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Endometriosis increases the risk of obstetrical and neonatal complications

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Conflict of interests

Øjvind Lidegaard has within the last three years received honoraria for talks on pharmaco-epidemiological issues. Janne Foss Berlac, Charlotte Wessel Skovlund, Dorthe Hartwell, and Jens Langhoff-Roos have no conflicts of interests to declare.

Abstract

Introduction: The objective was to assess obstetrical complications and neonatal outcomes in women with endometriosis as compared to women without endometriosis. *Material and methods:* National cohort including all delivering women and their newborns in Denmark 1997-2014. Data were extracted from the Danish Health Register and the Medical Birth Register. Logistic regression analysis provided odds ratios (OR) with 95% confidence intervals (CI). Sub-analyses were made for primiparous women with a singleton pregnancy and for women with endometriosis who underwent gynecological surgery before pregnancy. *Results:* The 19 331 women with endometriosis had a higher risk of severe preeclampsia (OR 1.7 95% CI, 1.5-2.0), hemorrhage in pregnancy (OR 2.3, 2.0-2.5), placental abruption (OR 2.0, 1.7-2.3), placenta previa (OR 3.9, 3.5-4.3), premature rupture of membranes (OR 1.7, 1.5-1.8), and retained placenta (OR 3.1, 1.4-6.6). The neonates had increased risks of preterm birth before 28 weeks (OR 3.1, 2.7-3.6), being small for gestational age (OR 1.5, 1.4-1.6), diagnosed with congenital malformations (OR 1.3, 1.3-1.4), and neonatal death (OR 1.8, 1.4-2.1). Results were similar in primiparous women with a singleton pregnancy. Gynecological surgery for endometriosis before pregnancy implied a further increased risk. *Conclusion:* Women with endometriosis had a significantly higher risk of several complications, such as preeclampsia and placental complications in pregnancy and at delivery. The newborns had increased risk of being delivered preterm, having congenital malformations, and higher neonatal death rate. Pregnant women with endometriosis need increased antenatal surveillance.

Keywords

Endometriosis, delivery, neonatal complications, pregnancy complications, obstetrical complications

Abbreviations

CI	confidence interval
OR	odds ratios
IVF	in vitro fertilization

Key message

Endometriosis increases the risk of obstetrical complications and neonatal morbidity and mortality. Preceding surgery indicating severe endometriosis further increases the risk. The magnitude of these complications calls for more intensive antenatal care of pregnant women with endometriosis.

Introduction

Endometriosis is a difficult chronic disease, which often affects quality of life with severe pain and reduced fertility. An aspect of this, which has received less attention, is the potential for a worse reproductive outcome.

The prevalence of endometriosis has been investigated in various ways and studies have provided different estimates, which reflect the differences in diagnostic criteria and the population. Articles published in 1980 and 1997 cite prevalence estimates of 5-10% in women of reproductive age and of 30-50% among women with pelvic pain and/or infertility (1). Population studies from Iceland and Norway have found annual incidence rates of endometriosis of 0.1-0.3% (2,3).

Increasingly, women with endometriosis have been able to counter their reduced fertility with assisted reproductive technologies, which have steadily improved. This includes the use of fertility preserving surgery (4).

Previous studies on obstetrical complications among women with endometriosis have demonstrated an increased risk of placental complications leading to a higher risk of obstetrical hemorrhage in pregnancy and during labor. They also indicate a possible increased risk of pre-eclampsia, preterm birth, and low birthweight (5-8). Artificial reproductive techniques as such may on the other hand also increase the risk of some of these obstetrical complications (9,10).

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These results have, however, been inconsistent and often based on small study populations. Also, the increased use of artificial reproductive techniques means that the women with endometriosis who become pregnant are different from populations studied earlier. Current consequences of endometriosis on pregnancy, birth and neonatal outcome need therefore to be clarified in a large contemporary cohort of women with endometriosis.

The aim of this study was to assess the risk of obstetrical complications and neonatal outcomes in a large cohort of women with endometriosis as compared to women without endometriosis.

Material and methods

We identified all women 15-49 years old who had a diagnosis of endometriosis (Supporting Information Table 1S) in the Danish Health Register – a comprehensive register with information on diagnoses and interventions in all Danish hospitals - between 1st of January 1977 and 31st of December 2014.

Women with endometriosis constituted the “exposed cohort”, and all women who were 15-49 years old at any time during the study period and did not have a diagnosis of endometriosis were regarded as the “unexposed cohort”. Women with severe endometriosis were defined as women who underwent surgical interventions for their disease before pregnancy. Surgical procedures were identified by using the surgical codes from the Nordic NOMESCO classification (Supporting Information Table 1S) (11).

The Danish Medical Birth Register provided information on infants born by these women. The data included information on body mass index (from 2004) and smoking habits (from 1997).

The National Health Register provided information on complications and interventions in pregnancy and at delivery.

The obstetrical complications were selected based on the criteria of being clinically relevant and having an acceptable code validity (12,13). International Classification of Diseases (ICD)-10 codes of these diagnoses and NOMESCO codes of surgery are specified and appended in Supporting Information Table 2S.

Gestational age was generally based on ultrasound and where this information was unavailable, on last menstrual period. Small-for-gestational age was defined as a birthweight less than two standard deviations below the gender and gestational age specific average as defined by Marsal et al. (14). Low Apgar score was considered <7 after 5 min.

Data on artificial reproductive technology were obtained through the Danish in vitro fertilisation (IVF)-register where all such pregnancies are recorded. Conception was presumed spontaneous for other women. Conception by assisted reproductive technologies among women with endometriosis was considered a consequence of the disease, and regarded as a mediator rather than a confounder that by definition must not be causally linked to the exposure (endometriosis). Women undergoing artificial reproductive techniques were generally expected to have more severe endometriosis than those with a natural conception. Therefore, we did not adjust for these reproductive variables.

Statistical analyses

All outcomes were analyzed by multivariate logistic regression to calculate odds ratios (OR) with 95% confidence interval (CI) all adjusted for year of delivery and maternal age. All data were analyzed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA)

Main analyses were made on all women with endometriosis regardless of parity and plurality. Additional analyses were made with adjustment for body mass index and smoking, and for first-born singleton maternities only. Further analyses were conducted on neonatal outcomes restricted to neonates born at term defined as 259 – 294 days of gestation, and on women with gynecological surgery before first pregnancy.

Ethical approval was not required according to Danish Research Ethics Committee Law (§ 8, section 3) as the study only involved register data. The Danish Data Protection Agency approved the study (J.no 2013-41-2229).

Results

Between 1977 and 2013, 11 739 women with a diagnosis of endometriosis gave birth to 19 331 infants during the period 1997-2013 equivalent to a birth rate of 1.65/woman. Of these women 4465 had had a gynecological surgical procedure before pregnancy and they gave birth to 3926 infants, a birth rate of 0.88/woman. The unexposed cohort of 615 533 women gave birth to 1 071 920 infants during the same period, a birth rate of 1.74/woman.

Women with endometriosis were slightly older, had similar body mass index, gave birth five days earlier, had more than twice as many twin deliveries, and the birthweight of their newborns was 166g lower than that of neonates to women without endometriosis (Table 1).

Almost all pregnancy complications occurred more frequently in women with endometriosis than in women without endometriosis (Table 2). The OR of pre-eclampsia was 1.4 (95% CI 1.3-1.5) and for severe pre-eclampsia, eclampsia or HELLP 1.7 (95% CI 1.5-2.0).

The OR of placenta previa was 3.9 (95% CI 3.5-4.3) and of placental abruption 2.0 (95% CI 1.7-2.3). Premature rupture of membranes and hemorrhage after 22 gestational weeks were both significantly increased in women with endometriosis.

Women with endometriosis had an OR of uterine rupture of 2.7 (95% CI 2.0-3.6), and of placenta accreta/percreta of 3.1 (95% CI 1.4-6.6). For retained placenta with manual removal the OR was 1.3 (95% CI 1.2-1.5) and for evacuation of the uterus after delivery 1.5 (95% CI 1.1-2.2) (Table 3).

The OR for postpartum hemorrhage was slightly lower in women with endometriosis as compared to the unexposed women. When stratified by mode of delivery, women with endometriosis who delivered by cesarean section had an OR of bleeding of 1.1 (95% CI 1.0-1.2). All types of cesarean section were more frequent in women with endometriosis and more than doubled for emergency cesarean before labor; (OR 2.1, 95% CI 2.0-2.3).

Women with endometriosis had more neonatal complications: stillbirth; (OR 1.2, 95% CI 1.0-1.5), neonatal death; (OR 1.8, 95% CI 1.3-2.3), preterm birth before 28 weeks; (OR 3.1, 95% CI 2.7-3.6), and preterm birth before 34 weeks; (OR 2.7, 95% CI 2.5-2.9) (Table 2).

Among neonates born by women with endometriosis the OR of small-for-gestational age was 1.5 (95% CI 1.4-1.6), of low Apgar score 1.4 (95% CI 1.2-1.6) and of malformations diagnosed within the first year 1.3 (95% CI 1.3-1.4) (Table 2).

In the sub-population of primiparous women with a singleton pregnancy (Tables 4 and 5) we found a reduction in the risk estimates of hypertension in pregnancy (not of pre-eclampsia) and of manual exploration of the uterine cavity because of a suspicion of retained placenta, but left all other risk estimates unchanged.

Sub-analyses of women with endometriosis who had had gynecological surgery showed a further increased risk of complications (Tables 2-5).

When the risk of neonatal death was restricted to term deliveries, the risk was no longer increased (Supporting Information Table 3S)

We also adjusted for body mass index, smoking, and assisted reproductive techniques (Table 6). Adjustment for body mass index and smoking did not significantly affect the increased risk of adverse maternal or infant outcomes, whereas adjustment for assisted reproductive techniques did. As women with severe endometriosis are more likely to conceive by in vitro fertilization or insemination, this last adjustment inevitably also adjusted for severe endometriosis. The reductions demonstrated were thus due to a combination of adjustment for assisted reproductive techniques in itself, twin pregnancies as a consequence of these techniques, and the severity of endometriosis. The risk estimates of some procedures and outcomes such as vacuum extraction, manual exploration of the uterine cavity and stillbirth were no longer significant, while the remaining outcomes were still increased although with slightly lower ORs.

Discussion

Women with endometriosis had a higher risk of several adverse outcomes in pregnancy and at delivery. Also, the neonates had increased risk of being delivered preterm, having congenital malformations, and suffering neonatal death. Stratification for parity and singleton pregnancy did not alter the results significantly, but severe endometriosis further increased the risk estimates. We adjusted for maternal age to counter the known increased risk of obstetrical complications seen with increasing maternal age. In general, these findings confirm the results of other sizable studies, whereas smaller studies have shown varying results likely due to small sample size.

In women with endometriosis functional and structural abnormalities in the inner myometrium called the junctional zone have been found in MRI-scans and biopsies (15), which means that endometriosis is related to adenomyosis, a junctional zone disease. This may result in defective transformation of the spiral arteries and thereby affect placentation (14). It has been theorized that this could contribute to the higher risk of preeclampsia, intrauterine growth restriction, preterm labor, and placental abruption (16, 17).

Our findings of increased risk of placental complications in conjunction with endometriosis are supported by studies on placenta previa. In an Australian study of 6730 singleton births of women, endometriosis was found to be a risk factor of placenta previa (6), a finding supported in a recent study of late pregnancy complications in 4232 women with endometriosis (18). A large Swedish register-based study showed an increased risk of antepartum hemorrhage/placental complications in women with endometriosis, but it was not possible to distinguish between the clinically different entities of antepartum bleeding, placental abruption and placenta previa (7). The higher risk of infertility in women with endometriosis implies more assisted conceptions, known to increase the risk of placenta previa (19). This is in accordance with the results of three other studies demonstrating endometriosis to be a risk factor for placenta previa even after adjustment for fertility treatment (8, 20, 21), suggesting artificial reproductive techniques to play a minor role for the increased risk of this complication in women with endometriosis.

A theory behind this increased risk of placenta previa has been suggested by Vercillini et al. (22): Throughout the menstrual cycle the uterus contracts regularly (“endometrial waves”) and women with endometriosis have been suggested to have altered uterine contractions, which may affect the location of blastocyst implantation, and thereby increase the risk of placenta previa (23).

A possible consequence of the increased risk of placenta previa is antepartum hemorrhage and subsequently ruptured membranes. In a small Italian study a high risk of preterm premature rupture of membranes in women with endometriosis was noted (24).

An aspect of placental complications is the controversy regarding the risk of preeclampsia in women with endometriosis: Smaller studies, and the Australian study of 3239 primiparous women with endometriosis did not show any difference in the risk of preeclampsia (8,18,23,25,26). In one small study it was even found that women with endometriosis had a lower risk of preeclampsia than controls (5). The Swedish study of 13 000 women with endometriosis (7) showed a 13% increased risk of preeclampsia in singleton pregnancies in agreement with 20% increased risk in this study. The 40-50 % higher risk of preeclampsia in all women with endometriosis in our study was partly explained by the higher frequency of twin pregnancies in this group due to the higher rate of assisted conceptions.

The increased risk of uterine rupture in pregnancy and during labor in women without previous cesarean section was only based on few cases. In other publications were also case

reports on spontaneous uterine rupture in women with endometriosis without previous cesarean section, but with adenomyosis (27) and defects in the myometrium after previous surgery for endometriosis (28).

Considering theories on defective placental implantation (15) and the higher risk of placenta accreta/percreta and retained placenta found in our study, we anticipated a higher risk of postpartum hemorrhage as previously reported (6, 18). We have no good explanation for this finding..

An increased rate of prelabor cesarean section has also been found in other studies (7,18,23). This was slightly reduced in singleton pregnancies, presumably explained by the known higher risk of pregnancy complications in twin pregnancies such as preeclampsia, preterm labor and premature rupture of membranes.

Women with endometriosis had a higher risk of extremely preterm birth regardless of parity and plurality, which is in accordance with most other studies (7-9,16,18,23). Petraglia et al. suggested that the inflammatory nature of endometriosis could be a possible explanation (29). Another factor is the higher rate of iatrogenic preterm delivery because of the higher incidence of placenta previa, premature rupture of membranes and preeclampsia. Preterm delivery likely explains the higher risk of neonatal death, as sub-analysis on neonates born at term removed this increased risk (Table 3S).

Surprisingly, we found a significantly higher risk of stillbirth in our large cohort, also in the sub-analysis with adjustment for smoking. Another study confirmed this finding (30), whereas Stephansson et al. could not find any difference (7).

Our study is so far the largest and most detailed study of obstetrical and neonatal complications in women with endometriosis. The health registers in Denmark enabled us link all women with a diagnosis of endometriosis to their respective deliveries and offspring and to compare obstetrical complications and neonatal outcome with those of the whole birth cohort of one million deliveries. We made sub-analyses including an analysis of singleton pregnancies in primiparous women. Also women with endometriosis undergoing gynecological surgery were analyzed separately, as the surgery may be considered a surrogate marker of severe endometriosis. Additionally, we adjusted for body mass index and smoking.

Sub-analysis on primiparous singletons did not alter the majority of the risks in women with endometriosis, whereas previous surgery for endometriosis increased the risks.

A limitation to our study was that not all women with endometriosis were admitted to hospital and therefore not recorded in our national registers. Thus, our “unexposed” cohort included some women with undiagnosed endometriosis. However, this misclassification would tend to underestimate the risk of complications in women with endometriosis.

The incidence rate and prevalence of endometriosis has been debated. Previous estimates of prevalence have been as high as 5-10% (1). However, population studies have – as mentioned in the introduction – found annual incidence rates of 0.1-0.3 (2,3) suggesting a lower prevalence. This probably reflects the challenges in diagnosing endometriosis. In our study we had an overall prevalence of 1.9%, but this was found among women who were able to conceive and give birth. One could speculate that the general prevalence would be higher due to increased infertility among women with endometriosis. The birth rate of 0.88 in our sub-group of women with a diagnosis of endometriosis and gynecological surgery supports this.

Our estimated prevalence of about 2 % also represents women referred to hospital for their disease. That figure is therefore a minimum of the real occurrence of the disease in our population. Some women with minimal endometriosis might have conceived spontaneously and therefore did not have a diagnosis in the patient diagnostic register.

Another limitation was that we did not have information on histologically confirmation of the diagnosis of endometriosis. Saraswat et al. only included women with surgically verified endometriosis (18). They studied a sample of 4232 women over their whole follow-up period, 1443 women in the period applicable to enhanced surgical techniques and improved obstetric care (2000-2009). They did not find an increased risk of stillbirth nor of neonatal deaths probably due to a small study sample looking at rare events.

In our study the women with a diagnosis of endometriosis and gynecological surgery before pregnancy had higher rates of complications than all women with endometriosis. The surgery could be a marker of more advanced/severe disease and therefore possibly affecting the intrauterine environment more seriously, leading to more complications. However, surgery as such may cause adhesions and influence the intrauterine environment. We need studies on a possible effect of abdominal surgery.

In conclusion, endometriosis increases the risk of obstetrical complications and adverse neonatal outcomes. The magnitude of these complications calls for increased attention and surveillance of women with endometriosis during pregnancy and childbirth .

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Supporting Information legends

Table S1. Included diagnoses and surgeries and their codes.

Table S2. Included obstetrical and neonatal outcomes.

Table S3. Neonatal outcomes in women with and without endometriosis. Infants born at term.

Table legends

Table 1. Characteristics of women with and without endometriosis. Includes all women with endometriosis, all parities, all pluralities.

Table 2. Pregnancy and neonatal outcomes in women with and without endometriosis. All women.

HELLP, hemolysis, elevated liver enzymes, low platelets; GA, gestational age; SGA, small-for-gestational age; OR, odds ratio; CI, confidence interval.

Table 3 Birth complications in women with and without endometriosis. All women. OR, odds ratio; CI, confidence interval.

Table 4 Pregnancy and neonatal outcomes in women with and without endometriosis. Primiparous. Singletons.

HELLP, hemolysis, elevated liver enzymes, low platelets; GA, gestational age; SGA, small-for-gestational age; OR, odds ratio; CI, confidence interval.

Table 5 Birth complications in women with and without endometriosis. Primiparous. Singletons.

OR, odds ratio; CI, confidence interval.

Table 6 Outcomes in women with and without endometriosis adjusted for body mass index, smoking and assisted reproductive technologies.

EM, endometriosis; HELLP, hemolysis, elevated liver enzymes, low platelets; GA, gestational age; SGA, small-for-gestational age; OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of women with and without endometriosis*Includes all women with endometriosis, all parities, all pluralities*

	Endometriosis	Endometriosis and surgery	No endometriosis
No. of women	11 739	4 465	615 533
No. of births	19 331	3 926	1 071 920
Age (years)	31.4	32.6	30.4
BMI (kg/m ²)	24.0	23.6	24.3
Smoking (%)	18.8%	10.8%	18.0%
Gest. Age (days)	273	272	278
Birthweight (grams)	3 308	3 232	3 474
Primiparous n (%)	9 545 (49.4)	2 257 (57.5)	469 270 (43.8)
Twins n (%)	2 100 (10.9)	676 (17.2)	43 968 (4.1)
ART n (%)	3 619 (19)		35 116 (3.3)

ART: Artificial reproductive techniques

Table 2 Pregnancy and neonatal outcomes in women with and without endometriosis*All women*

Outcome	Endometriosis n (%)	Endometriosis and surgery n (%)	No endometriosis n (%)	Adjusted* OR (95% CI)
Number of births	19 331	3 926	1 071 920	
Complications in pregnancy				
Hypertension in pregnancy	404 (2.1)	116 (3.0)	18 984 (1.8)	1.2 (1.0-1.3) 1.3 (1.1-1.6)
Preeclampsia	588 (3.0)	130 (3.3)	23 625 (2.2)	1.4 (1.3-1.5) 1.5 (1.3-1.8)
Severe preeclampsia, eclampsia and HELLP	220 (1.1)	48 (1.2)	7 083 (0.7)	1.7 (1.5-2.0) 1.7 (1.3-2.3)
Placental abruption	219 (1.1)	35 (0.9)	6 023 (0.6)	2.0 (1.7-2.3) 1.7 (1.2-2.3)
Premature rupture of membranes	449 (2.3)	107 (2.7)	15 334 (1.4)	1.7 (1.5-1.8) 1.6 (1.3-1.9)
Placenta previa	402 (2.1)	136 (3.5)	5 454 (0.5)	3.9 (3.5-4.3) 5.5 (4.6-6.5)
Antepartum hemorrhage after GA 22	280 (1.4)	97 (2.5)	7 458 (0.7)	2.3 (2.0-2.5) 2.6 (2.1-3.1)

Neonatal complications				
Birth before 28 weeks**	181 (0.9)		3 243 (0.3)	3.1 (2.7-3.6)
		44 (1.1)		3.5 (2.6-4.8)
Birth before 34 weeks**	960 (5.0)		20 295 (1.9)	2.7 (2.5-2.9)
		231 (6.0)		3.2 (2.8-3.6)
SGA**	1 360 (7.1)		51 309 (4.8)	1.5 (1.4-1.6)
		337 (8.7)		2.0 (1.8-2.2)
Apgar score (<7 after 5 min)**	215 (1.1)		8517 (0.8)	1.4 (1.2-1.6)
		56 (1.5)		1.8 (1.4-2.3)
Early neonatal death (< 7 days)	91 (0.5)		2716 (0.3)	1.8 (1.5-2.3)
		20 (0.5)		2.1 (1.4-3.3)
Neonatal death (<28 days)	105 (0.5)		3315 (0.3)	1.8 (1.4-2.1)
		23 (0.6)		2.0 (1.3-3.0)
Congenital malformations	1 349 (7.0)		57 666 (5.4)	1.3 (1.3-1.4)
		296 (7.6)		1.3 (1.2-1.5)
Stillborn	110 (0.6)		4912 (0.5)	1.2 (1.0-1.5)
		23 (0.6)		1.3 (0.9-1.9)

* Adjusted for age and calendar year. Upper all endometriosis women, lower those with prior surgery

** Only liveborn

Table 3 *Birth complications in women with and without endometriosis*
All women.

Outcome	Endometriosis n (%)	Endometriosis and surgery n (%)	No endometriosis n (%)	Adjusted* OR (95% CI)
Number of births	19 331	3 926	1 071 920	
Complications in labor				
Perineal laceration grade 3 and 4**	532 (3.6)	314 (5.1)	29 951 (3.2)	1.0 (0.9-1.1) 1.6 (1.3-1.9)
Rupture of the uterus (before and during labor)	52 (0.3)	15 (0.4)	1041 (0.1)	2.7 (2.0-3.6) 2.7 (1.6-4.4)
Postpartum hemorrhage (All deliveries first week)	1 698 (8.8)	550 (14.0)	108 161 (10.1)	0.9 (0.9-1.0) 0.9 (0.8-0.9)
Postpartum hemorrhage after Cesarean	475 (10.3)	167 (13.2)	17 099 (10.9)	1.1 (1.0-1.2) 0.9 (0.8-1.1)
Postpartum hemorrhage after vaginal delivery	1 223 (8.3)	383 (14.4)	91 062 (9.9)	1.0 (0.9-1.0) 0.9 (0.8-1.0)
Retained placenta (placenta accreta/percreta)	7 (0.0)	4 (0.1)	120 (0.0)	3.1 (1.4-6.6) 4.2 (1.5-11.4)
Procedures in labor				
Vacuum extraction**	1 507 (10.2)		81 049 (8.8)	1.2 (1.1-1.3)

		355 (13.3)		1.6 (1.5-1.8)
Evacuation of the uterus**	33 (0.2)	9 (0.3)	1 401 (0.2)	1.5 (1.1-2.2)
				1.9 (1.0-3.6)
Intrauterine palpation**	173 (1.2)	46 (1.7)	9 461 (1.0)	1.2 (1.0-1.4)
				1.4 (1.0-1.8)
Manual removal of the placenta (<i>Vaginal delivery</i>)	319 (2.2)	71 (2.7)	15 089 (1.6)	1.3 (1.2-1.5)
				1.4 (1.1-1.8)
Cesarean section - emergency before labor	813 (4.2)	244 (6.2)	22 075 (2.1)	2.1 (2.0-2.3)
				2.3 (2.0-2.6)
Cesarean section - planned***	2 148 (11.6)	580 (15.8)	72 746 (6.9)	1.7 (1.7-1.8)
				1.7 (1.5-1.8)
Cesarean section - emergency in labor****	1 645 (10.0)	442 (14.2)	61 422 (6.2)	1.8 (1.7-1.9)
				1.8 (1.6-2.0)

* Adjusted for age and calendar year. Upper all endometriosis women, lower those with prior surgery

** Only vaginal delivery

*** Emergency cesarean before labor excluded

**** Emergency (before labor) and planned cesarean excluded

Table 4 *Pregnancy and neonatal outcomes in women with and without endometriosis*
Primiparous. Singletons.

Outcome	Endometriosis n (%)	Endometriosis and surgery n (%)	No endometriosis n (%)	Adjusted* OR (95% CI)
Number of births	8 190	1 773	447 574	
Complications in pregnancy				
Hypertension in pregnancy	210 (2.6)	57 (3.2)	9 960 (2.2)	1.1 (0.9-1.2)
				1.0 (0.8-1.4)
Preeclampsia	300 (3.7)	65 (3.6)	13 605 (3.0)	1.2 (1.1-1.3)
				1.2 (0.9-1.5)
Severe preeclampsia, eclampsia and HELLP	106 (1.3)	25 (1.4)	4 180 (0.9)	1.3 (1.1-1.6)
				1.3 (0.9-2.0)
Placental abruption	85 (1.0)	17 (1.0)	2 491 (0.6)	1.8 (1.5-2.2)
				1.7 (1.1-2.8)
Premature rupture of membranes	162 (2.0)	45 (2.5)	6 798 (1.5)	1.3 (1.1-1.5)
				1.3 (1.0-1.8)
Placenta previa	180 (2.2)	60 (3.4)	1 897 (0.4)	4.6 (4.0-5.4)
				5.7 (4.4-7.4)
Antepartum hemorrhage after GA 22	120 (1.5)	48 (2.7)	3 495 (0.8)	2.0 (1.7-2.4)
				2.6 (2.0-3.5)
Neonatal complications				
Birth before 28 weeks**	62 (0.8)		1 156 (0.3)	2.8 (2.8-3.6)

		17 (1.0)		3.4 (2.1-5.5)
Birth before 34 weeks**	265 (3.3)	60 (3.4)	7 280 (1.6)	2.0 (1.7-2.2)
SGA**	533 (6.6)	122 (7.0)	25 131 (5.7)	1.2 (1.1-1.3)
Apgar score (<7 after 5 min)**	87 (1.1)	17 (1.1)	4139 (0.9)	1.1 (1.0-1.4)
Early neonatal death (< 7 days)	33 (0.4)	5 (0.3)	947 (0.2)	1.8 (1.3-2.6)
Neonatal death (<28 days)	38 (0.5)	6 (0.3)	1176 (0.3)	1.7 (1.2-2.4)
Congenital malformations	560 (6.8)	136 (7.7)	26 338 (5.9)	1.2 (1.1-1.3)
Stillborn	42 (0.5)	10 (0.6)	1 829 (0.4)	1.2 (0.9-1.7)

* Adjusted for age and calendar year. Upper all endometriosis women, lower those with prior surgery

** Only liveborn

Table 5 *Birth complications in women with and without endometriosis Primiparous. Singletons*

Outcome	Endometriosis n (%)	Endometriosis and surgery n (%)	No endometriosis n (%)	Adjusted* OR (95% CI)
Number of births	8 190	1 773	447 574	
Complications in labor				
Perineal laceration grade 3 and 4**	399 (6.2)	109 (8.5)	21 258 (5.6)	1 (0.9-1.1) 1.4 (1.3-1.7)
Rupture of the uterus (before and during labor)	5 (0.1)	0	87 (0.02)	3.0 (1.2-7.4) 0
Postpartum hemorrhage (All deliveries first week)	741 (9.0)	243 (13.7)	44 340 (9.9)	1 (0.9-1.1) 0.9 (0.8-1.1)
Postpartum hemorrhage after Cesarean	191 (2.3)	77 (15.6)	6362 (1.4)	1.7 (1.5-2) 1.3 (1.0-1.8)
Postpartum hemorrhage after vaginal delivery	550 (6.7)	166 (13.0)	37 978 (8.5)	0.9 (0.8-0.9) 0.9 (0.7-1.0)
Retained placenta (placenta accreta/percreta)	4 (0)	2 (0.1)	47 (0)	4.2 (1.5-11.8) 5.0 (1.2-21.0)
Procedures in labor				
Vacuum extraction**	1 100 (17.1))	247 (19.3)	61 854 (16.2)	1.0 (1.0-1.1) 1.1 (0.9-1.2)
Evacuation of the	17 (0.3)		628 (0.2)	1.6 (1.0-2.7)

uterus**		6 (0.5)		2.3(1.0-5.1)
Intrauterine palpation**	85 (1.3)	24 (1.9)	4901 (1.3)	1.1 (0.9-1.3)
Manual removal of the placenta**	175 (2.7)	41 (3.2)	7783 (2.0)	1.3 (1.1-1.5)
Cesarean section - emergency before labor	313 (3.8)	95 (5.4)	9281 (2.1)	1.8 (1.6-2.0)
Cesarean section - planned***	563 (7.1)	171 (10.2)	18 774 (4.2)	1.6 (1.4-1.7)
Cesarean section - emergency in labor****	896 (12.3)	228 (15.1)	37 504 (8.9)	1.4 (1.3-1.5)

* Adjusted for age and calendar year. Upper all endometriosis women, lower those with prior surgery

** Only vaginal delivery

*** Emergency cesarean before labor excluded

**** Emergency (before labor) and planned cesarean excluded

Table 6 Outcomes in women with and without endometriosis adjusted for body mass index, smoking and assisted reproductive technologies

Outcome	Adjusted ¹	Adjusted ²	Adjusted ³	Adjusted ⁴
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Births with EM	19 331	10 162	18 627	19 331
Births without EM	1 071 920	579 787	1 040 711	1 171 920
<u>Complications in pregnancy</u>				
Hypertension in pregnancy	1.2 (1.0-1.3)	1.1 (1.0-1.3)	1.2 (1.0-1.3)	1.1 (1.0-1.2)
Preeclampsia	1.4 (1.3-1.5)	1.5 (1.4-1.7)	1.4 (1.3-1.5)	1.2 (1.1-1.3)
Severe preeclampsia, eclampsia and HELLP	1.7 (1.5-2.0)	2.0 (1.7-2.4)	1.8 (1.6-2.1)	1.4 (1.3-1.7)
Placental abruption	2.0 (1.7-2.3)	1.9 (1.6-2.4)	1.9 (1.7-2.2)	1.8 (1.5-2.3)
Premature rupture of membranes	1.7 (1.5-1.8)	1.6 (1.4-2.4)	1.7 (1.5-1.8)	1.3 (1.2-1.4)
Placenta previa	3.9 (3.5-4.3)	4.2 (3.7-4.8)	3.9 (3.5-4.3)	3.1 (2.8-3.4)
Antepartum hemorrhage after GA 22	2.3 (2.0-2.5)	2.2 (1.9-2.5)	2.2 (2.0-2.5)	1.8 (1.6-2.1)
<u>Complications in labor</u>				
Perineal laceration grade 3 and 4	1.0 (0.9-1.1)	1.3 (1.2-1.5)	1.2 (1.1-1.3)	1.0 (1.0-1.1)
Rupture of the uterus (before and during labor)	2.7 (2.0-3.6)	2.1 (1.5-3.0)	2.6 (1.9-3.4)	2.9 (2.0-4.1)*
Postpartum hemorrhage (first week)	0.9 (0.9-1.0)	0.9 (0.9-1.0)	0.9 (0.9-1.0)	0.9 (0.9-1.0)
Retained placenta (placenta accreta/percreta)	3.1 (1.4-6.6)	3.1 (1.4-6.7)	3.1 (1.4-6.7)	3.0 (1.4-6.5)

Procedures in labor				
Vacuum extraction	1.2 (1.1-1.3)	1.3 (1.2-1.4)	1.2 (1.1-1.3)	1.0 (1.0-1.1)
Evacuation of the uterus	1.5 (1.1-2.2)	1.5 (0.9-2.3)	1.5 (1.1-2.2)	1.4 (1.0-1.9)
Intrauterine palpation	1.2 (1.0-1.4)	1.2 (1.0-1.5)	1.2 (1.0-1.4)	1.1 (0.9-1.3)
Manual removal of the placenta	1.3 (1.2-1.5)	1.5 (1.3-1.8)	1.3 (1.2-1.5)	1.2 (1.1-1.3)
Cesarean section - emergency before labor	2.1 (2.0-2.3)	2.1 (2.0-2.3)	2.1 (2.0-2.3)	1.7 (1.6-1.9)
Cesarean section - planned	1.7 (1.7-1.8)	1.7 (1.6-1.8)	1.8 (1.7-1.8)	1.6 (1.6-1.7)
Cesarean section - emergency in labor	1.8 (1.7-1.9)	1.8 (1.7-1.9)	1.8 (1.7-1.9)	1.5 (1.4-1.6)
Neonatal complications				
Birth before 28 weeks	3.1 (2.7-3.6)	3.3 (2.7-4.0)	3.1 (2.7-3.7)	2.1 (1.8-2.5)
Birth before 34 weeks	2.7 (2.5-2.9)	2.8 (2.6-3.1)	2.7 (2.5-2.9)	1.9 (1.8-2.0)
SGA	1.5 (1.4-1.6)	1.7 (1.6-1.8)	1.5 (1.4-1.6)	1.2 (1.2-1.3)
Apgar score (<7 after 5 min)	1.4 (1.2-1.6)	1.6 (1.3-1.9)	1.4 (1.2-1.6)	1.2 (1.1-1.4)
Early neonatal death (< 7 days)	1.8 (1.5-2.3)	2.1 (1.5-2.8)	1.9 (1.5-2.4)	1.5 (1.2-1.9)
Neonatal death (<28 days)	1.8 (1.4-2.1)	2.0 (1.5-2.6)	1.8 (1.5-2.2)	1.4 (1.2-1.8)
Congenital malformations (diagnosed first year)	1.3 (1.3-1.4)	1.4 (1.3-1.5)	1.3 (1.3-1.4)	1.2 (1.2-1.3)
Stillborn	1.2(1.0-1.5)	1.1 (0.8-1.5)	1.2 (1.0-1.44)	1.1 (0.9-1.3)

1) Adjusted for age and calendar year

2) Additionally adjusted for BMI

3) Additionally adjusted for smoking

4) Adjusted for age, calendar year, parity and ART

*only rupture in labor