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Impact of ectopic pregnancy for reproductive prognosis in next generation

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Conflict of interest
All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that: Øjvind Lidegaard within the last three years has received honoraria for speeches in pharmacoepidemiological issues. Line Lund Kårhus, Pia Egerup and Charlotte Wessel Skovlund have stated explicitly that they have no conflicts of interest in connection with this article.

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Abstract

The impact of an ectopic pregnancy in the next generation is unknown. Our aim was to compare reproductive outcomes in daughters of women with and without ectopic pregnancy. Designed as a historical prospective controlled cohort study with data collected in four Danish registries from 1977–2009, women with ectopic pregnancy during 1977–1982 were age-matched to women without ectopic pregnancy. Daughters of these two cohorts were followed until 2009. We compared 5126 daughters of women with ectopic pregnancy with 19 928 daughters of women without ectopic pregnancy. The daughters of women with ectopic pregnancy had a 1.5-fold (95% confidence interval 1.2–1.9) increased risk of ectopic pregnancy, while for deliveries this was 1.0 (1.0–1.1), for miscarriages 1.1 (1.0–1.2), and for induced abortions 1.3 (1.2–1.4). Daughters of mothers with ectopic pregnancy have a 50% higher risk of ectopic pregnancy than daughters of women without an ectopic pregnancy, but a normal delivery rate.

Abbreviations: CI, confidence interval; EP, ectopic pregnancy; ICD, International Classification of Diseases.

Introduction

About 1% of pregnancies in Denmark are ectopic (www.tigrab.dk). Ectopic pregnancies (EP) are an important cause of maternal morbidity and occasionally mortality in early pregnancy (1–3). Anything that hampers the migration of the embryo through the tubes will increase the risk of an EP. Among known risk factors are tubal damage from previous infection or surgery, previous EP and higher age (1–3). Smoking is associated with an increased risk of EP in a dose–response relation (4), and assisted reproduction increases the risk of EP two to three times (1–3). Whereas exogenous risk factors for EP are well described, knowledge about possible inherited factors is limited. The objective of this study was to explore if women of mothers with a history of an EP had a differential risk of EP and other reproductive outcomes, as compared with women of mothers without an EP.

Material and methods

The study was designed as a historical controlled cohort study. Since 1977, all discharge diagnoses from public and private hospitals have by law been collected in the

National Health Registry. This infrastructure made it possible to establish a historical prospective controlled cohort study with a follow-up time of up to 32 years, and to assess the reproductive prognosis in daughters of women with and without a history of EP.

Data for the study were provided from four national registries: the National Health Registry, Statistics of Denmark, the National Birth Registry, and the Registry of Induced Abortions. Women were censored at emigration or death.

All women with the diagnosis EP during the period 1 January 1977 through 31 December 2009 were identified in the National Health Registry. A subgroup who had an EP during the period 1977–1982 were age-matched (within one year) with four otherwise randomly selected control women without a recorded EP. The controls were randomly selected from a list of numbers by our research assistant, without knowing anything about the women other than age. Daughters of the women with an EP were considered the exposed cohort and daughters of the control women without an EP the control daughters. The exposed daughters and the control daughters were followed until the end of 2009 for all pregnancy outcomes including deliveries [International Classification of Diseases (ICD)-8:650-666 and ICD-10: O600-849], EPs (ICD-8:631.09-99 and ICD-10: O000-009), miscarriages (ICD-8:643+645.1 and ICD-10: O021 and O030-039), and induced abortion (ICD-8:640-642 and ICD-10: O040-059).

The reproductive outcomes were calculated as rates and as rate ratios with 95% confidence intervals. Differences were tested by *z*-test, and *p*-values under 0.01 were considered significant. This low *p*-value was chosen due to the large sample size. Time to any emigration or death was noticed to calculate the average time of follow-up. The study was approved by the National Board of Health (journal no. 7-201-03-08/1) and the Danish Data Protection Agency (journal no. 2006-41-6907). Ethical approval is not required for registry-based studies in Denmark

Results

We identified 40 101women with a diagnosis of EP during the period 1 January 1977 through 31 December 2009. Of these, 5692 women had an EP during 1977–1982, and this subgroup gave birth to 5126 daughters (exposed daughters). The women without an EP (n = 22 776) during the same period gave birth to 19 928 daughters (control daughters). The proportion of emigrated or dead women before end of follow-up was 5.6% in the exposed group and 7.2% in the control daughters (Table 1). However, the average follow-up time was similar; 30.6 and 30.5 years, respectively.

Table 1. Pregnancy outcomes in daughters of mothers with and without an ectopic pregnancy. Follow-up 1977–2009.

	Mother with ectopic pregnancy				
	Yes		No		
	n	%	*n*	%	
Mothers 1977–1982	5692		22776		
Daughters	5126	100%	19 928	100%	
Died during follow-up	111	2.2%	338	1.7%	
Emigrated during follow-up	175	3.4%	1104	5.5%	
Emigrated or dead (total)	286	5.6%	1442	7.2%	
Follow-up time (years)	30.6		30.5		
Pregnancy outcomes					
All pregnancies	8146	100%	29 059	100%	
Deliveries	5422	66%	20452	70%	
Ectopic pregnancies	103	1.3%	267	0.9%	
Miscarriages	763	9.4%	2774	9.5%	
Induced abortions	1858	22.8%	5566	19.2%	
Per 100 daughters					Rate ratio Yes/No
All pregnancies	158.9		145.8		1.1*
Deliveries	105.8		102.6		1.0
Ectopic pregnancies	2.0		1.3		1.5*
Miscarriages	14.9		13.9		1.1
Induced abortions	36.2		27.9		1.3*

*$p < 0.01$ (*z*-test).

The number of EPs in the exposed daughters was 103 (1.3%) compared with 267 (0.9%) among the control daughters (Table 1). Thus, daughters of women with an EP, had a significantly higher incidence rate of EP than daughters of women without EP; rate ratio 1.50 [95% confidence interval (CI) 1.19–1.88) (Figure 1). There was no significant difference between daughters of women with and without EP with regard to deliveries (rate ratio 1.03; 95% CI 1.00–1.06) or miscarriages (rate ratio 1.07; 95% CI 0.99–1.16) but we noted a significantly higher rate of induced abortions (rate ratio 1.30; 95% CI 1.23–1.37) and of total pregnancies (rate ratio 1.09; 95% CI 1.06–1.12) (Table 1, Figure 1).

Discussion

We found that daughters of mothers with a history of EP had a 50% higher risk of EP and 30% more induced abortions, whereas the rate of deliveries and miscarriages

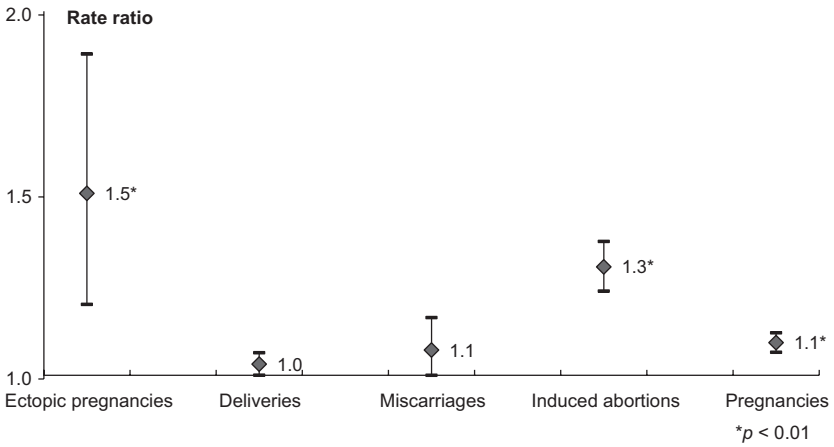

Figure 1. Rate ratio of pregnancy outcomes in daughters of women who had a history with ectopic pregnancy compared with women without such a history (*z*-test).

was not different. To our knowledge, the increased risk of EP among daughters of mothers with a history of EP has not been reported before. The increased risk is not necessarily due to a genetically transmitted disposition, but could also be influenced by similar lifestyles in mother and daughter, for example in sexual and contraceptive practices. Whereas pelvic inflammatory disease is a clearly acquired condition, the susceptibility for tubal damage in case of infection might also be influenced by inherited factors. The 30% increased risk of induced abortion may give a hint about the differences in lifestyle. An increased risk for unwanted pregnancies could well be due to differences in sexual and contraceptive habits, i.e. lifestyle factors likely to influence the risk of EP. As the risk of miscarriages and deliveries was the same in the two groups of daughters, infertility and consequently assisted reproduction are unlikely to differ materially between the two groups.

Behavioral patterns, such as smoking and alcohol, are socially transmitted and children of smokers or alcohol users are more likely to smoke or drink than children of non-smokers or those who do not drink alcohol (5,6). Therefore other behavioral patterns might be affected by social heritage as well. Studies on the effects of psychosocial factors on pregnancy outcomes show that many factors can affect behavior; for example, stress can indirectly affect pregnancy outcomes through unhealthy coping and lifestyle behavior (7,8).

Among the strengths of this study are the large exposed cohort, the even larger unexposed group, the long and equal follow-up time, and the 100% follow-up rate limited only by emigration or deaths. The validity of the Danish registries depends on the validity of the diagnostic ICD codes. Pregnancy outcome diagnoses are in general valid and should be accompanied by gestational age information. Surgical codes are also more valid than medical diagnoses (9). The validity of delivery, EP and induced abortion codes is fairly high in the National Health Registry, but is slightly lower for the diagnoses of miscarriage. It is unlikely, however, that misclassification should be different between the two cohorts and thus bias the rate ratio estimates. If anything, misclassification bias will tend to underestimate the difference in outcomes between the two cohorts. It is a limitation that we had no other information about the women besides the pregnancy outcomes. Their intentions to get pregnant, their lifestyle, risk factors such as smoking and other aspects affecting reproduction were not known and could have influenced our results. On the other hand, we have no reason to believe in differences between the two cohorts beyond the possible sexual and contraceptive lifestyle aspects mentioned. A possible further way of discriminating between acquired and genetically transmitted pre-disposition to EP could be through twin analyses comparing the concordance of EP in monozygotic and dizygotic female twins.

In conclusion, in this national follow-up of two large cohorts of daughters of mothers with and without an EP we found a 50% increased risk of EP and a 30% increased risk of induced abortions, but the same delivery and miscarriage rates in the exposed cohort, compared with daughters of women without a history of EP.

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