–23.3 years) (Table 1), and slightly shorter, however, in the cohort of women with no pregnancy at time of matching with an average follow-up of 21.1 years, because of a higher proportion (10.0%) of emigrated women in this cohort.

## Deliveries

Women who had a first EP had the lowest long-term rate of deliveries of 69 per 100 (Table II). Women with a first miscarriage, a first induced abortion and a first delivery had during follow-up 126, 77 and 73 deliveries per 100, respectively, while women without pregnancies before matching had 101 deliveries per 100. Thus, women in the first delivery cohort had 1 + 0.73 or 1.73 deliveries compared with the 0.69 per woman in the first ectopic cohort.

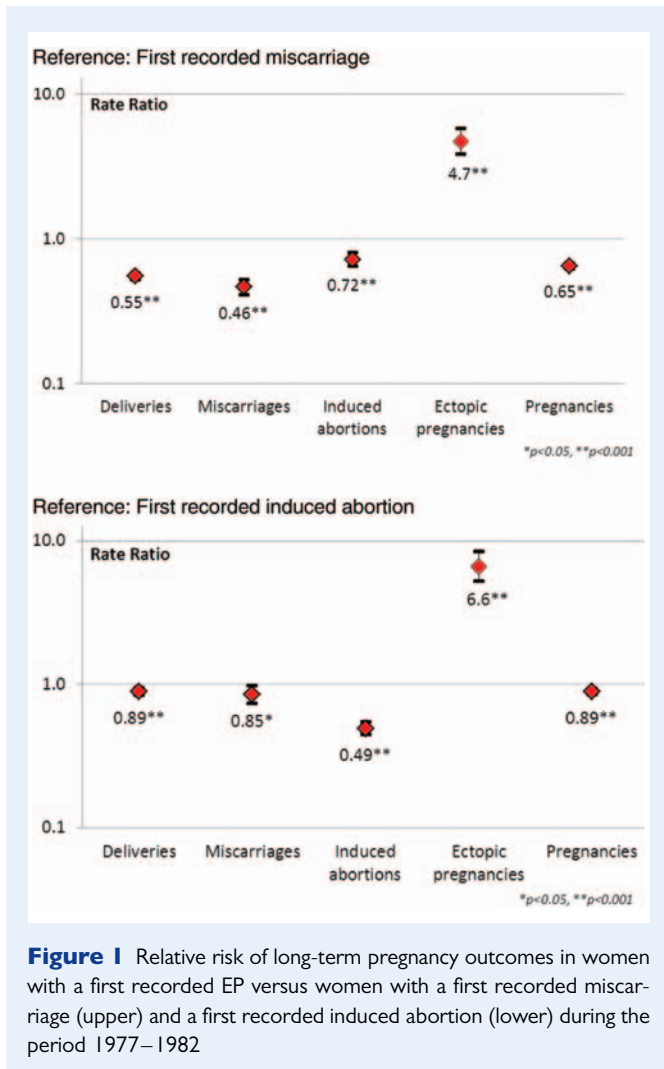
The corresponding RRs between the exposed women and the control groups were 0.55 (95% CI 0.52–0.58), 0.89 (0.84–0.95),

**Table II** Pregnancy outcomes in the different cohorts.

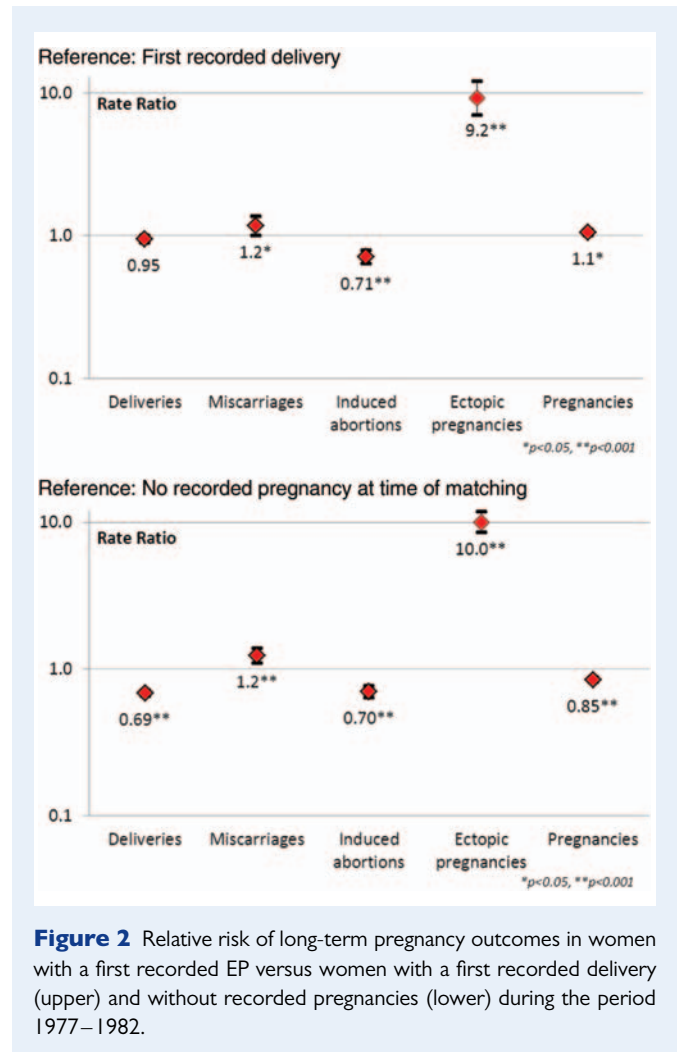
Cohorts 1977–1982	Pregnancy outcomes 1977–2009				
	Deliveries	Miscarriages	Induced abortions	Ectopic pregnancies	All pregnancies
First ectopic ( <i>n</i> = 2917)					
Pregnancy outcomes ( <i>n</i> )	2013	368	556	517	3454
Pregnancy outcomes per 100	69.0	12.6	19.1	17.7	118.4
Outcomes among 100 pregnant <sup>a</sup>	131.4	24.0	36.4	33.7	225.5
Per cent of all outcomes <sup>b</sup>	58.3	10.6	16.1	15.0	100.0
Difference in outcomes per 100	Index	Index	Index	Index	Index
First miscarriage ( <i>n</i> = 2917)					
Pregnancy outcomes ( <i>n</i> )	3668	796	773	110	5347
Pregnancy outcomes per 100	125.7	27.3	26.5	3.8	183.3
Outcomes among 100 pregnant <sup>a</sup>	177.0	38.5	37.3	5.4	258.2
Per cent of all outcomes <sup>b</sup>	68.6	14.9	14.5	2.1	100.0
Difference in outcomes per 100	–56.7	–14.7	–7.4	13.9	–64.9
First induced abortion ( <i>n</i> = 2917)					
Pregnancy outcomes ( <i>n</i> )	2258	433	1131	78	3900
Pregnancy outcomes per 100	77.4	14.8	38.8	2.7	133.7
Outcomes among 100 pregnant <sup>a</sup>	140.2	26.8	70.3	4.9	242.2
Per cent of all outcomes <sup>b</sup>	57.9	11.1	29.0	2.0	100.0
Difference in outcomes per 100	–8.4	–2.2	–19.7	15.0	–15.3
First delivery ( <i>n</i> = 2917)					
Pregnancy outcomes ( <i>n</i> )	2121	313	783	56	3273
Pregnancy outcomes per 100	72.7	10.7	26.8	1.9	112.2
Outcomes among 100 pregnant <sup>a</sup>	122.0	18.0	45.0	3.2	188.3
Per cent of all outcomes <sup>b</sup>	64.8	9.6	23.9	1.7	100.0
Difference in outcomes per 100	–3.7	1.9	–7.7	15.8	6.2
No pregnancy ( <i>n</i> = 11,668)					
Pregnancy outcomes ( <i>n</i> )	11 726	1190	3173	206	16 295
Pregnancy outcomes per 100	100.5	10.2	27.2	1.8	139.7
Outcomes among 100 pregnant <sup>a</sup>	167.5	17.0	45.3	3.0	232.8
Per cent of all outcomes <sup>b</sup>	72.0	7.3	19.5	1.3	100.0
Difference in outcomes per 100	–31.5	2.4	–8.1	15.9	–21.3

<sup>a</sup>This is among 100 women who achieved at least one pregnancy after the ectopic pregnancy.

<sup>b</sup>This is the percentage for each pregnancy outcome of the total outcomes during follow-up.



**Figure 1** Relative risk of long-term pregnancy outcomes in women with a first recorded EP versus women with a first recorded miscarriage (upper) and a first recorded induced abortion (lower) during the period 1977–1982



**Figure 2** Relative risk of long-term pregnancy outcomes in women with a first recorded EP versus women with a first recorded delivery (upper) and without recorded pregnancies (lower) during the period 1977–1982.

0.95 (0.89–1.01) and 0.69 (0.65–0.72), respectively (Figs. 1 and 2). As compared with the miscarriage group, women with a first EP thus had a 45% reduced long-term delivery rate. Compared with the women with a first delivery, no significant difference was found for further deliveries, indicating that women with a first recorded delivery get about one child more than women with a first recorded EP.

When stratified according to age at first EP, the RR of deliveries decreased with increasing age from 0.9 in women with a first EP at 15–19 years, to 0.1 in women with a first EP at 35–39 years compared with the first miscarriage cohort, while no major changes were seen in the RR of deliveries with increasing age compared with the first induced abortion cohort.

## Miscarriages

The long-term incidence rate of clinically detectable miscarriages among women with a first EP was 13 per 100, which was 54% lower than the corresponding incidence rate of 27 per 100 among women with a first miscarriage, slightly lower than in women with a first induced abortion, and slightly higher than in women with a first delivery and with no pregnancies (Table II, Figs. 1 and 2). The proportions of pregnancies resulting in miscarriages in the five cohorts were

10.6% for the first recorded EP group, 14.9% for the first recorded miscarriage group, 11.1% for the first recorded induced abortion group, 9.5% for the first recorded delivery cohort and 7.3% for the group with no recorded pregnancies at the time of matching.

## Induced abortion

While EPs and miscarriages are un-intended, induced abortions are decided. Women with a first EP had 19 induced abortions per 100 during the follow-up. The corresponding figures for women with a first miscarriage, a first induced abortion and a first delivery were 26.5, 38.8 and 26.8 per 100, respectively, while women with no pregnancy had 27.2 induced abortions per 100. Thus, the ectopic cohort had the lowest rate of induced abortions (Table II).

The corresponding RRs between the exposed women and the control cohorts were 0.72 (0.65–0.80), 0.49 (0.44–0.54), 0.71 (0.64–0.79) and 0.70 (0.64–0.77), respectively (Figs. 1 and 2).

## Ectopic pregnancies

Women with a first EP had a overall 17.7% risk of further EPs (Table II). The corresponding figures for women with a first miscarriage, a first induced abortion, a first delivery and with no pregnancies were 3.8, 2.7, 1.9 and 1.8%, respectively.

The corresponding RRs between the exposed women and the control groups were 4.7 (3.8–5.8), 6.6 (5.2–8.4), 9.2 (7.0–12.2) and 10.0 (8.5–11.8), respectively (Figs. 1 and 2).

The number of women with hydatidiform mole during the follow-up period was between 0 and 13 in the different cohorts, in total 22, and therefore too few to make meaningful further calculations.

During the follow-up period 1532 (53%) of the exposed women had at least one pregnancy outcome after the first EP, compared with 2072 (71%) of the women with a first miscarriage, 1610 (55%) of the women with a first induced abortion, 1738 (60%) of the women with a first delivery and 7005 (60%) of the women with no pregnancies at matching. The outcomes among those achieving pregnancy are indicated in Table II, as is the percent distribution of the different pregnancy outcomes in the exposed cohort.

During the first 5 years of follow-up, 1231 (42%) of the exposed women had at least one pregnancy outcome, compared with 1900 (65%) of the women with a first miscarriage, 1144 (39%) of the women with a first induced abortion, 1410 (48%) of the women with a first delivery and 5804 (50%) of the women with no pregnancies at matching.

## Discussion

In summary, we found that the women with a first EP had a 4.7–10.0-fold increased risk of further EPs compared with different control cohorts, the lowest delivery rate in the study and lower rates of miscarriages, induced abortions and total pregnancies, compared with the women with a first miscarriage or a first induced abortion.

The intrauterine pregnancy rate after EP is reported in several studies to be ~60% (Mol *et al.*, 1998; Gervaise *et al.*, 2004). This is lower than the rate in our study, but this might be a result of our long follow-up, as the other studies only have a follow-up for 1–3 years. When looking on term delivery or late ongoing pregnancy, Fernandez *et al.* (1998b) found a rate of 42% (both spontaneous and aided). Bouyer *et al.* (2000) found that 102 of 197 women who conceived spontaneously after an EP achieved a live birth, and 18 were still ongoing, giving a rate of 60.9% for delivery or ongoing pregnancy. In our study, two-thirds of the 85% intrauterine pregnancies terminated in a delivery. Also here the difference must be due to the long follow-up and the large study population.

The higher probability of miscarriages in the women with a first induced abortion compared with the exposed cohort probably reflects the generally higher fertility in women becoming pregnant unwantedly than in women with a first EP. Therefore, the former group will also have a higher risk of future pregnancies (intended and unintended) and thereby a higher risk of miscarriages also. We found no other studies assessing this risk in a controlled design.

The increased risk of further EP among women with a first EP is in accordance with several previous studies (Ankum *et al.*, 1996; Bernoux *et al.*, 2000; Farquhar, 2005). The incidence rate of EP in the four control groups varies and was higher in the women with a first miscarriage or an induced abortion than in the women with a first delivery or with no pregnancy during the recruitment period.

We found that 15% of pregnancies after a first EP were ectopic again. Banz *et al.* (2010) found an 18.9% recurrence rate of EP in a cohort of 208 women followed through 9 years after an EP. Lundorff

*et al.* (1992) studied the reproductive outcomes after conservative surgical treatment of EP during a 2-year period between May 1987 and June 1989. The women were followed until August 1990. They found 16% of the first pregnancies to be new EPs, while 84% of the pregnancies were intrauterine, results close to ours.

## Strengths and limitations

Two principal reservations have to be taken for the figures in this study. First, we had no information about pregnancy outcomes in the included women before 1977. For the older fertile women entering the cohort in 1977, the proportion with previous pregnancy outcomes is substantial. Although the distribution of previous pregnancies might vary between the different cohorts, the close age matching of women in the different cohorts will diminish this potential bias.

Secondly, we were not able to discriminate between intended and unintended pregnancies (except for induced abortions). A substantial part of the difference between the different considered cohorts might therefore reflect different intentions rather than consequences of previous pregnancy outcomes. That was the very reason for establishing four different control cohorts, because these cohorts represent different intentions according to reproduction. The comparison group that probably matches the exposed group best concerning intention to be pregnant is the group of women with a first miscarriage. Consequently, the significance of the EP *per se* is probably best illustrated by comparison between these two cohorts. It strengthens the consistency of the delivery results, however, that the RRs of deliveries in the follow-up period were below one for all comparisons.

Although the treatment of EP has developed since the cohorts were established, the reproductive prognosis is not influenced much by the medical versus surgical treatment of EP (Mol *et al.*, 1998; Bouyer *et al.*, 2000; Buster and Krotz, 2007; Moeller *et al.*, 2009). The emergence of *in vitro* techniques, on the other hand, has improved the chances of becoming pregnant after EP significantly. These circumstances might have improved the delivery chance for later cohorts of women with EP.

To our knowledge, no other country has recorded systematically all the reproductive outcomes admitted to hospital through now >33 years. Although the validity of diagnoses in the National Registry of Patients is not always 100%, reproductive end points have been found to have fairly high validity (Nickelsen, 2001). This may be further improved in this study, because only reproductive end points with a simultaneously recorded gestational age were included. Furthermore, we have no reason to believe in a differential misclassification between the different cohorts for the different reproductive end points. Any misclassification of end points will tend to underestimate rather than overestimate the detected differences between the cohorts.

Except for the few emigrated women, the study is further strengthened by the complete follow-up, the large number of patients in the study subgroups and the fact that it was based on registry data, which eliminates recall bias and other detection bias during follow-up.

It is also a strength that we were able to establish four different control groups to women with a first recorded EP, so that the exposed cohort could be compared with all possible first-pregnancy outcomes.

The control group of women without pregnancies at the time of matching may be heterogeneous, as we do not know whether these women have chosen not to be pregnant or were infertile. Our results showed that the 'no pregnancy' control group had the next highest delivery rate and total pregnancy rate, and about the same frequency of miscarriages, induced abortions and EPs as the 'first delivery' control group, suggesting that few were in fact infertile.

The price for a full-length reproductive follow-up is that our results reflect the consequences of events and treatments 30 years back in time. A further clarification of the reproductive prognosis could be to assess reproductive outcomes for successive cohorts with the same (shorter) length of follow-up.

## Conclusion

Women who had a first recorded EP during the period 1977–1982 had a 5–10-fold increased risk of further EP compared with age-matched control women. Compared with women with a first recorded miscarriage, they had lower long-term incidence of deliveries, miscarriages and induced abortions.

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Ethical approval is not requested for registry-based studies in Denmark.

## Authors' roles

Ø.L. is guarantor of the study. L.L.K., Ø.L. and P.E. planned the study. L.L.K. made the analysis, interpreted the results and wrote the manuscript. Ø.L. supervised the analysis and revised the manuscript. C.W.S. prepared all data from the National Registry of Patients, the National Birth Registry, National Registry of Induced Abortions and National Registry of Danish citizens. All the authors discussed and approved the final manuscript.

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## Conflict of interest

All authors completed the unified competing interest form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare that: Ø.L. within the last 3 years has received honoraria for speeches on pharmacoepidemiological issues. L.L.K., P.E. and C.W.S. had nothing to declare.

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