Endometriosis and preterm birth: A Danish cohort study

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Abstract
Introduction: Emerging evidence shows that women with endometriosis face a higher risk of preterm birth. However, the pathways are unclear. The objective of this study is to further investigate at different gestational ages the association between endometriosis and different pathways of preterm birth including, medically indicated preterm birth, premature pre-labor rupture of membranes (PPROM), and spontaneous labor contractions.

Material and methods: In this population-based cohort study we linked singleton pregnancies from the Aarhus Birth Cohort to the Danish National Patient Registry, the Danish Medical Birth Registry, the Danish National Pathology Registry and Data Bank, and the Danish in vitro fertilization registry to gather information on endometriosis status, outcomes and maternal characteristics. We investigated preterm birth before 37 completed weeks of gestation and very preterm birth before 32 completed weeks of gestation. We explored different pathways including medically indicated preterm birth defined as induction of labor with intact membranes and no prior labor contractions, PPROM defined as rupture of membranes, and spontaneous labor contractions defined as contractions with intact membranes resulting in labor.

Results: We found that women with endometriosis had an increased risk of preterm birth before 37 gestational weeks overall (adjusted hazard rate [aHR] 1.6, 95% confidence interval [CI] 1.3–1.9) and very preterm birth before 32 gestational weeks (aHR 1.8, 95% CI 1.1–2.9) compared with women without endometriosis. Medically indicated preterm birth was more prominent in women with endometriosis in deliveries before 37 gestational weeks (aHR 2.4, 95% CI 1.8–3.2) whereas spontaneous labor contractions were more common before 32 gestational weeks (aHR 2.2, 95% CI 1.1–4.5) in women with endometriosis compared with women without endometriosis. Further, in the analyses restricted to women with a histologically verified diagnosis of endometriosis, the results were strengthened overall and showed that women with endometriosis had an increased risk of PPROM before 32 gestational weeks (aHR 3.49, 95% CI 1.36–8.98).

Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; DAG, directed acyclic graph; ICD, International Classification of Disease; PPROM, premature preterm rupture of membranes.

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1 | INTRODUCTION

Endometriosis is a chronic, inflammatory, gynecological disease estimated to affect up to 10% of women in the reproductive age.1 Emerging evidence fairly consistently shows that women with endometriosis face a higher risk of preterm birth.2–4 However, the underlying pathways remain unclear. Knowledge of the processes involved in preterm birth among women with endometriosis may provide some clues related to the potential causality.5 Whether preterm birth in women with endometriosis may be due to spontaneous labor contractions, preterm pre-labor rupture of membranes (PPROM),6,7 or is medically indicated due, for example, to pre-eclampsia or fetal growth restriction8 has rarely been studied.

With this large population-based cohort study, we, therefore, aimed to investigate further the association between endometriosis and preterm birth. The cohort presented has previously formed the basis for research on pregnancy complications in women with endometriosis.9 However, the current study included more women from the Danish National Pathology Registry and Data Bank. With this approach, we revisited the prevailing hypotheses of higher risk of preterm birth among women suffering from endometriosis. We performed more detailed analyses, both assessing the timing of preterm birth and distinguishing between the potential underlying pathways, including medically indicated preterm birth, PPROM, and preterm spontaneous labor contractions.

2 | MATERIAL AND METHODS

We performed a population-based cohort study using data from 1989 to 2013 from the Aarhus Birth Cohort. The Aarhus Birth Cohort invited all women attending routine antenatal care at the Department of Obstetrics and Gynecology, Aarhus University Hospital, Denmark, to complete questionnaires regarding lifestyle (eg smoking habits and alcohol consumption), sociodemographic (eg years of education and country of birth) and health-related characteristics (eg body mass index [BMI]) before and during pregnancy, providing the opportunity to adjust for several potential confounders. Detailed data on pregnancy outcomes (eg mode of delivery, indication for cesarean section and PPROM) were recorded by a research assistant midwife using a structured codebook while extracting the information from the women’s medical record at or after birth.10

Within the cohort, we identified all women giving birth to a single child with a gestational age of 24–44 weeks between September 1, 1989 until December 31, 2013 and linked the data to the Danish National Patient Registry,11 the Danish Medical Birth Registry,11 the Danish National Pathology Registry and Data Bank,11 and the Danish in vitro fertilization (IVF) registry11 using each woman’s unique Civil Registration Number.

The Danish National Patient Registry holds information on all somatic patients admitted to hospitals since 1977 as well as outpatient contact since 1995. For all hospital contacts, one primary and, if necessary, secondary diagnoses are recorded according to the International Classification of Disease (ICD). The 8th revision of ICD was used until the end of 1993 and the 10th revision since 1994.11 The Danish Medical Birth Registry has provided information on all in-hospital as well as home deliveries in Denmark since 1973.11 The Danish National Pathology Registry and Data Bank contains records of all pathology specimens analyzed in Denmark since the 19070s.11 The Danish IVF Registry holds information from private and public clinics on all pregnancies conceived by medically assisted reproduction since 1994.11

We identified all women with endometriosis from the Danish National Patient Registry using ICD-8 and ICD-10 codes (ICD-8: 625.3; ICD-10: N80). All subtypes of endometriosis were included. Since the diagnosis of endometriosis on average is shown to be delayed for up to 8 years, we included women diagnosed both before

Conclusions: Endometriosis was associated with both preterm and very preterm birth; however, apparently through different pathways. Women with endometriosis were more prone to have medically indicated preterm births before 37 gestational weeks and spontaneous preterm births before 32 gestational weeks compared with women without endometriosis.

KEYWORDS
endometriosis, labor, induced labor onset, premature birth, preterm premature rupture of the membranes

Key message

Overall, women with endometriosis had higher risk of preterm birth, with medically indicated preterm birth being most prominent, compared with women without endometriosis. Furthermore, endometriosis was associated with very preterm birth mainly due to spontaneous labor contractions.
and after pregnancy. We obtained information on biopsy-verified cases of endometriosis from the Danish Pathology Registry and Data Bank.

Information on maternal characteristics was mainly retrieved from the Aarhus Birth Cohort and subsequently missing information was obtained from the Danish Medical Birth Registry, if possible. The covariates included were as follows: maternal age at the time of birth, maternal pre-pregnancy BMI, parity, years of school at the time of pregnancy, country of origin, smoking during pregnancy, and alcohol consumption during pregnancy. Lastly, information on medically assisted reproduction was obtained from the Aarhus Birth Cohort and the Danish IVF Registry. Please see Table 1 for categorization of the included covariates.

Information on outcomes was primarily obtained from the Aarhus Birth Cohort. If possible, missing information was obtained from the Danish Medical Birth Registry.

Gestational age was estimated based on routine ultrasonography at approximately gestational week 12. If no routine ultrasonography was available, gestational age was estimated from the first day of the last menstrual period. In the following, gestational weeks are reported as completed weeks.

The primary outcome of interest was preterm birth defined as birth prior to 37 gestational weeks and very preterm birth as birth prior to 32 gestational weeks. We distinguished between medically indicated preterm birth (including prostaglandin administration, Foley bulb induction, artificial rupture of membranes and preterm cesarean section with intact membranes and no prior labor contractions), PPROM and spontaneous preterm labor with intact membranes (spontaneous labor contractions).

PPROM was defined as rupture of membranes before 37 weeks of gestation from the Aarhus Birth Cohort and, in the rare case of missing information, according to ICD-10: DO420, DO422 and DO424 from the Danish Medical Birth Registry for preterm birth and as rupture of membranes before 32 weeks of gestation from the Aarhus Birth Cohort for very preterm birth. Women with intact membranes and labor contractions resulting in preterm birth were included in the spontaneous labor contractions.

2.1 | Statistical analyses

The proportion of missing values was as follows: pre-pregnancy BMI 2.7%; years of education 12.3%; country of birth 0.3%; smoking during pregnancy 0.2%; alcohol consumption during pregnancy 14.4%. Other variables were complete. The total proportion of mother and child dyads with at least one missing value on any variable was 27%.

We performed chained multiple imputation to account for any missing information. Please see Supporting Information S1 for details.

We used a time to event model and performed Cox regression analyses, thus calculating crude hazard ratios and adjusted hazard ratios with 95% confidence intervals comparing women with endometriosis and women without endometriosis. We created Kaplan–Meyer plots and log-log plots to ensure that data fulfilled the proportional hazards assumptions for Cox regression.

The models were adjusted for the following potential confounders depicted by a priori knowledge as well as directed acyclic graphs (DAGs): maternal age, maternal pre-pregnancy BMI, parity, socioeconomic status, ethnicity, smoking during pregnancy, alcohol consumption during pregnancy and year of birth (Figure S1). We allowed intergroup correlations making the observations independent across clusters using the unique maternal Civil Registration Number, thus taking repeated pregnancies into account.

We conducted five sub-analyses to assess the robustness of our findings. First, we only included women with a histologically verified diagnosis of endometriosis from the Danish Pathology Registry and Data Bank. Secondly, we only used the complete cases. Thirdly, we only included nulliparous women. Fourthly, we only included women with a diagnosis of endometriosis prior to pregnancy. Lastly, we stratified women by medically assisted reproduction status.

Further, we tested for interaction between endometriosis and medically assisted reproduction using linear regression.

We used STATA 16 (STATAcorp) for all statistical analyses.

2.2 | Ethical approval

The Scientific Ethical Committee approved the Aarhus Birth Cohort when it was established in 1989. Informed consent was obtained from all participants at the time of recruitment. The Danish Data Protection Agency and the Danish National Board of Health approved the present study on February 14, 2014 (J. no. 2013-41-2563 and file no. 3-3013-1017/1/).

3 | RESULTS

We included 83087 women with singleton pregnancies who gave birth between 24 and 44 gestational weeks from September 1, 1989, through December 31, 2013. We excluded stillbirths (n = 294) and pregnancies with missing information on gestational age (n = 78) or how labor was initiated (spontaneous or medically indicated) (n = 873). Thus, the final study population was comprised of 81842 women. Of these, 1983 (2.4%) were conceived by women with endometriosis according to the Danish National Patient Registry.

Women with endometriosis were on average older and had a higher prevalence of medically assisted reproduction compared with women without endometriosis. Pre-pregnancy BMI, parity, years of education, country of birth, frequency of maternal smoking during pregnancy and maternal alcohol consumption during pregnancy were similar for women with and without endometriosis (Table 1).

Overall, we found that women with endometriosis had a higher risk of preterm birth before 37 weeks of gestation compared with women without endometriosis. With respect to potential pathways, women with endometriosis had an overall higher risk of giving
We found that women with endometriosis face a 55% increased risk of preterm birth before 37 weeks of gestation and an 81% increased risk of very preterm birth before 32 weeks of gestation. When distinguishing between potential pathways, women with endometriosis showed an increased risk of spontaneous labor contractions but no significant differences were found for medically indicated births or PPROM (Table 2, Figure 1). However, among women with a histologically verified diagnosis of endometriosis, the associations were even stronger, especially for very preterm birth before 32 gestational weeks. Here we found that women with histologically verified endometriosis had a higher risk of both PPROM and preterm spontaneous labor contractions before 32 weeks of gestation (Table 2).

Furthermore, endometriosis was overall associated with very preterm birth before 32 weeks of gestation. When distinguishing between potential pathways, women with endometriosis showed an increased risk of spontaneous labor contractions but no significant differences were found for medically indicated births or PPROM (Table 2, Figure 1). However, among women with a histologically verified diagnosis of endometriosis, the associations were even stronger, especially for very preterm birth before 32 gestational weeks. Here we found that women with histologically verified endometriosis had a higher risk of both PPROM and preterm spontaneous labor contractions before 32 weeks of gestation (Table 2).

The results were similar when the analysis was based on complete cases (Table S1 and Appendix S1) and when restricted to nulliparous women (Table S2); however, for the association between endometriosis and very preterm birth before 32 weeks of gestation, the results were slightly attenuated with wide confidence intervals overlapping 1 (Tables S1 and S2). When repeating the analyses restricted to women with a diagnosis of endometriosis prior to pregnancy (Table S3) we found similar results.

Finally, we stratified the results by medically assisted reproduction (Table S4). Irrespective of medically assisted reproduction, endometriosis increased the risk of preterm birth before 37 weeks of gestation with medically indicated preterm birth being most prominent. However, the strata were too small to investigate very preterm birth before 32 weeks of gestation and the results are not described further. We tested for interaction between endometriosis and medically assisted reproduction and did not find a significant interaction.

4 | DISCUSSION

We found that women with endometriosis face a 55% increased risk of preterm birth before 37 weeks of gestation and an 81% increased risk of very preterm birth before 32 weeks of gestation. Medically indicated preterm birth dominated before 37 weeks of gestation (142%), whereas spontaneous labor contractions dominated before 32 weeks of gestation (118%). Overall, all risks were even higher if endometriosis was verified by histology, and these women had more than twice the risk of PPROM before 32 weeks of gestation.
TABLE 2 Crude hazard ratios and adjusted hazard ratios with 95% confidence intervals for spontaneous and medically indicated preterm birth among 81842 pregnancies overall and 80716 pregnancies when restricted to women with a biopsy-verified diagnosis of endometriosis, Aarhus Birth Cohort, 1989–2013, Denmark

|                          | No endometriosis | Endometriosis | aHR (95% CI) |
|--------------------------|------------------|---------------|--------------|
| GA <37 weeks             | 3440 (4.3)       | 136 (6.9)     | 1.61         |
| Medically indicated      | 957 (1.2)        | 60 (3.0)      | 2.55         |
| PPROM                    | 1510 (1.9)       | 45 (2.3)      | 1.30         |
| Labor contractions       | 973 (1.2)        | 31 (1.6)      | 1.80         |
| GA <32 weeks             | 423 (0.5)        | 20 (1.0)      | 1.91         |
| Medically indicated      | 123 (0.2)        | <7            | <7           |
| PPROM                    | 155 (0.2)        | 7 (0.4)       | 1.82         |
| Labor contractions       | 145 (0.2)        | 8 (0.4)       | 2.23         |

|                          | Biopsy verified  | cHR | aHR (95% CI) |
|--------------------------|------------------|-----|--------------|
| GA <37 weeks             | 68 (7.9)         | 1.89| 1.83 (1.40–2.39) |
| Medically indicated      | 26 (3.0)         | 2.60| 2.47 (1.65–3.69) |
| PPROM                    | 25 (2.9)         | 1.59| 1.50 (0.95–2.36) |
| Labor contractions       | 17 (2.0)         | 1.67| 1.70 (0.97–2.96) |

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; GA, gestational age; PPROM, preterm pre-labor rupture of membranes.

aAdjusted for maternal age (≤24, 25–34 and ≥35 years), BMI (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m²), parity (0 or ≥1 children), years of schooling (≤9, 10–11 and ≥11 years) country of birth (Denmark or other), smoking during pregnancy (none, 1–9 and ≥10 cigarettes/day), alcohol consumption during pregnancy (<1, 1–2, and ≥3 drinks/day) and year of birth (1989–1995, 1996–2001, 2002–2007 and 2008–2013).

Previous studies rather consistently found an association between endometriosis and preterm birth overall.2–4 Only a few studies investigated the association between endometriosis and very preterm birth, and the definition of very preterm birth varied throughout the studies. A large Danish study by Berlac et al. found an increased risk of preterm birth before 28 weeks of gestation.13 Two Japanese studies by Harada et al. found similar results when investigating preterm birth before 22 weeks of gestation7 and birth between 22 and 27 weeks of gestation.6 An Italian study by Exacoustos et al. found no association between endometriosis and very preterm birth before 32 weeks of gestation.16

To our knowledge, only two previous studies have investigated the association between endometriosis and spontaneous or medically indicated preterm birth.17,17 A large Swedish register-based study by Stephansson et al.17 found an association between endometriosis and both spontaneous (OR 1.22, 95% CI 1.11–1.34) and medically indicated (OR 1.61, 95% CI 1.41–1.83) birth before 37 weeks of gestation. No results on very preterm birth were presented. On a subset of the cohort used in the present study, Glavind et al. conducted a sub-analysis excluding all medically indicated preterm births and still found endometriosis to be associated with preterm birth before 37 gestational weeks in the remaining spontaneous births.9

A major strength of the study is the large cohort with a high participation rate, limiting the risk of selection bias. Additionally, selection bias was limited by the small exclusion rate (1.5%) and the conduction of multiple imputation to account for missing values, increasing the precision of the results.18

A further strength of the study is the high validity of the investigated outcomes, since information on gestational age and type of preterm birth was reported by a research assistant midwife. When compared with medical records, the reported information showed high validity. Information on gestational age was 2–3 days shorter in the Danish National Patient Register has not previously been assessed. Ovarian20 and bowel endometriosis21 can be diagnosed by ultrasound and/or MRI, whereas for diagnosis of peritoneal disease, laparoscopy, preferable with biopsy, is needed.22 In the main analysis, we included all women regardless of how endometriosis was diagnosed, using the register-based information on the diagnosis codes. Some misclassification is most likely present; however, the misclassification will be independent of the outcome, eg non-differential, and therefore will potentially only bias the results towards the null. In this study we had the ability to restrict the analysis to women with a
histologically verified endometriosis diagnosis, thus limiting the possible misclassification and strengthening the internal validity of the study. This analysis showed even higher risks than the main analysis, strengthening the hypothesis of an association between endometriosis and the investigated outcomes.

We had detailed information from the questionnaire data on maternal characteristics before and during pregnancy, allowing for adjustment for various potential confounders identified a priori using directed acyclic graphs (Figure S1). Because the uniformity of the diagnosis of endometriosis has changed over time, we adjusted for year of birth in the multivariate analyses. We conducted a sub-analysis including only the complete cases. This showed similar results as the main analysis when looking at preterm birth before 37 weeks of gestation. However, the results for very preterm birth before 32 weeks of gestation decreased and became nonsignificant, which may be due to the small number of women included in the endometriosis group. We further investigated parity as an intermediate factor by including only nulliparous women. That analysis showed similar results to the main analysis for preterm birth; however, the association decreased for very preterm birth. As the diagnosis of endometriosis on average is shown to be delayed for up to 8 years, we conducted an analysis restricted to women with a diagnosis of endometriosis prior to pregnancy to ensure endometriosis was present during pregnancy. This showed similar results to the main analysis, supporting the hypothesis that endometriosis may be present long before diagnosis.

We also explored the possible impact of medically assisted reproduction, which has been shown to possibly increase the risk of preterm birth. It is well established that endometriosis is associated with subfertility and with the use of medically assisted reproduction to conceive. Thus, medically assisted reproduction may act as an important intermediate factor in the association between endometriosis and preterm birth. A strength of the study was the ability to stratify by medically assisted reproduction status. This stratification supported the results of the main analysis, showing an increased risk for medically indicated preterm birth before 37 weeks of gestation, irrespective of medically assisted reproduction. However, for women conceiving by medically assisted reproduction, the association between endometriosis and very preterm birth decreased and became nonsignificant; this, again, may be due to the small number of women included in the endometriosis group.

A limitation of the study was that we only had information on endometriosis diagnosed in hospitals. Women with milder forms of endometriosis may not have been referred by their general practitioner and may have been included in the reference group, leading to potential bias towards the null. Further, we did not have information on severity or subtype of endometriosis and were unable to stratify by this. Thus, the results of this study can be generalized to Danish women with more severe endometriosis. Women who did not speak or understand Danish were not included in the Aarhus Birth Cohort and the current study does not apply to this population. Further, we only included singleton pregnancies, which increased the generalizability of the study with other cohorts that only included singleton pregnancies.

Various potential mechanisms may play a role if women with endometriosis have higher risk of medically indicated and spontaneous preterm birth. First, studies have shown that women with endometriosis have a thickened junctional zone compared with women without endometriosis. Abnormal remodeling of the spiral arteries during pregnancy will reduce blood flow to the intervillous space due to the lack of physiological changes in the spiral arteries, with replacement of the elastic and muscular structures with fibrinoid material in the placental bed. Kim et al. found that deficient remodeling of the spiral arteries was associated with preterm birth with intact membranes and PPROM. This phenomenon has also been shown in obstetrical syndromes such as preeclampsia and intrauterine growth restrictions (IUGR). Thus, the thickening of the junctional zone seen in women with endometriosis may lead to maternal and fetal complications, with medically indicated preterm birth, as well as directly causing spontaneous preterm birth.

Another potential mechanism for spontaneous preterm birth is the increased inflammation due to the extravillous endometrial cells seen in women with endometriosis. These lesions increase the peritoneal levels of prostaglandins, cytokines and macrophages, leading to parturition. Further, the increased activity of proteases breaks down the extracellular matrix, which may lead to PPROM. Additionally, this chronic, systemic inflammation as well as the increased levels of low-density lipoproteins seen in women with endometriosis may increase the risk of atherosclerosis, resulting in an increased risk of cardiovascular disease such as hypercholesteremia and hypertensive disorders. This may increase the risk of cardiovascular complications during pregnancy, such as preeclampsia and IUGR.

Previous studies have investigated the association between endometriosis and preeclampsia or IUGR with conflicting results. None investigated these complications as the cause of medically indicated preterm birth, and future studies on this aspect are encouraged to identify these complications and better prevent and treat them in the future.

### 5 | Conclusion

We found women with endometriosis face a higher risk of preterm birth before 37 weeks of gestation and very preterm birth before 32 weeks. However, the pathways to preterm birth differed depending on gestational age. These results provide novel insights into the reason for preterm birth in women with endometriosis and may improve the future obstetrical care of these women. Future research should include the role of vascular dysfunction in young women with endometriosis, which may lead to medically indicated preterm birth, and the inflammation processes, which may play lead to both preterm contractions and PPROM.
CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTION
All authors were involved in the conceptualization of the study. KB wrote the original draft. All authors reviewed and edited the final draft. All authors have read and agreed to the published version of the manuscript.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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