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Improving reproductive long-term prognosis for women with a first ectopic pregnancy. A national controlled follow-up study

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Key words
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Conflict of interest
All authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declared the following: Øjvind Lidegaard has within the last 3 years received honoraria for presentations on pharmacoepidemiological issues. Pia Egerup, Line Kårhus and Charlotte Wessel Skovlund had nothing to declare.

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Abstract

Objective. To describe developments in reproductive long-term prognosis in women with a first ectopic pregnancy as compared with two control cohorts. *Design.* Controlled cohort study. *Setting.* Data were collected from four national Danish registries. *Population.* All Danish women of reproductive age (15–49 years) through the period 1977–2009 and all reproductive outcomes in these women. *Methods.* Data were collected from four national Danish registries. Three cohorts of women with a first recorded ectopic pregnancy during the periods 1980–84, 1985–89, and 1990–94, were compared with age-matched controls with a first miscarriage and a first induced abortion and followed for 15 years for all further pregnancy outcomes. *Main outcome measures.* Pregnancy outcomes included deliveries, miscarriages, induced abortions and ectopic pregnancies. *Results.* The birth rate for women with a first ectopic pregnancy increased significantly through the three cohorts from 85 to 122 deliveries/100 women during the follow-up period. The risk of miscarriages also increased over time, whereas the risk of further ectopic pregnancies remained unchanged at 22–24 events/100 women. Compared to women with a first miscarriage, the rate ratio for deliveries increased from 0.59 (95% CI 0.56–0.63) to 0.71 (95% CI 0.68–0.75) over the time covering the three cohorts. *Conclusion.* The long-term delivery rate among women with a first ectopic pregnancy has improved significantly over time.

Abbreviations: ICD, International Classification of Diseases.

Introduction

Long-term fertility after a first ectopic pregnancy is not well described. Existing studies have mainly analyzed short-term fertility according to different treatment methods (1–8). We recently described a compromised long-term fertility prognosis in women whose first pregnancy was ectopic (9), but we found no study assessing the development over time

Key Message

Long-term delivery rates among women with a first ectopic pregnancy have improved over time, but the risk of another ectopic pregnancy was constant.

as regards the long-term reproductive prognosis in women after an ectopic pregnancy. Reproduction is influenced by women's intention to become pregnant, and by the availability of effective fertility treatment. Through recent decades, in vitro fertilization and related artificial reproductive techniques have become increasingly available and could have improved the reproductive prognosis for women after an ectopic pregnancy.

The objective of this study was to describe the development over time in the long-term reproductive prognosis in women after a first ectopic pregnancy, and to compare this with changes in the long-term reproductive prognosis among women with a first miscarriage and a first induced abortion, respectively.

Material and methods

Since 1968, all Danish citizens have had a personal identification number, and from 1977 all discharge diagnoses have been recorded in the National Health Register. This unique registration system made it possible to conduct three concurrent and consecutive historical controlled cohort studies where information was obtained from four national registries: the Civil Registration System, the National Health Register, the Danish Birth Register and the Danish Register of Induced Abortions. All Danish women aged 15–49 years were identified in the Civil Registration System for the period 1 January 1980 to 31 December 2009, and if applicable the time of emigration or death was recorded. Women with ectopic pregnancies and other reproductive outcomes during the follow-up periods were identified in the health register, the birth register and the induced abortions register. The following International Classification of Diseases (ICD)8/ICD10 codes were included: Delivery (650–666/DO600–849), miscarriage (643+645.1/DO021, 030–039), induced abortion (640–642/DO040–059) and ectopic pregnancy (631.09–99/DO000–009).

Ethics committee approval is not requested for anonymous register-based studies in Denmark, but the study was approved by the National Board of Health (Approval number 7-201-03-08/1) and the Danish Data Protection Agency (Approval number 2006-41-6907).

First, all women diagnosed with ectopic pregnancy during the period from 1 January 1977 to 31 December 2009 were identified. Next, women with their first ectopic pregnancy during the period 1980–95 were selected and divided into the three sub-periods of 1980–84, 1985–89 and 1990–94, constituting the three "exposed" cohorts. Then, pregnancy outcomes among these women within a 15-year follow-up period were recorded, including deliveries, miscarriages [spontaneous abortion, missed abortion, and anembryonic pregnancies (blighted ovum)], induced abortions, ectopic pregnancies, and hydatidiform moles. Figure 1 illustrates the follow-up design. An age-matched control population of women, whose first pregnancy was a miscarriage or an induced abortion, was established by an otherwise random selection of 1:1 for each of the women in the exposed cohorts. All pregnancy

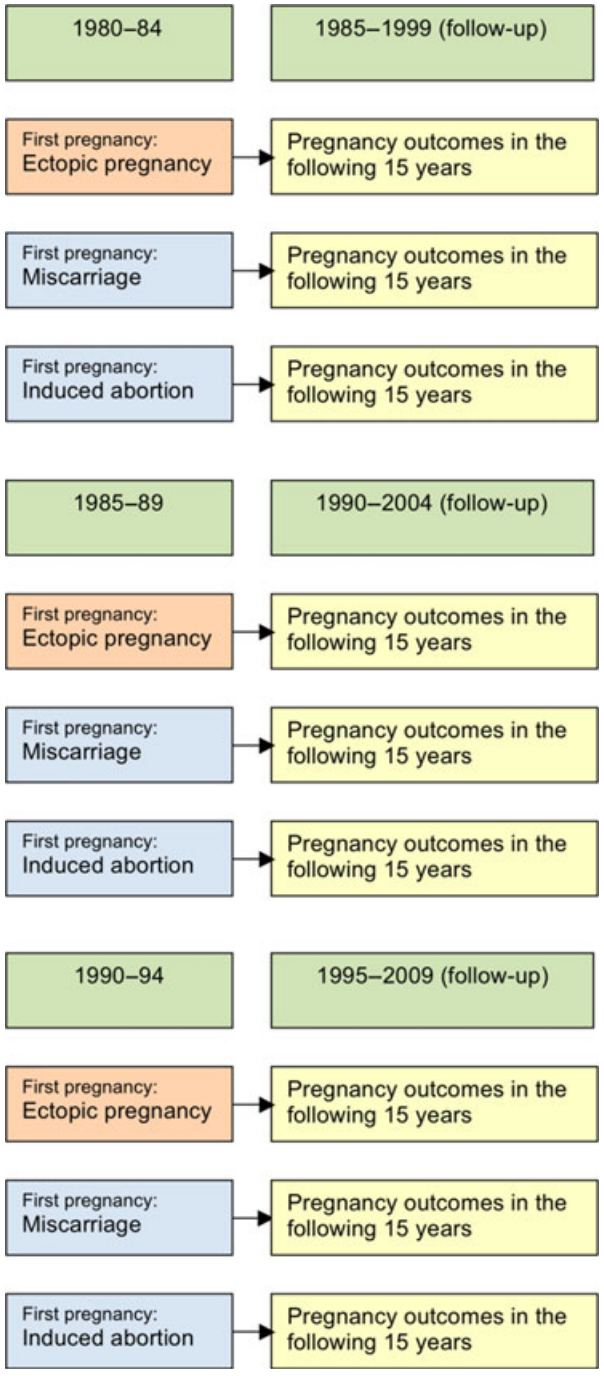

Figure 1. Study design. The two control groups were matched on age and year of first pregnancy.

outcomes within the 15-year follow-up period were then recorded for these 2 × 3 control cohorts.

Data analysis

The reproductive prognosis was calculated as incidence rates and rate ratios with 95% confidence intervals. Differences were tested by the *z*-test, and *p*-values <0.05 were considered significant. Time to emigration or death was calculated, as was the average time of follow up to ensure a comparable risk time for the two cohorts.

Results

The three exposed cohorts included 2280, 2378 and 2621 women with a first ectopic pregnancy, respectively. Since the three groups together only included 15 events of hydatidiform mole during the follow-up period, those results were not analyzed further.

The proportion of emigrated or dead women by the end of the follow-up period for the exposed cohorts was 3.3, 4.2 and 4.4%, respectively. The corresponding percentages in the first miscarriage cohorts were 3.5, 4.0 and 4.5% and in the first induced abortion cohorts were 7.0, 7.0 and 7.3%, respectively. The mean follow-up time was 14.7 years in the three exposed cohorts, 14.6 years in the miscarriage cohorts, and 14.3 years in the induced abortion cohorts. Hence, the follow-up time was approximately the same for all cohorts.

The development in the incidence/100 women of the different pregnancy outcomes in the exposed and control cohorts is presented in Figure 2. The birth rate increased during the three follow-up periods in both the exposed and the control cohorts. The largest percentage increase was in women with a first ectopic pregnancy, who experienced a 43% increase in the birth rate through the three sub-periods. The corresponding birth rate increased by 19% in women with a first miscarriage and by 13% in women with a first induced abortion. Women with a first miscarriage had the highest absolute birth rate.

The exposed cohort and the control cohort both showed an increase in miscarriages (Figure 2). The percentage increase was greatest for women with an ectopic pregnancy, who experienced a 62% increase from the first to the last sub-period. Women with a first miscarriage demonstrated a 30% increase, whereas women with a first induced abortion experienced a 37% increase over the three follow-up periods.

The induced abortion rate decreased slightly over time in the ectopic and miscarriage cohorts, and was somewhat stable in women with a first induced abortion. However, the induced abortion rate during follow up was significantly higher for women with a first induced abortion compared with women with a first ectopic pregnancy or a first miscarriage.

The incidence rate of ectopic pregnancies was relatively stable over the three sub-periods. Women with a first ectopic pregnancy, however, had a significantly higher incidence rate of new ectopic pregnancies compared with the two control cohorts.

Table 1 illustrates that the increasing trend for deliveries and miscarriage for both the exposed and the control cohorts was significant. The trend for induced abortions and ectopic pregnancies was stable for both the exposed and the control cohorts.

The rate ratios for the different pregnancy-outcomes between women with a first ectopic pregnancy and

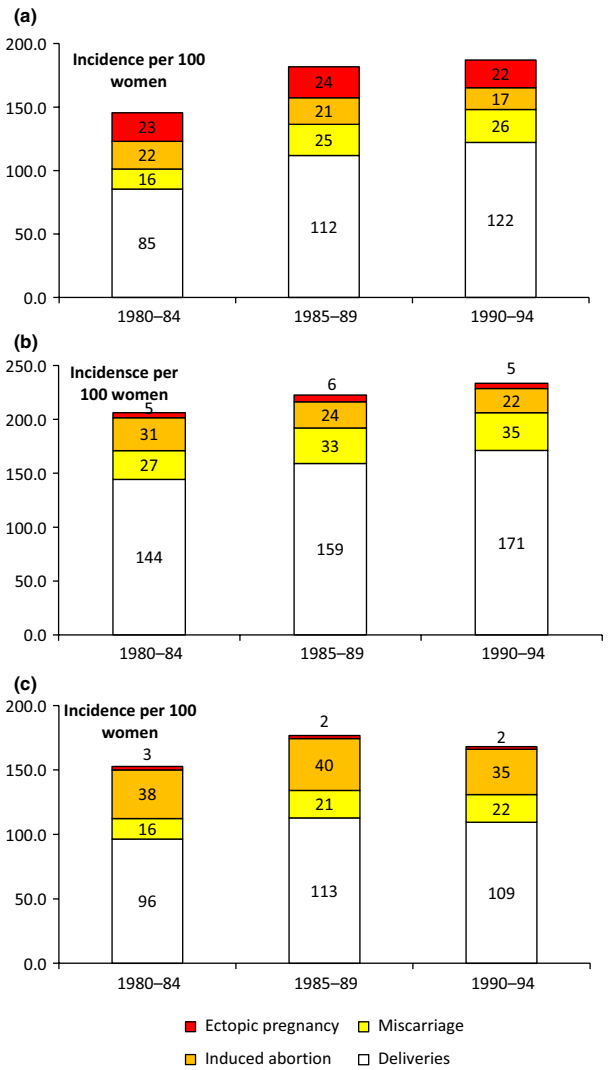

Figure 2. Reproductive outcomes (incidence/100 women) during the three sub-periods 1980–84, 1985–89 and 1990–94 among women with a first ectopic pregnancy (a), a first miscarriage (b) or a first induced abortion (c), respectively.

Table 1. Rate ratios (RR) of reproductive outcomes in 1990–94 as compared with the same outcomes in 1980–84 for specific reproductive outcomes.

	Cohort size	Deliveries	Miscarriage	Induced abortion	Ectopic pregnancy
First pregnancy: Ectopic					
1980–84	2280	1947	359	497	515
1985–89	2378	2659	583	498	579
1990–94	2621	3202	679	447	574
RR		1.43	1.65	0.78	0.97
95% CI		1.35–1.52	1.45–1.87	0.69–0.89	0.86–1.09
p		<0.0001	<0.0001	0.0002	0.61
First pregnancy: Miscarriage					
1980–84	2280	3289	607	699	104
1985–89	2378	3781	782	576	152
1990–94	2621	4483	920	587	129
RR		1.19	1.32	0.73	1.08
95% CI		1.13–1.24	1.19–1.46	0.65–0.82	0.83–1.40
p		<0.0001	<0.0001	<0.0001	0.56
First pregnancy: Induced abort					
1980–84	2280	2200	362	859	63
1985–89	2378	2685	506	958	56
1990–94	2621	2867	565	922	52
RR		1.13	1.36	0.93	0.72
95% CI		1.07–1.20	1.19–1.55	0.85–1.02	0.50–1.04
p		<0.0001	<0.0001	0.15	0.08

women with a first miscarriage and a first induced abortion, respectively, are displayed in Figure 3.

The birth rate ratio with the miscarriage cohort as reference increased through the three sub-periods by 20% from 1980–84 to 1990–94, implying that women with a first ectopic pregnancy reduced their lag of deliveries from −41% to −29% (Figure 3).

The ectopic pregnancy cohort experienced an increase in the relative risk of miscarriages from 40% fewer in 1980–84 to 25% fewer through 1990–94 as compared with the miscarriage cohort. The rate ratio for induced abortion was relatively stable through the three sub-periods. However, women with ectopic pregnancy had 14–29% fewer induced abortions. The relative risk of ectopic pregnancies decreased slightly over the three sub-periods, and women in the ectopic pregnancy cohorts had 3.8–5 times more ectopic pregnancies compared with women in the miscarriage cohort (Figure 3).

The development in the reproductive rate ratios between women with a first ectopic pregnancy and women with a first induced abortion is illustrated in the lower part of Figure 3. Women in the ectopic cohorts had approximately the same rate of deliveries and a small increase in miscarriages compared with women in the induced abortion cohorts, but successively fewer induced abortions and increasing rates of ectopic pregnancies (Figure 3).

The incidence of women with an ectopic pregnancy as their first pregnancy in the three sub-periods according to age is demonstrated in Figure 4. Over time, the incidence of women whose first pregnancy was ectopic increased most significantly over time for the age groups 25–29 and 30–34 years. In the younger age groups the number of women with a first ectopic pregnancy actually fell.

Discussion

The trends in rate of deliveries and miscarriages must necessarily follow each other closely. For all cohorts, there was a significant increase in the rate of both of these outcomes over time. The highest percentage increase in deliveries was seen in the ectopic pregnancy cohort, which indicates improved fecundity in women after an ectopic pregnancy. This improvement could be a result of both better surgical treatment methods and the developments in artificial reproductive techniques. In vitro fertilization was introduced in Denmark by the end of the 1980s and has since increased its share of pregnancies from <1% to about 6% during our study period. The national register for in vitro fertilization was established in 1994 and includes, therefore, the vast majority of in vitro fertilization procedures and related techniques in Denmark (10). The rising incidence of miscarriages through the three sub-periods in all the cohorts is not only a result of more pregnancies, but is also influenced by the increasing age at first planned attempt to become pregnant due to the increasing risk of miscarriages with increasing age (11).

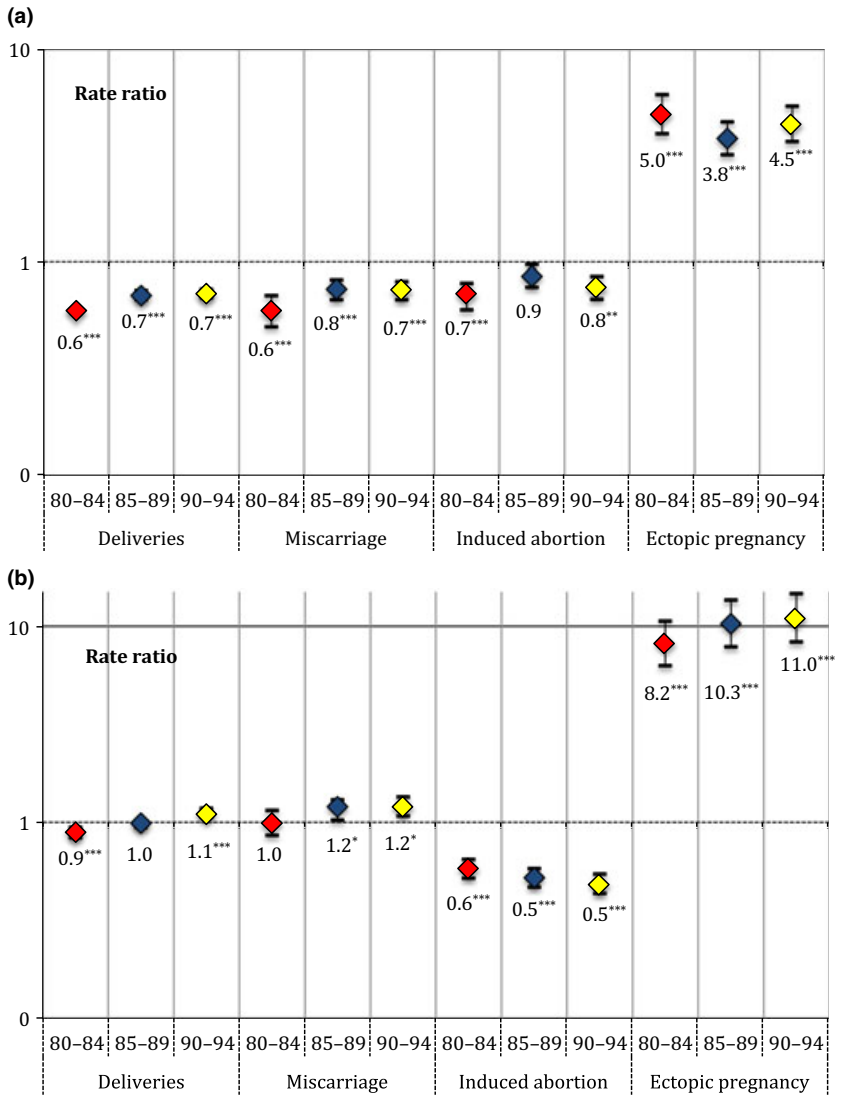

Figure 3. Pregnancy outcomes in women with a first ectopic pregnancy as compared with women with a first miscarriage (a) or a first induced abortion (b). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

The decreasing incidence in ectopic pregnancies in the two control cohorts could be explained by an increasing use of barrier contraceptive methods in the 1980s after the discovery of human immunodeficiency virus, and the increasing screening for *Chlamydia trachomatis*, followed by decreasing rates of chlamydial infections through the 1980s and 1990s (12). Despite an improvement in the birth rate ratios over time, the estimates compared with women with a first miscarriage still leaves women with a first ectopic pregnancy 29% behind, but also with a 26% lower risk of miscarriages.

Several changes were seen during the long follow-up period. The advantage of rate ratio estimates is that we compared the rates with control cohorts, which had been through the same general reproductive changes (e.g. age at first pregnancy, wish for children, contraceptive practices). As a miscarriage is usually an unwanted event, like an ectopic pregnancy, this comparison cohort is probably less influenced by the most important potential confounding factors in a study like this, i.e. the lack of knowledge about the intention or wish to become pregnant. On the other hand, the induced abortion cohort women probably had a reduced intention to become pregnant, but were likely to be more fertile than the ectopic cohort.

The aspect of intention to become pregnant is demonstrated by comparing the rate ratio estimates in the two different reference cohorts. With the miscarriage cohort

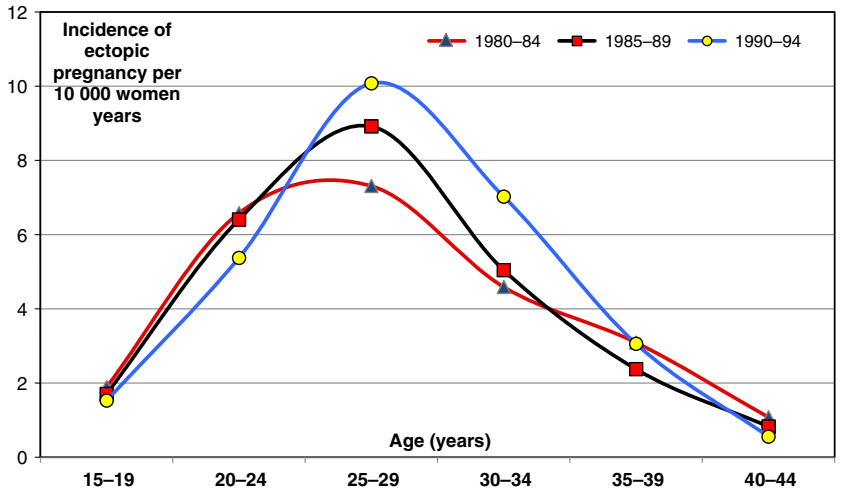

Figure 4. Incidence of ectopic pregnancy/10 000 women-years in the three sub-periods 1980–84, 1985–89 and 1990–94 according to age.

as reference, the ectopic cohort had 25% fewer induced abortions, whereas compared with the induced abortion cohort they had 50% fewer induced abortions. The delivery rate ratio of 0.7 when compared with the miscarriage cohort probably expresses the real long-term reproductive impact of a first ectopic pregnancy. The corresponding rate ratio of 1.1, if compared with the latest induced abortion cohort, probably reflects that the better fertility in the latter is counterbalanced by the lower intention to become pregnant in these cohorts.

Finally, the four- to five-fold increased risk of ectopic pregnancies in women with a first ectopic pregnancy compared with the miscarriage cohorts, is about half the rate ratio when compared with women with a first induced abortion. This difference could be explained by a generally slightly compromised reproductive capability in women experiencing miscarriages (and ectopic pregnancies) as compared with women undergoing induced abortions.

This is supported by other studies indicating an increased risk of ectopic pregnancies among women with miscarriages (11). If women experiencing miscarriages are more likely to become pregnant by use of artificial reproductive techniques, that circumstance could also influence the results, as artificial reproductive techniques imply around 4% risk of ectopic pregnancies (13).

To our knowledge, no previous study has described changes in the long-term reproductive prognosis over time for women with a first (recorded) ectopic pregnancy. We were restricted, however, to a 15-year follow-up period to ensure equal follow-up lengths for the different cohorts. This circumstance underestimates the number of life-long reproductive outcomes, but should not disturb the results within the 15 years of follow up.

Since the study is based on registers, recall bias and lack of follow up are limited. The results were based on pregnancy codes generated from a national health Register, providing comprehensive population coverage and high validity, which is recognized by several independent studies (14,15). In general, the register has a validity of 75–90%. The validity is highest for surgical codes (14). The ICD codes for deliveries have a high validity because in addition to the birth diagnosis, much other relevant information is registered (such as gestational age, weight and length of the baby). With respect to induced abortion, the registered data also include information about gestational age and relevant surgical and medical procedures (16). The diagnostic codes for spontaneous abortion have likewise a positive predictive value of 97.4% (17). The validity of ectopic pregnancy diagnoses is also considered to be high for the same reasons. As mentioned, we had no information about the women's intentions to become pregnant. The use of two different control cohorts, however, permitted us to evaluate the potential confounding impact of this lack of information.

Conclusion

The long-term delivery rate for women with a first ectopic pregnancy has improved significantly over time. Women with a first ectopic pregnancy continue to have a poorer reproductive prognosis compared with women with a first miscarriage. However, the relative delivery rate improved by about 20% over time, despite a consistent five- to ten-fold increased risk of further ectopic pregnancies.

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