Endometriosis and risk of adverse pregnancy outcomes: a retrospective multicenter cohort study

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Objective: To investigate first, the association between endometriosis and preterm birth; second, the associations between endometriosis and preeclampsia, placenta previa, postpartum hemorrhage, stillbirth, and small-for-gestational-age infants (assessed by birthweight); and third, the risk of these adverse pregnancy outcomes with and without the use of medically assisted reproduction.
Design: Multicenter retrospective cohort study.
Patients: Deliveries by 368,935 women (377,338 infants) from 1999 through 2016.
Exposure: Endometriosis, defined as a single disease entity (endometriosis and/or ademyosis)
Main Outcomes Measures: The main outcome was the preterm birth rate (both <37 and <33 weeks). The secondary outcomes were rates of preeclampsia, placenta previa, postpartum hemorrhage, stillbirth, and small-for-gestational-age neonates.
Results: Women in the endometriosis group had more frequent histories of infertility before the included pregnancy (34.7 vs. 5.0%), more hospitalizations during the pregnancy (27.4 vs. 19.8%), and more planned cesarean sections (14.0 vs. 8.7); they more often were nulliparous (51.7 vs. 43.4%). The prevalence of preterm birth at <37 weeks was 11.1% in the endometriosis group and 7.7% in the unexposed group, and for <33 weeks, it was 3.1% and 2.2%, respectively. The adjusted relative risk for confounding factors was higher in the endometriosis than the unexposed group for preterm delivery <37 weeks (1.40, 95% confidence interval, 1.18–1.67) or <33 weeks (1.53, 95% confidence interval, 1.08–2.16). For the secondary outcomes, the adjusted risk ratios for preeclampsia, placenta previa, postpartum hemorrhage, and small-for-gestational-age status of <10th and <5th percentiles were higher in the endometriosis group. The adjusted risk ratios for stillbirth and small-for-gestational-age status of <3rd percentile did not differ between the two groups, and those after stratification by medically assisted reproduction for preterm birth at <37 and <33 weeks did not differ statistically significantly between them, for the secondary outcomes, only the risk of placenta previa was higher in the medically assisted reproduction and non–medically assisted reproduction subgroups.
Conclusion: Pregnant women with endometriosis had higher risks of preterm birth and other poor pregnancy outcomes than women without endometriosis. (Fertil Steril® 2025;123:137–47. ©2024 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Assisted reproductive technologies, endometriosis, placenta previa, preterm delivery, spontaneous preterm birth

Endometriosis is a hormone-dependent chronic disease, defined by ectopic occurrence of endometrium-like tissue abnormally implanted in various locations outside the uterine cavity and accompanied by subsequent peritoneal or uterine inflammation, adhesions, pain, or infertility (1). The best-supported hypothesis explaining ectopic endometrial implantation is retrograde bleeding through the fallopian tubes because of dysperistaltic uterine contractions. The formation of fibrosis and adhesion, impeding oocyte pickup and transport, and abnormal uterine

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Data sharing statement: The individual data underlying the findings cannot be made freely available because of French legal restrictions, as the present study includes variables that, together, could be used to re-identify the participants based on key characteristics and thus obtain access to other personal data. French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés) accordingly strictly forbids making these data freely available. Nonetheless, aggregated anonymous data of the cohort can be obtained upon request from the AUDIPOG scientific committee. Readers may contact the corresponding author to request the data.
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contractility at the endometrial-myometrial interface, interfering with favorable implantation, may explain the negative impact on fertility. Endometriosis also may induce oxidative stress, aberrant mitochondrial energy metabolism, and inappropriate steroid production in granulosa cells, thus impairing oocyte quality to variable degrees (2). Furthermore, abnormal remodeling of the spiral arteries in the junctional zone could cause defective deep placentation, increasing the risk of adverse pregnancy outcomes.

The true prevalence of endometriosis is unknown. Estimates range from 1%–11% for the general premenopausal female population and are higher among infertile or symptomatic women (30%–50%) (3–5).

With the association of endometriosis with adverse pregnancy outcomes controversial, no definitive conclusions can be drawn currently (6). Some studies have found no association between adverse maternal, perinatal, or neonatal outcomes and endometriosis (7–9). Others have reported that women with endometriosis have a higher risk of some (but not all) of the following complications: spontaneous abortion, ectopic pregnancy, gestational diabetes mellitus, preeclampsia, preterm birth, prepartum hemorrhage, cesarean delivery, postcesarean complications, small-for-gestational-age (SGA) infants, placenta previa, and stillbirth (6, 10–19). The conflicts in the literature are strong especially for preterm birth; some investigators report its risk is higher in woman with endometriosis (6, 11, 13–15, 17, 18, 20) and others no increased risk (7, 12, 16). Nonetheless, the exact mechanism inducing preterm birth in women with endometriosis remains unknown (21), and any medically assisted reproduction (MAR) method used to achieve pregnancy, a well-known risk factor for this outcome, must be considered (22). The differences between the studies may be due to differences in their study designs, lack of adjustment for confounding factors (15), lack of power (7, 18, 23), or inadequate diagnosis of exposure (i.e., endometriosis) and/or outcome data (i.e., preterm birth, placenta previa) (17). Exposure assessment differed between studies (endometriosis confirmed by laparoscopy, ultrasonography, or magnetic resonance imaging), as did the populations (infertile women who did or did not need MAR) (9, 10). Most of these studies used administrative or medical birth databases (6, 8, 11, 12, 14, 15, 17), self-administered questionnaires (13), or interviews (18). Only a few came from prospective observational studies (7). Two systematic reviews and meta-analyses noted high heterogeneity among the studies they included (20, 24).

Our main objective was to investigate the association between endometriosis and preterm birth (<37 and <33 weeks of gestation). Our secondary objectives were to investigate associations of endometriosis with other pregnancy complications: preeclampsia, placenta previa, immediate postpartum hemorrhage (PPH), stillbirth, and SGA. Finally, we aimed to investigate whether and how MAR affected these outcomes' risks.

MATERIALS AND METHODS

Study population

This retrospective cohort study analyzed deliveries included in the AUDIPOG (Association des utilisateurs de dossiers informatisés en pédiatrie, obstétrique et gynécologie) sentinel network database (25). This network, created in 1994, comprises public and private maternity units from every region in France; they voluntarily contribute individual data on mothers and infants for pooling and analysis. Each hospital participates for a given period each year, chosen by them, usually 1 month but sometimes the entire year. They forward all data (continuously collected) about women who give birth during this period at a gestational age of ≥22 weeks (or a birthweight of ≥500 g if the gestational age is unknown) and about the newborns. Midwives or obstetricians collect these data and send them to us as computer files, paper files (questionnaire furnished by AUDIPOG), or by direct entry on our website, in a file intended for assessment (25). A statistician-computer specialist employed by AUDIPOG, a nonprofit association, verifies the data quality. Its validity is demonstrated by the consistency of its national perinatal indicators with national surveys commissioned by the French Ministry of Health. A glossary is available to remind professionals how to code the variables defined at the national level (e.g., preclampsia). The data collection methods have been published elsewhere, in publications available at our website (25, 26). When this study was conducted, the database included 1,051,785 pregnancies from 1994 through 2016, from 256 maternity units.

We first selected the 887,495 deliveries in 1999–2016, then excluded cases with pertinent data missing: lacking a positive or negative response to the question about "the existence of other gynecologic disorders" (n = 470,572) or with gestational age at birth unknown (n = 240). Finally, this study included 368,935 pregnancies and 377,338 infants from 103 maternity units.

The study was approved by the institutional review board (IRB) #1 (IRB00013412) of the CHU (University Hospital Center) de Clermont-Ferrand 1 (IRB00013412, IRB number 2023-CF055).

Exposure assessment

An endometriosis diagnosis appeared in our database only after a question about "gynecologic diseases (yes/no)," was answered positively and endometriosis was chosen from 12 listed responses to "if yes, what?" ("other" and a free response also were available). Accordingly, we coded this variable as a structured variable (endometriosis yes/no). We had no information on how care providers diagnosed endometriosis or if adenomyosis potentially coexisted. Our study defined the term "endometriosis and/or adenomyosis" as a single disease entity.

Outcome assessment

The main outcome was the preterm birth rate, defined as birth at <37 and <33 weeks of gestation. Secondary outcomes were the preeclampsia rate during pregnancy, defined as a systolic blood pressure of ≥140 mmHg or a diastolic pressure of ≥90 mmHg, and proteinuria (>0.3 g/24 hours) after 20 weeks of gestation; placenta previa, defined as placental insertion wholly or partially into the uterine lower segment,

with a distance between the placental edge and the internal cervical os of <2 cm; PPH, defined as blood loss of ≥1,000 mL during the first 24 hours after childbirth; SGA, designating neonates with a birthweight of <10th, <5th, or <3rd percentile for gestational age and sex, on the basis of data derived from the reference population in the AUDIPOG database (25).

Covariates

Maternal age was defined as completed years at conception. Maternal prepregnancy body mass index (BMI) was calculated with self-reported prepregnancy weight and height values and used the World Health Organization's BMI categories. Parity was categorized as nulliparous (0 birth) and parous (≥1 birth). The medical files contained information on MAR, defined as any intervention including in vitro handling of both human oocytes and sperm or of embryos for the purpose of reproduction (e.g., in vitro fertilization-embryo transfer [IVF], intrauterine insemination from donor or spouse) and systematically recorded in the medical file at the first obstetric appointment. Other covariates were noted during pregnancy or at delivery and in the immediate postpartum period, during care consistent with French guidelines that describe the appropriate management of pregnant women (27, 28).

Statistical analyses

We first used descriptive statistics to compare the social, demographic, obstetric, and delivery characteristics of the exposed group with a diagnosis of endometriosis and unexposed group without a diagnostic of endometriosis. Categorical variables were compared by the χ^2 test (or Fisher's exact test, as appropriate) and continuous variables by Student's t test. Crude relative risks (RRs) of perinatal complications in patients with prenatally identified endometriosis were calculated with their 95% confidence intervals (CIs).

Next we compared the selected outcomes between the two groups. For each outcome studied, a log-binomial model was used to adjust for covariates known from the literature to be confounding factors (maternal age, smoking, BMI, and socioeconomic status) (20). Finally, the principal models also included the a priori–identified potential confounding variables selected with directed acyclic graphs (29): maternal age and prepregnancy BMI (both continuous variables), living alone (yes/no), geographic origin (other/metropolitan France, i.e., European France), mother smoked tobacco during pregnancy (yes/no; model 1). A second model included the confounding factors and clinically relevant prognostic factors: MAR (yes/no), parity (≥1/0), previous cesarean section (yes/no), delivery year (1999–2003/2004–2008/2009–2013/2014–2016), singleton fetus (yes/no), maternity unit level (3/2/1), and pathology during pregnancy (yes/no) (model 2). We used a Poisson regression with a sandwich error term for models that failed to converge.

To investigate MAR's influence on the association between endometriosis and our selected outcomes, we stratified the analysis by MAR use.

Adjusted RRs (aRR) were calculated with their 95% CIs. Interactions between endometriosis and other outcome variables were tested.

Missing data were not imputed. Statistical significance was set at $P<.05$. Statistical analysis was performed with SAS software (version 9; SAS Institute, Inc, Cary, NC).

RESULTS

The mean age in the overall cohort was 30.0 ± 5.4 years, and the mean BMI was 23.5 ± 4.8 (Table 1); 43.4% were nulliparous and 97.8% had singleton pregnancies (Table 1). A previous cesarean delivery was noted for 9.7% of these women and labor began by induction for 20.2% of deliveries (Table 1). Supplemental Table 1 (available online) describes diseases during pregnancy. The mean birthweight was 3229.7 ± 609.7 g (Table 2).

The women in the endometriosis group were older than those without a diagnosis (32.3 ± 4.7 vs. 30.0 ± 5.4, $P<.0001$), and their mean BMI was lower (respectively, 22.9 ± 4.1 vs. 23.5 ± 4.8, $P<.0001$) (Table 1). Patients in the endometriosis group also had more frequent histories of infertility before their pregnancy (34.7 vs. 5.0%, $P<.0001$), more frequently were nulliparous (51.7 vs. 43.4%, $P<.0001$), hospitalized during the pregnancy (27.4 vs. 19.8%, $P<.0001$), and scheduled for cesarean deliveries (14.0 vs. 8.7, $P<.0001$) (Table 1). In addition, more frequent among the women in the endometriosis group were preterm labor (9.2 vs. 6.5%, $P<.0001$) and preterm rupture of membranes (4.2 vs. 2.3%, $P<.0001$) (Supplemental Table 1). They also had fewer spontaneous vaginal deliveries (57.3 vs. 68.1%, $P<.0001$) and their infants a lower mean birthweight (3,110.6 ± 674.0 g vs. 3,230.5 ± 609.2 g, $P<.0001$) (Table 2).

The percentage of preterm births at <37 and <33 weeks was 11.1% and 3.1%, respectively, in the endometriosis group vs. 7.7% and 2.2%, respectively, in the unexposed group (Table 3), with a higher crude RR among the former: <37 weeks (1.46; 95% CI, 1.29–1.64) and <33 weeks (1.38; 95% CI, 1.08–1.75). After adjustment for the confounding factors (maternal age, BMI, living alone, geographic origin, and smoking during pregnancy), the aRRs for preterm births at <37 and <33 weeks were statistically significantly higher in the endometriosis-diagnosed than in the nonexposed group, with 1.40 (95% CI, 1.18–1.67) and 1.53 (95% CI, 1.08–2.16), respectively (Table 3). After adjustment for the confounding factors and the clinically relevant prognostic factors (MAR, parity, year of delivery, singleton fetus, previous cesarean delivery, maternity unit level, and pathology during pregnancy), the aRR for preterm births at <37 and <33 weeks were not statistically significantly different, with 0.91 (95% CI, 0.77–1.07) and 0.82 (95% CI, 0.58–1.15), respectively (Table 3).

For the secondary outcomes, after adjustment for confounding factors (model 1), the risks of preclampsia, placenta previa, PPH, SGA of <10th percentile and SGA of <5th percentile rose in the endometriosis group, respectively: 1.64 (95% CI, 1.09–2.47), 4.29 (95% CI, 2.79–6.60), 1.30 (95%

TABLE 1

Description of women's sociodemographic data, medical and obstetric history, and the pregnancy under study in the overall cohort and in the groups with and without known endometriosis

	Total N = 368,935 *n*% (m ± SD)[a]	Endometriosis n = 2,108 *n*% (m ± SD)[a]	No endometriosis n = 366,827 *n*% (m ± SD)[a]	*P*
Maternal age[b]	368,836 (30.0 ± 5.4)	2,108 (32.3 ± 4.7)	366,728 (30.0 ± 5.4)	<.0001
Mean				
BMI[c]	353,622 (23.5 ± 4.8)	2,012 (22.9 ± 4.1)	351,610 (23.5 ± 4.8)	<.0001
Mean				
<18.5	7.9	7.4	7.9	<.0001
≥18.5–<25.0	63.6	70.5	63.6	
≥25.0–<30.0	18.3	15.7	18.3	
≥30.0–<35	6.9	4.8	6.9	
≥35	3.3	1.7	3.3	
Smoker[d]	316,835	1,703	315,132	
Yes	13.1	11.2	13.1	.02
Family situation	299,425	1,557	297,868	
Lives alone	6.9	4.2	7.0	<.0001
With a partner	91.2	95.5	91.2	
Other	1.8	0.3	1.8	
Geographic origin	328,314	1,944	326,370	
France[e]	67.3	81.2	67.3	<.0001
Southern Europe	2.7	1.9	2.7	
North Africa	13.1	6.5	13.2	
Sub-Saharan Africa	6.7	2.3	6.8	
Other	10.1	8.2	10.1	
Infertile before pregnancy	345,544	2,012	343,532	
	5.2	34.7	5.0	<.0001
If yes,	41,409	877	40,532	
MAR	33.6	61.9	33.0	<.0001
Induction of ovulation	8.5	5.5	8.5	
IVF	13.4	38.7	12.8	
IUI D	0.2	0.3	0.2	
IUI S	0.4	1.0	0.4	
ICSI	3.5	6.3	3.4	
Other MAR	7.7	10.1	7.6	
Parity	352,964	2,077	350,887	
Mean	(0.9 ± 1.1)	(0.7 ± 0.9)	(0.9 ± 1.1)	<.0001
Nulliparous[f]	43.4	51.7	43.4	<.0001
Previous cesarean	351,016	2,066	348,950	
	9.7	10.2	9.6	.43
Singleton pregnancy	368,935	2,108	366,827	
	97.8	93.6	97.8	<.0001
Pregnancy-related disease	347,740	1,997	345,743	<.0001
	37.7	44.9	37.7	
Hospitalization during pregnancy	319,220	1,801	317,419	<.0001
	19.8	27.4	19.8	
Onset of labor	366,778	2,098	364,680	
Spontaneous	71.1	65.7	71.1	<.0001
Induced	20.2	20.3	20.2	
Cesarean	8.8	14.0	8.7	

Note: Gestational carriers are forbidden in France. MAR = medically assisted reproduction; IVF = in vitro fertilization-embryo transfer; IUI D = intrauterine insemination from donor; IUI S = intrauterine insemination from spouse; ICSI = intracytoplasmic sperm injection; Other MAR = oocyte donation, fertility preservation, frozen embryo transfer.

[a] Mean ± SD.
[b] Maternal age is defined as age in completed years at conception.
[c] BMI was calculated by using self-reported prepregnancy weight and height values (weight/height^2,kg/m^2).
[d] Smoked tobacco during pregnancy.
[e] Metropolitan (European) France only.
[f] Nulliparous defined as 0 history of birth.

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CI, 1.04–1.62), 1.21 (95% CI, 1.05–1.40), and 1.23 (95% CI, 1.01–1.49) (Table 3). The groups did not differ for risk of stillbirth or SGA of <3rd percentile did not differ between the two groups (Table 3). In model 2, the only risk statistically significantly higher in the endometriosis group was that for placenta previa: 3.14 (95% CI, 2.00–4.93).

The RRs of the associations between endometriosis and the nine adverse pregnancy or neonatal outcomes were essentially the same in women who did and did not receive MAR (Table 4). The aRR for preterm birth at <37 and <33 weeks (model 1), after stratification by MAR (yes/no), did not differ statistically significantly between the groups. The only aRR differing significantly between the exposed and unexposed groups was that for placenta previa and was higher in the MAR and non-MAR subgroups (4.04; 95% CI, 2.15–7.59 and 3.13; 95% CI, 1.68–5.81, respectively) (Table 4). The

TABLE 2

Descriptive neonatal data for the global cohort and for the infants born to mothers with and without known endometriosis.

	Total N = 377,338 *n*% (m ± SD)[a]	Endometriosis n = 2244 *n*% (m ± SD)[a]	No endometriosis n = 375,094 *n*% (m ± SD)[a]	*P*
Type of birth	376,978	2,241	374,737	
Spontaneous delivery	68.0	57.3	68.1	<.0001
Operative VD[b]	12.6	15.1	12.6	
Cesarean	19.3	27.7	19.3	
Before labor	9.2	15.2	9.2	<.0001
During labor	10.1	12.4	10.1	.0002
Transfer of newborn[c]	315,469	1,958	313,511	
Yes	10.9	16.4	10.9	<.0001
5-min Apgar	372,385	2,206	370,179	
Mean	(9.7 ± 1.1)	(9.6 ± 1.2)	(9.7 ± 1.1)	<.0001
<7	2.1	3.1	2.1	.002
Birthweight (g)	375,258	2,229	373,029	
Mean	(3,229.7 ± 609.7)	(3,110.6 ± 674.0)	(3,230.5 ± 609.2)	<.0001
<2,500	9.0	15.2	8.9	<.0001
≥2,500–<4,000	83.8	78.7	83.9	
≥4,000	7.2	6.1	7.2	

[a] Mean ± SD.
[b] Operative VD, operative vaginal delivery.
[c] Transfer from the delivery room or maternity ward to a neonatology department or a neonatal intensive care unit.

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aRRs for Models 1 and 2 remained very similar with higher risks of placenta previa among women with and without MAR (Supplemental Table 2).

The study's a posteriori power for preterm birth at <37 weeks was 99% and at <33 weeks, it was 97.5%.

DISCUSSION

Our analysis demonstrates that the percentage of preterm birth at <37 weeks was 11.1% in the endometriosis group and 7.7% in the unexposed group, and at <33 weeks, it was 3.1% and 2.2%, respectively. The aRR in model 1 was higher in the endometriosis-diagnosed group than the nondiagnosed group for preterm delivery at <37 weeks (1.40; 95% CI, 1.18–1.67) and <33 weeks (aRR, 1.53; 95% CI, 1.08–2.16). All risks for our secondary outcomes were higher in the endometriosis group except for the risks of stillbirth and SGA of <3rd percentile. In model 2, the only risk that remained higher in the endometriosis group was that of placenta previa. The aRRs after stratification by MAR (yes/no) for preterm births at <37 and <33 weeks did not differ statistically significantly between the two groups.

Our study's findings add to the literature describing the association between endometriosis and adverse pregnancy outcomes (20, 24). After adjustment, we found a higher risk of preterm birth at <37 and <33 weeks only for model 1, consistent with the meta-analysis by Horton et al. (24), which reported higher risk in women with endometriosis conceiving either naturally or by assisted reproduction technology than in the unexposed group (OR, 1.38; 95% CI, 1.01–1.89; n = 11 studies with 25,283 exposed women vs. 1,609,742 unexposed women; I^2 = 94% (24). Not all studies included details on how they obtained the outcome information, and some collected data with questionnaires or telephone interviews, potentially linked to potential information bias (24). A more recent meta-analysis also including cohort and case-control studies likewise found a higher preterm birth rate in women with endometriosis (OR, 1.46; 95% CI, 1.26–1.69; n = 13 studies) (20). The investigators reported their principal limitation was the studies' high heterogeneity (I^2 = 96%), with adjustment for potential confounders varying between studies. Breintoft et al. (20) noted that the covariates for which the included studies adjusted most often were BMI, parity, maternal age, and smoking status. Our multivariable model 1 also adjusted for variables linked to socioeconomic status (living alone and geographical origin), which is a confounding factor.

In our study, the aRRs with model 1 after stratification by MAR for preterm birth at <37 weeks and <33 weeks did not show statistically significant differences between these two groups (Table 4). Inversely, Breintoft et al. (20) found a higher OR for preterm birth among women with spontaneous pregnancies (OR, 1.81; 95% CI, 1.29–2.54; n = 5 studies; I^2 = 72%), whereas Horton et al. (24) noted a higher OR for IVF/intracytoplasmic sperm injection (ICSI) conception among women with endometriosis compared with without diagnosed endometriosis (OR, 1.50; 95% CI, 1.10–2.03; n = 6 studies; I^2 = 62%) (24). Multivariable models should compare spontaneous with MAR pregnancies, given that the risk of spontaneous preterm birth at <37 or <34 weeks appears higher among singleton pregnancies conceived after IVF or ICSI than those conceived spontaneously (22). A French study from the anonymized national health system database reports assisted reproduction technology in the endometriosis group had an effect independent of that of endometriosis alone, with preterm birth rates higher in this

TABLE 3

Crude and adjusted relative risks of adverse pregnancy outcomes for women with endometriosis compared with women without known endometriosis among 368,935 French women, 1999–2016.

	Total N = 368,935 *n*%	Endometriosis n = 2,108 *n*%	No endometriosis n = 366,827 *n*%	Crude RR (95% CI)	Adjusted RR1 (95% CI)	Adjusted RR2 (95% CI)
Preterm birth[a]	368,935	2,108	366,827			
<37 wk	7.7	11.1	7.7	1.46 (1.29–1.64)	1.40 (1.18–1.67)[e]	0.91 (0.77–1.07)[f]
<33 wk	2.2	3.1	2.2	1.38 (1.08–1.75)	1.53 (1.08–2.16)[e]	0.82 (0.58–1.15)[f]
Preeclampsia[b]	320,102	1,835	318,267			
	1.4	2.0	1.4	1.48 (1.07–2.04)	1.64 (1.09–2.47)[e]	1.22 (0.81–1.83)[g]
Placenta previa	322,286	1,857	320,429			
	0.4	2.2	0.4	5.60 (4.12–7.62)	4.29 (2.79–6.60)[e]	3.14 (2.00–4.93)[f]
PPH[c]	340,290	2,028	338,262			
	4.2	4.9	4.2	1.16 (0.95–1.40)	1.30 (1.04–1.62)[e]	1.14 (0.91–1.42)[h]
Stillbirth	376,967	2,239	374,728			
	0.6	0.5	0.6	0.86 (0.49–1.51)	1.14 (0.57–2.29)[e]	0.46 (0.17–1.23)[g]
SGA[d]	375,099	2,226	372,873			
SGA <10th percentile	10.0	11.7	10.0	1.17 (1.04–1.31)	1.21 (1.05–1.40)[e]	0.92 (0.79–1.08)[g]
SGA <5th percentile	5.7	6.5	5.7	1.15 (0.98–1.34)	1.23 (1.01–1.49)[e]	0.90 (0.73–1.10)[g]
SGA <3rd percentile	3.9	4.3	3.8	1.12 (0.92–1.36)	1.20 (0.94–1.54)[e]	0.81 (0.62–1.05)[g]

Note: RR = relative risk; aRR = adjusted relative risk; RR1 = RR with only confounding factors; RR2 = RR with confounding factors and clinical relevant prognostic factors.

[a] Defined as birth before completed weeks of gestation.

[b] Preeclampsia is defined as persistent hypertension (diastolic blood pressure ≥90 mm Hg and/or systolic blood pressure ≥140 mm Hg), ≥20 weeks of amenorrhea, and substantial proteinuria (>0.3 g/24 hours).

[c] PPH: Postpartum hemorrhage, defined as ≥1,000 mL during the first 24 hours after childbirth.

[d] SGA: Small for gestational age at birth, defined as a neonate whose birth weight of <10th, <5th, or <3rd percentile according to the infant's gestational age and sex, on the basis of data derived from the reference population included in the French AUDIPOG database.

[e] Adjusted only for confounding factors (model 1): maternal age (continuous variable), maternal prepregnancy BMI (continuous variable), lives alone (yes/no), geographic origin (other/metropolitan [European] France), and used tobacco during pregnancy (yes/no).

[f] Adjusted for confounding factors: maternal age (continuous variable), maternal prepregnancy BMI (continuous variable), lives alone (yes/no), geographic origin (other/metropolitan (European) France), tobacco use during this pregnancy (yes/no), and clinically relevant prognostic factors: MAR (yes/no), parity (≥1/0), year of delivery (1999–2003/2004–2008/2009–2013/2014–2016), singleton pregnancy (yes/no), level of maternity units (3/2/1), previous cesarean delivery (yes/no), and pathology during pregnancy (yes/no). The maternity unit at birth was defined as level I when no neonatal department was available, level II when a neonatal department and special care were available in the same building or at immediate proximity to the delivery site, and level III when a neonatal intensive care unit was available in the same building (in addition to neonatology units) or in immediate proximity to the delivery room.

[g] Adjusted for confounding factors: maternal age (continuous variable), maternal prepregnancy BMI (continuous variable), lives alone (yes/no), geographical origin (other/metropolitan [European] France), used tobacco during the pregnancy (yes/no), and clinically relevant prognostic factors: MAR (yes/no), parity (≥1/0), year of delivery (1999–2003/2004–2008/2009–2013/2014–2016), singleton pregnancy (yes/no), maternity unit level (3/2/1), and pathology during the pregnancy (yes/no).

[h] Adjusted for confounding factors: maternal age (continuous variable), maternal prepregnancy BMI (continuous variable), lives alone (yes/no), geographic origin (other/metropolitan [European] France), tobacco use during the pregnancy (yes/no), and clinically relevant prognostic factors: MAR (yes/no), parity (≥1/0), previous cesarean delivery (yes/no), year of delivery (1999–2003/2004–2008/2009–2013/2014–2016), singleton (yes/no), maternity unit level (3/2/1), birthweight (≥4000 g/<4000 g), placenta previa (yes/no), and pathology during the pregnancy (yes/no).

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TABLE 4

Crude and adjusted relative risks for confounding factors only (model 1) in pregnant women with and without known endometriosis, stratified by MAR, among 344,648 births, France, 1999–2016.

	Medically assisted reproduction				No medically assisted reproduction			
Adverse pregnancy outcomes	Endom n = 543 %	No endom n = 13,382 %	Crude RR (95% CI)	aRR (95% CI)	Endom n = 1,444 %	No endom n = 329,279 %	Crude RR (95% CI)	aRR (95% CI)
Preterm birth	543	13,382			1,444	329,279		
<37 wk	21.0	18.3	1.15 (0.97–1.36)	1.12 (0.87–1.45)[d]	8.0	7.2	1.11 (0.93–1.32)	1.11 (0.87–1.41)[d]
<33 wk	7.2	6.3	1.13 (0.83–1.54)	1.42 (0.91–2.22)[d]	1.6	2.1	0.75 (0.50–1.13)	0.81 (0.45–1.46)[d]
Preeclampsia[a]	481	10,885			1,255	288,212		
	3.3	2.5	1.33 (0.81–2.18)	1.40 (0.72–2.72)[d]	1.7	1.3	1.27 (0.83–1.94)	1.44 (0.85–2.42)[d]
Placenta previa	487	10,944			1,270	290,103		
	5.3	1.1	4.99 (3.30–7.56)	4.04 (2.15–7.59)[d]	1.2	0.4	3.16 (1.90–5.25)	3.13 (1.68–5.81)[d]
PPH[b]	524	12,529			1,394	305,957		
	6.9	7.5	0.92 (0.67–1.27)	1.27 (0.88–1.82)[d]	4.4	4.2	1.04 (0.81–1.33)	1.09 (0.82–1.45)[d]
Stillbirth	647	15,770			1,470	334,324		
	0.5	1.3	0.37 (0.12–1.15)	0.85 (0.27–2.69)[d]	0.4	0.6	0.68 (0.31–1.52)	0.64 (0.21–1.99)[d]
SGA[c]	642	15,641			1,464	333,152		
SGA <10th percentile	15.7	15.4	1.02 (0.85–1.23)	0.97 (0.75–1.25)[d]	9.4	9.7	0.97 (0.83–1.13)	1.07 (0.88–1.29)[d]
SGA <5th percentile	9.0	9.7	0.93 (0.72–1.19)	1.01 (0.73–1.39)[d]	5.1	5.5	0.93 (0.75–1.16)	1.05 (0.81–1.36)[d]
SGA <3rd percentile	5.9	7.0	0.85 (0.62–1.16)	1.00 (0.68–1.47)[d]	3.2	3.7	0.86 (0.65–1.15)	0.96 (0.69–1.35)[d]

Note: RR = relative risk; aRR = adjusted relative risk.

[a] Preeclampsia, defined as persistent hypertension (diastolic blood pressure of ≥90 mm Hg and/or systolic blood pressure of ≥140 mm Hg), ≥20 weeks of amenorrhea, and proteinuria of >0.3 g/24 hours.

[b] PPH: Postpartum hemorrhage, defined as ≥1,000 mL during the 24 hours after delivery.

[c] SGA: small-for-gestational-age at birth, defined as a neonate with a birthweight of <10th, <5th, or <3rd percentile for gestational age and sex, on the basis of data derived from the reference population included in the French AUDIPOG database.

[d] Adjusted for confounding factors: maternal age (continuous variable), maternal prepregnancy BMI (continuous variable), lives alone (yes/no), geographic origin (other/metropolitan [European] France), and tobacco use during the pregnancy (yes/no).

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group than in either the unexposed group with spontaneous conception without endometriosis (aOR, 1.92; 95% CI, 1.78–2.07) or the spontaneous conception-endometriosis group (aOR, 1.42; 95% CI, 1.29–1.55) (6).

The adjusted risk of preeclampsia in the endometriosis group was higher only with our model 1: 1.64 (95% CI, 1.09–2.47), similar to the findings by Breintoft et al. (20), who found a pooled OR of 1.19; 95% CI, 1.08–1.31; n = 10 studies; $I^2 = 76\%$).

We found a higher risk of placenta previa in women with endometriosis (aRR1, 4.29; 95% CI, 2.79–6.60 and aRR2, 3.14; 95% CI, 2.00–4.93) (Table 3) as did the meta-analysis by Breintoft et al. (pooled OR, 2.99; 95% CI, 2.54–3.53; n = 8 studies; $I^2 = 86\%$) (20). In our study, with model 1, this risk remained higher in the subanalysis for the women with (aRR, 4.04; 95% CI, 2.15–7.59) and without (aRR, 3.13; 95% CI, 1.68–5.81) MAR (Table 4) and still higher in the same subanalysis in model 2 (Supplemental Table 2). Horton et al. (24) also found a higher risk of placenta previa in women with endometriosis and IVF/ICSI (pooled OR, 3.31; 95% CI, 1.26–8.71; n = 6 studies; $I^2 = 80\%$), and those with endometriosis who conceived naturally compared with unexposed groups (pooled OR, 3.09; 95% CI, 2.04–4.68; $I^2 = 83\%$). The higher risk of placenta previa among endometriosis-diagnosed women may be explained by the frequent association between endometriosis and adenomyosis and the higher rate of miscarriage in endometriosis-adenomyosis, and thus of uterine curettage (30, 31). Endometriosis and uterine curettage can induce placentation defects.

Our study found an increased risk of PPH only with our model 1 (aRR1, 1.30; 95% CI, 1.04–1.62). A few investigators have found an increased risk of PPH (23), although the Breintoft et al. meta-analysis (20) did not. We found no difference for stillbirth between the groups with and without endometriosis (Table 3). These result remained statistically nonsignificant after stratification by MAR (Table 4). Inversely, Breintoft et al. (20) found a higher stillbirth risk with endometriosis (pooled OR, 1.27; 95% CI, 1.07–1.51; n = 8 studies; $I^2 = 66\%$), whereas Horton et al. (24) described a higher risk of intrauterine fetal death among women conceiving naturally with compared with without endometriosis (pooled OR, 1.25; 95% CI, 1.08–1.45; n = 5 studies; $I^2 = 30\%$).

With model 1, the risks of SGA <10th and <5th percentiles were higher, but not that for SGA <3rd percentile (Table 3). Breintoft et al. (20) did not find a statistically significant risk difference between the two groups for SGA (pooled OR, 1.12; 95% CI, 0.94–1.33; n = 8 studies; $I^2 = 92\%$) except after including all studies regardless of study quality (aOR, 1.18; 95% CI, 1.02–1.36, 22 studies; $I^2 = 82\%$) and studies with spontaneous pregnancies (OR, 1.05; 95% CI, 1.02–1.06; 5 studies; $I^2 = 0\%$) (20). However, they did not define SGA in their publication.

The strengths of our study are its power (99% for preterm birth at <37 weeks and 97.5% <33 weeks), its study design (multicenter retrospective cohort study), and the consideration of MAR through a subanalysis stratified by its use, given endometriosis is linked to infertility. Mechanisms that interfere with fertility in women with endometriosis also may have adverse maternal and neonatal outcomes.

The first limitation of this study is the lower prevalence of endometriosis in our database than in published prevalence rates estimated in the literature (0.57% vs. 1%–11%) (3–5). Endometriosis appeared as a self-reported diagnosis in most medical files and, thus, also in our database. Nonetheless, it appears only after a positive answer to a question about the "existence of other gynecologic diseases," and as one potential response (12 multiple choices plus another with a free response) to "if yes, what?" Accordingly, we recoded this variable as a structured variable (endometriosis, yes/no). However, women can have endometriosis without any diagnosis, and its cumulative prevalence varies with age (2.9% at 30–34 years to 6.0% at 40–44 years). The pregnant women in our study are younger than the mean age of the general population (5). Differential misclassification of exposure status, i.e., "presence of undiagnosed endometriosis" in the unexposed group (information bias) might have attenuated the reported association.

The second limitation is our failure to collect the diagnostic method (histology or magnetic resonance imaging) and thus, the potential coexistence of adenomyosis. Despite the well-known strong association between endometriosis and adenomyosis (31), the different anatomic locations of endometriosis may reflect different pathogenic mechanisms and clinical manifestations.

The third limitation of our work is the potential absence in our database of reliable data about how pregnancies were dated: this information frequently is missing. Nonetheless, fetal ultrasound is the most common dating method in France because the national health insurance fund reimburses three ultrasounds during pregnancy (the first two at 70% and the last at 100%). The first takes place at 11–14 weeks and uses crown-rump length to determine term. In 2010 and 2016, the national perinatal survey found, respectively, that only 1.6% and 1.0% of women had <3 ultrasounds during pregnancy (32).

The fourth limitation is our inability to confirm specific diagnoses, such as preeclampsia in our database. Nonetheless, most of these variables had been defined initially at a national level through guidelines, and contributors had a glossary available to help them with coding.

The voluntary participation of maternity units in the database that prevents us from ruling out the risk of a nondifferential selection bias is a fifth limitation. This bias is, however, very unlikely because we regularly compare our results with those of the national perinatal survey conducted every 5 years or so and have been unable to demonstrate that the maternity units participating in the AUDIPOG database behave differently than those who did not.

A sixth limitation is the inclusion in model 2 of prognostic factors that may be considered intermediate factors (parity and MAR). Their inclusion may lead to underestimating the association we are studying.

The final limitation to note is that we stratified our analysis by MAR because of the association of endometriosis with fertility problems, and the higher risk of obstetric complications among singletons conceived by MAR (22). These points suggest some pitfalls to be considered. As mentioned above, MAR use can be regarded as an intermediate factor when

assessing the direct effect of endometriosis on adverse maternal, perinatal, and neonatal outcomes. Because other possible unmeasured confounding variables might affect MAR and these poor outcomes, stratifying by MAR may introduce bias. Nonetheless, the highest aRR, in our study was for placenta previa, and it remained the highest whether or not we stratified by MAR.

CONCLUSION

In our cohort, but only in model 1, which was adjusted for confounding factors, pregnant women with endometriosis were at higher risk for preterm birth (<37 and <33 weeks), preeclampsia, placenta previa, SGA (<10th and <5th), and PPH than women without this disease. They did not, however, have a higher risk of stillbirth. The only increased risk in both women with and without MAR was for placenta previa.

Research to assess the most appropriate diagnostic and treatment options for endometriosis is recommended (33). Large prospective population-based cohort studies may then investigate the risk of adverse maternal and neonatal outcomes among women with endometriosis, treated and untreated.

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CRediT Authorship Contribution Statement

Françoise Vendittelli: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization, Funding acquisition. **Chloé Barasinski:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis. **Olivier Rivière:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Validation, Methodology, Investigation, Formal analysis, Data curation. **Nicolas Bourdel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis. **Xavier Fritel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis.

Declaration of Interests

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Endometriosis y riesgo de resultados adversos en el embarazo: un estudio de cohorte multicéntrico retrospectivo

Objetivo: Investigar, en primer lugar, la asociación entre la endometriosis y el parto prematuro; en segundo lugar, las asociaciones entre la endometriosis y la pre-eclampsia, la placenta previa, la hemorragia posparto, la muerte fetal y los recién nacidos pequeños para la edad gestacional (evaluados por el peso al nacer); y en tercer lugar, el riesgo de estos resultados adversos del embarazo con y sin el uso de reproducción asistida.

Diseño: Estudio de cohorte retrospectivo multicéntrico.

Entorno: Un total de 103 maternidades francesas.

Pacientes: partos de 368.935 mujeres (377.338 bebés) desde 1999 hasta 2016.

Exposición: Endometriosis, definida como una sola entidad patológica (endometriosis y/o adenomiosis)

Principales medidas de resultado: El resultado principal fue la tasa de nacimientos prematuros (ambos <37 y <33 semanas). Los resultados secundarios fueron las tasas de pre-eclampsia, placenta previa, hemorragia posparto, muerte fetal y neonatos pequeños para la edad gestacional.

Resultados: Las mujeres del grupo de endometriosis presentaron antecedentes más frecuentes de infertilidad antes del embarazo incluido (34,7 vs. 5,0%), más hospitalizaciones durante el embarazo (27,4 vs. 19,8%) y más cesáreas programadas (14,0 vs. 8,7); con mayor frecuencia fueron nulíparas (51,7 vs. 43,4%). La prevalencia de parto prematuro a las <37 semanas fue del 11,1% en el grupo de endometriosis y del 7,7% en el grupo no expuesto, y durante <33 semanas fue del 3,1% y del 2,2%, respectivamente. El riesgo relativo ajustado de factores de confusión fue mayor en el grupo de endometriosis que en el grupo no expuesto para el parto prematuro <37 semanas (1,40, intervalo de confianza del 95 %, 1,18–1,67) o <33 semanas (1,53, intervalo de confianza del 95 %, 1,08–2,16). Para los resultados secundarios, los cocientes de riesgo ajustados para la pre-eclampsia, la placenta previa, la hemorragia posparto y el estado de pequeño para la edad gestacional de los percentiles <10 y <5 fueron más altos en el grupo de endometriosis. Los cocientes de riesgo ajustados para la muerte fetal y el estado de edad gestacional pequeño del percentil <3 no difirieron entre los dos grupos, y después de la estratificación por reproducción médicamente asistida para el parto prematuro a las <37 y <33 semanas no difirieron estadísticamente significativamente entre ellos, para los resultados secundarios, solo el riesgo de placenta previa fue mayor en los subgrupos de reproducción médicamente asistida y reproducción no médicamente asistida.

Conclusión: Las mujeres embarazadas con endometriosis tuvieron mayor riesgo de parto prematuro y otros resultados adversos del embarazo que las mujeres sin endometriosis. (FertilSteril 2024. 2024por la Sociedad Americana de Medicina Reproductiva.)