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Reproductive prognosis in endometriosis. A national cohort study

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Conflicts of interests
Maj V. Hjordt Hansen, Torur Dalsgaard, Dorthe Hartwell, and Charlotte Wessel Skovlund have stated explicitly that there are no conflicts of interest in connection with this article. Øjvind Lidegaard has, within the last 3 years, received honoraria for lectures on pharmacoepidemiological issues.

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Abstract

Objective. To assess the reproductive long-term prognosis of women with and without endometriosis, to explore changes over time, and to quantify the contribution of artificial reproductive techniques. *Design.* Cohort study. *Setting.* Denmark 1977–2009. *Sample.* Data retrieved from four national registries. Among 15–49-year-old women during the period 1977–82, 24 667 were diagnosed with endometriosis and 98 668 (1:4) women without endometriosis were age-matched. *Methods.* To assess long-term reproductive prognosis, all pregnancy outcomes were identified among the women with and without endometriosis until the end of 2009. To explore changes over time, the endometriosis cohorts were followed for 15 years from the years 1980, 1986, 1992 and 1998, with the corresponding control cohorts. All pregnancy outcomes were categorized into naturally or artificially conceived pregnancies. *Main outcome measures.* Births, miscarriages, induced abortions, ectopic pregnancies and hydatidiform moles. *Results.* Compared with women without endometriosis, women with endometriosis had a lowered relative risk for childbirth of 0.93 (95% confidence interval 0.92–0.95), for miscarriages the relative risk was 1.2 (95% confidence interval 1.2–1.3), ectopic pregnancies were almost twice as many (relative risk 1.9, 95% confidence interval 1.8–2.1), while frequencies of induced abortions were equivalent. The chances for childbirth increased over time from 0.82 to 0.92 ($p < 0.001$) with successive cohorts, but this was restricted to pregnancies from assisted reproduction. *Conclusion.* Women with endometriosis have slightly fewer children, but this lessened over time due to artificially conceived pregnancies. The risk for miscarriages and ectopic pregnancies was increased compared with women without the disease.

Abbreviations: ART, assisted reproductive techniques; ICD, International Classification of Diseases; RR, relative risk.

Introduction

Endometriosis is one of the more common conditions encountered in gynecology, but the cause remains enigmatic. The reported prevalence varies widely because some women have few or atypical clinical symptoms, and a certain diagnosis of endometriosis demands laparoscopy with histological verification. An Icelandic nationwide study described an annual incidence rate of 0.05% for

Key Message

During 15 years of follow up, women with endometriosis had between 8 and 18% fewer childbirths than women without endometriosis; the rate improved through the years mainly due to assisted reproductive techniques. Higher rates of miscarriage and ectopic pregnancy were persistent through the study period.

pelvic endometriosis in women aged 15–49 years (1). In general it is difficult to compare prevalence estimates of endometriosis because diagnostic methods differ and clinical expertise and diagnostic proficiency vary. Assessment of the long-term reproductive prognosis for women with endometriosis is challenged by better surgical techniques, and for those affected by infertility assisted reproductive techniques (ART) have made a difference (2–5). While the reduced immediate reproductive consequences of endometriosis are well-known, we found only a few long-term reproductive follow-up studies and none with a control population. The existence of national health registries in Denmark going back to 1977 makes it possible to establish cohorts of women with and without recorded endometriosis, to follow these cohorts over decades, and to assess the reproductive outcomes in the affected and non-affected cohorts.

The purpose of this study was first to assess the reproductive long-term prognosis in women with endometriosis, and to compare it with the prognosis in women without endometriosis. Additional aims were to assess changes over time and to quantify the contribution of ART to changes in reproductive prognosis.

Material and methods

Data were retrieved from four National Danish registries. The National Civil Registration provided personal identification codes of Danish women 15–49 years old at any time during the 33-year-long study period of 1977–2009. The National Health Registry provided discharge diagnoses for patients with endometriosis by the International Classification of Diseases, 8th revision (ICD-8; 1977–1993) and 10th revision (ICD-10; 1994–2009) codes 625, 625.30–38 and N80, N80.0-6, N80.8A/B, N80.9, respectively. The Danish Birth Register and the National Fertility Database provided data on deliveries and all in vitro fertilizations since 1994, as well as all intrauterine inseminations since 2007. Other pregnancy outcomes were identified in the National Health Registry, including deliveries (ICD-8: 650-666, ICD-10: O60.0-O84.9), miscarriages (spontaneous abortion, missed abortion and pregnancy without fetus; ICD-8: 643 and 645.1, ICD-10: O02.1 and O03.0–O03.9, respectively), ectopic pregnancies (ICD 8: 631.09-99, ICD-10: O00.0–00.9), induced abortions (ICD-8: 640-642, ICD-10: O04.0–O05.9) and hydatidiform moles (ICD-8: 634.29, ICD-10: O01.0–O01.9 and O02.0B/C). Using the National Civil Registration (CPR national identity numbers) and the National Patient Registry, all women with at least one diagnosis of endometriosis during the study period were first identified. Next, for each woman with endometriosis, four age-matched cohorts of control women without endometriosis (born within the same year and month) were identified. We assumed that endometriosis, once diagnosed, was present throughout reproductive age. Then, we established a cohort of women with endometriosis who were 15–49 years old at some time during the period from 1977 to 1982. All women were censored upon reaching their 50th birthday or at death or emigration. To assess long-term reproductive prognosis, all pregnancy outcomes were identified among women with endometriosis and the corresponding control cohorts until the end of 2009, including deliveries, miscarriages (spontaneous abortion, missed abortion and pregnancy without fetus), ectopic pregnancies, induced abortions, and hydatidiform moles. Four successive cohorts of women with endometriosis, who were 15–49 years old by 1st January in 1980, 1986, 1992, and 1998, respectively, were established to obtain 6-year age groupings within the study period. In addition to births we estimated the number of children born in the different cohorts to account for eventual differences in the proportion of multiple pregnancies.

To assess changes over time, the four successive endometriosis cohorts and their corresponding controls were followed for 15 years, from 3 years before the index date (date of matching to controls) to 12 years after it, or until age 50 whichever was first, to ensure that all the cohorts were followed over the same length of time for trend analysis.

All pregnancy outcomes were categorized into naturally or artificially conceived pregnancies by merging data from the fertility database with those from the birth register. This stratification was effective regarding in vitro fertilizations. The reproductive outcomes were calculated as incidence rates/100 women and as a relative risk (RR) of outcomes between women with and without endometriosis. For all RRs, 95% CI were calculated. SAS software statistical program version 9.1.3 (SAS Institute, Cary, NC, USA) was used, and differences were tested by the *Z*-test. Values of $p < 0.05$ were considered significant. A sensitivity analysis was performed, in which we excluded all women having their first endometriosis diagnosis at the same time as a diagnosis of ectopic pregnancy, as some women with recorded endometriosis could have been diagnosed because of their ectopic pregnancy. The corresponding matched controls were also excluded.

The study was approved by the Danish Data Protection Agency (J no 2009-41-3867). Anonymous register studies do not by official regulation require ethical committee approval in Denmark.

Results

We identified 34 628 women with endometriosis, of whom 24 667 were of reproductive age (15–49 years old)

Table 1. Characteristics of the endometriosis and control cohorts before the age of 50.

	Endometriosis cohort	Per 100	Control cohort	Per 100
Cohort size (*n*)	24 667		98 668	
Dead	436	1.8	2961	3.0
Emigrated	262	1.1	8817	8.9
Average time in study	24.7 years		22.7 years	
Reproductive outcomes				
Liveborn	26 859	108.9	114 385	115.9
Stillborn	131	0.5	563	0.6
All born children	26 990	109.4	114 948	116.5
Childbirth: relative risk	0.94 (0.93–0.95)		1 (ref.)	
0 births (deliveries)	10 006	40.6	40 331	40.9
1 birth	5800	23.5	19 255	19.5
2 births	6516	26.4	26 705	27.1
3+ births	2345	9.5	12 377	12.5
Number of births	1.07		1.15	
Age at first birth	26.4 years		26.6 years	

during 1977–82. The corresponding age-matched control cohort included 98 668 women. Fewer women with endometriosis died or emigrated compared with women in the control cohort, with an average length of follow up of 24.7 and 22.7 years, respectively, i.e. an 8% shorter follow-up time in the control cohort (Table 1).

Overall, 39 555 pregnancies were detected in the endometriosis cohort, compared with 161 083 in the control cohort (Table 2). There were slightly fewer deliveries and children born in the endometriosis cohort, corresponding to an RR of 0.93 for deliveries (Figure 1) and 0.94 for children born after accounting for multiple pregnancies. The average age at first birth in the cohorts was almost the same, 26.4 and 26.6 years, respectively (Table 1). Women with endometriosis had 24% more miscarriages, almost twice as many ectopic pregnancies, but equivalent frequencies of induced abortions and hydatidiform moles (Table 2, Figure 1).

The sensitivity analysis controlling for incidental endometriosis diagnosis noted during surgery for an ectopic pregnancy demonstrated a slight reduction in RR from 1.9 (95% CI 1.8–2.1) to 1.8 (95% CI 1.6–1.9) (data not shown).

After stratification by mode of conception, we found 8% fewer naturally conceived deliveries among women with endometriosis than in the control cohort, 21% more miscarriages, and still a doubled risk of ectopic pregnancy. Overall, 1.9% of women with endometriosis and 0.5% of women without endometriosis achieved pregnancy after ART. In women with endometriosis, there were 3.4 times (95% CI 3.0–3.8) more ART-deliveries, 4.3 (95% CI 3.4–5.5) more ART-miscarriages, and a 2.7 times (95% CI 1.4–5.0) higher incidence of ART-ectopic pregnancies, compared with women without endometriosis. The number of induced abortions after in vitro fertilization was too low for reliable interpretations (Table 2).

Table 2. Reproductive outcomes in women with and without endometriosis stratified by mode of conception.

	Endometriosis cohort (*n* = 24 667)			Control cohort (*n* = 98 668)		
	All	Natural	ART	All	Natural	ART
Outcomes (*n*)						
Deliveries	26 427	25 834	593	113 320	112 617	703
Miscarriages	4029	3887	142	12 954	12 823	131
Ectopic pregnancies	1076	1060	16	2227	2203	24
Induced abortion	7984	7975	9	32 457	32 452	5
Hydatidiform mole	39	39	0	125	124	1
All pregnancies	39 555	38 795	760	161 083	160 219	864
Outcomes per 100 (*n*)						
Deliveries	107.14	104.73	2.40	114.85	114.14	0.71
Miscarriages	16.33	15.76	0.58	13.13	13.00	0.13
Ectopic pregnancies	4.36	4.30	0.06	2.26	2.23	0.02
Induced abortion	32.37	32.33	0.04	32.90	32.89	0.01
Hydatidiform mole	0.16	0.16	0.00	0.13	0.13	0.00
All pregnancies	160.36	157.27	3.08	163.26	162.38	0.88
Relative risk (95% CI)						
Deliveries	0.93 (0.92–0.95)	0.92 (0.91–0.93)	3.37 (3.02–3.76)	1 (ref.)	1 (ref.)	1 (ref.)
Miscarriages	1.24 (1.20–1.29)	1.21 (1.17–1.26)	4.34 (3.42–5.50)	1 (ref.)	1 (ref.)	1 (ref.)
Ectopic pregnancies	1.93 (1.80–2.08)	1.92 (1.79–2.07)	2.67 (1.42–5.02)	1 (ref.)	1 (ref.)	1 (ref.)
Induced abortion	0.98 (0.96–1.01)	0.98 (0.96–1.01)	7.20 (2.41–21.48)	1 (ref.)	1 (ref.)	1 (ref.)
Hydatidiform mole	1.25 (0.87–1.79)	1.26 (0.88–1.80)	0.00	1 (ref.)	1 (ref.)	1 (ref.)
All pregnancies	0.98 (0.97–0.99)	0.97 (0.96–0.98)	3.52 (3.19–3.88)	1 (ref.)	1 (ref.)	1 (ref.)

The overall chances (RR) for delivery among women with endometriosis compared with corresponding controls increased from 0.8 in 1980 to 0.9 by the end of the study period (Table 3, Figure 2). The RR of miscarriages increased significantly in both the endometriosis and control cohorts throughout the study period, and the RR increased from 1.1 in 1980 to 1.3 in 1998. The RR for naturally conceived ectopic pregnancies increased from 1.6 in the first cohort to 2.2 in 1998 ($p < 0.001$) (Table 3, Figure 2). No consistent trend was seen for induced

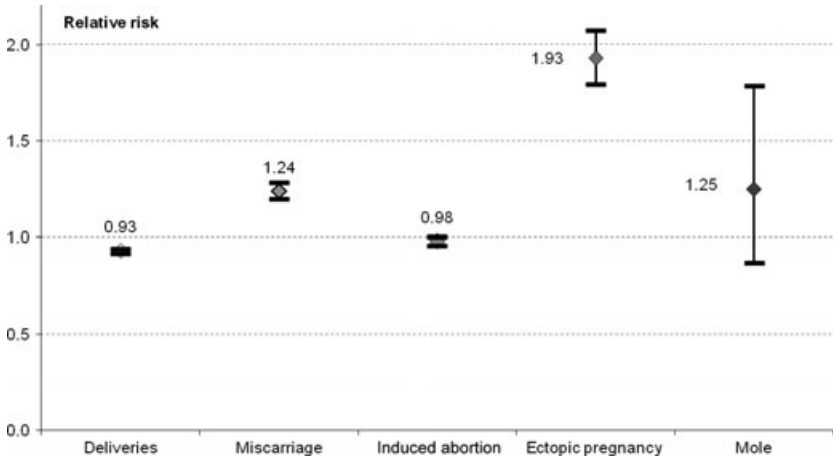

Figure 1. Relative risk calculations for different reproductive outcomes among women with and without endometriosis. Follow up 1977–2009.

Table 3. Reproductive outcomes in successive cohorts and the number of women emigrated and dead before the age of 50 years.

	Cohort 80	Cohort 86	Cohort 92	Cohort 98
With endometriosis				
Cohort size (*n*)	7757	8725	9441	8236
Dead	176	171	136	61
Emigrated	63	91	141	166
Follow-up time	15.03	15.02	14.99	14.87
Outcomes (*n*)				
Deliveries	4185	5948	7617	7087
Miscarriages	744	1153	1610	1546
Ectopic pregnancies	217	365	437	284
Without endometriosis				
Size (*n*)	31 028	34 900	37 764	32 944
Dead	1052	1101	1025	686
Emigrated	2782	3651	4162	4169
Follow-up time	13.86	13.67	13.54	13.07
Outcomes (*n*)				
Deliveries	20 309	27 318	34 275	30 871
Miscarriages	2600	3877	5160	4787
Ectopic pregnancies	536	850	816	521
Relative risk (95% CI)				
Deliveries	0.82 (0.80–0.85)	0.87 (0.85–0.90)	0.89 (0.87–0.91)	0.92 (0.89–0.94)
Miscarriages	1.14 (1.06–1.24)	1.19 (1.11–1.27)	1.25 (1.18–1.32)	1.29 (1.22–1.37)
Ectopic pregnancies	1.62 (1.38–1.90)	1.72 (1.52–1.94)	2.14 (1.91–2.41)	2.18 (1.89–2.52)
Naturally conceived				
Deliveries	0.82 (0.80–0.85)	0.86 (0.84–0.89)	0.85 (0.83–0.87)	0.81 (0.79–0.83)
Miscarriages	1.14 (1.06–1.24)	1.16 (1.09–1.24)	1.18 (1.12–1.25)	1.17 (1.10–1.24)
Ectopic pregnancies	1.62 (1.38–1.90)	1.73 (1.53–1.95)	2.12 (1.88–2.38)	2.06 (1.77–2.39)
Artificially conceived				
Deliveries	–	3.47 (2.50–4.83)	3.66 (3.22–4.17)	4.53 (4.14–4.96)
Miscarriages	–	10.91 (5.47–21.77)	5.86 (4.35–7.89)	5.42 (4.34–6.77)
Ectopic pregnancies	–	0.67 (0.08–5.54)	3.50 (1.71–7.17)	5.14 (2.91–9.10)

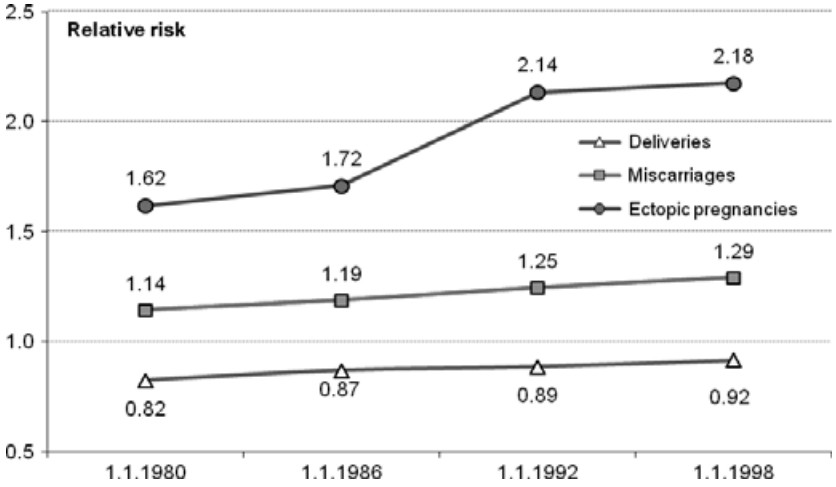

Figure 2. Trend in relative risk calculations for reproductive outcomes in succeeding cohorts of women with and without endometriosis. Follow-up time 15 years.

abortions over time, and the number of women with hydatidiform moles was too low for time trend analyses (data not shown).

The sensitivity analysis with the exclusion of women having their first endometriosis diagnosis at the same admission as a diagnosis of ectopic pregnancy demonstrated slightly reduced risk estimates, but still a significant increase in RR from 1.4 (95% CI 1.2–1.7) in 1980 to 2.1 (95% CI 1.8–2.4) in the 1998 cohort (data not shown).

After stratification according to the mode of conception, the RR for naturally conceived deliveries in women with endometriosis was stable throughout the four periods. For miscarriages, the RR increased from 1.1 in 1980 to 1.2 in 1998. The risk of ectopic pregnancy increased from an RR of 1.6 in 1980 to 2.1 in 1998 (Table 3). No consistent trend was seen for induced abortions over time (data not shown).

In the trend analysis on successive cohorts, the RR for childbirth after natural conception was stable, whereas the RR after ART increased from 3.5 in 1986 to 4.5 in the latest cohort ($p < 0.001$) (Table 3). The RR of miscarriage after ART in women with endometriosis decreased from 10.9 in 1986 to 5.4 in 1998. In spite of this decline, there was still a noticeably greater risk of miscarriage (Table 3). The risk of artificially conceived ectopic pregnancies increased over time from 0.67 in 1986 to 5.1 in 1998 ($p < 0.001$). No consistent trend was seen for induced abortions and the number of hydatidiform moles was too low for time trend analyses (data not shown).

Discussion

These data indicate that women with endometriosis had about 7% fewer childbirths and 8% fewer naturally conceived deliveries than the control cohort, as well as a substantially increased risk of miscarriages and ectopic pregnancies.

This study was conducted on the assumption that endometriosis is a chronic disease. If some women had pregnancies before endometriosis was discovered, this circumstance would have tended to underestimate the impact of the disease. Two studies found up to a 12-year interval between the onset of symptoms and diagnosis being established (6,7). This supports the assumption that endometriosis is a lifelong disease affecting reproduction throughout a woman's fertile age. An improvement in the delivery rates over time was primarily ascribed to ART.

Better and earlier diagnosis of miscarriages due to improvements in ultrasound diagnostics and equipment may explain the increased incidence of miscarriage rates. Positive associations between endometriosis and spontaneous abortions have been described as well as a decrease in spontaneous abortions after medical or conservative surgical therapy for endometriosis (8–10), but control groups were lacking in these studies, and where such an approach has been used these findings have not been replicated for endometriosis patients (11–13). Follow up in these studies was relatively short. After assisted reproduction, closer follow up in the weeks after the treatment is used and so more early miscarriages are detected, whereas a decrease in the risk for ART-miscarriages in the 1986–92 cohort may have been the result of an initial registration of biochemical pregnancy as miscarriage. This practice ceased in the mid-1990s. ART was not introduced until the 1980s, explaining the missing data in Table 3.

The two-fold increased risk for natural ectopic pregnancies, and an even higher risk of ART-ectopic pregnancy in women with endometriosis, is in line with a

higher frequency of ectopic pregnancies among women undergoing assisted reproduction (14,15). There are different views on why women with endometriosis have an increased risk of ectopic pregnancy, including the reflux of endometrial tissue fragments into the fallopian tube providing uterine cavity epithelial characteristics (16). In two studies no added risk of ectopic pregnancy was found (17,18), whereas others have shown the converse (19). Our results suggest that it is unlikely that the increased risk was associated with an incidental endometriosis diagnosis during surgery for ectopic pregnancy.

A limitation of this study was that we were not able to follow all women throughout their entire reproductive period. Therefore, the total number of deliveries and other pregnancy outcomes does not represent the full lifelong reproductive history, but that circumstance applies to the control cohorts as well because of the close age matching. Despite this we nevertheless had a slightly longer mean follow-up period for the endometriosis cohort, due to their lower frequency of emigration, which may have lead to an underestimate in the reproductive consequences of endometriosis.

Some of the women with endometriosis were diagnosed solely based on clinical suspicion, some of which, therefore, could be misclassified (a too high numerator for deliveries, and too low numerator for miscarriages and ectopic pregnancies). Some women without a diagnosis of endometriosis could, on the other hand, have had endometriosis (too low denominator for deliveries and too high for miscarriages and ectopic pregnancies). Both of these potential biases tend to underestimate any differences in deliveries, miscarriages and ectopic pregnancies. This potential bias was reduced by classifying a woman as a woman with endometriosis, whenever she was diagnosed with the disease during the 33-year study period. Hence, the real risk of miscarriages and ectopic pregnancies in women with endometriosis could indeed be even higher if we had been able to remove all misclassifications.

Conclusion

Despite a substantially higher risk of ectopic pregnancy and more miscarriages, women with endometriosis have experienced a significant improvement in their chances for childbirth over the last three decades, as compared with women without endometriosis, and the delivery lag is today <10%. This improvement is, according to this study, mainly due to developments in ART.

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