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Endometriosis and assisted reproductive techniques independently related to mother–child morbidities: a French longitudinal national study

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Abstract

Research question: Does endometriosis increase obstetric and neonatal complications, and does assisted reproductive technology (ART) cause additional risk of maternal or fetal morbidity?

Design: A nationwide cohort study (2013–2018) comparing maternal and perinatal morbidities in three groups of single pregnancies: spontaneous pregnancies without endometriosis; spontaneous pregnancies with endometriosis; and ART pregnancies in women with endometriosis.

Results: Mean maternal ages were 30.0 (SD = 5.3), 31.7 (SD = 4.8) and 33.1 years (SD = 4.0), for spontaneous conceptions, spontaneous conceptions with endometriosis and ART

pregnancies with endometriosis groups, respectively ($P < 0.0001$). Comparison of spontaneous conceptions with endometriosis and spontaneous conceptions: endometriosis independently increased the risk of venous thrombosis (adjusted OR [aOR] 1.51, $P < 0.001$), pre-eclampsia (aOR 1.29, $P < 0.001$), placenta previa (aOR 2.62, $P < 0.001$), placental abruption (aOR 1.54, $P < 0.001$), premature birth (aOR 1.37, $P < 0.001$), small for gestational age (aOR 1.05, $P < 0.001$) and malformations (aOR 1.06, $P = 0.049$). Comparison of ART pregnancies with endometriosis and spontaneous conceptions with endometriosis: ART increased the risk of placenta previa (aOR 2.43, 95% CI 2.10 to 2.82, $P < 0.001$), premature birth (aOR 1.42, 95% CI 1.29 to 1.55, $P < 0.001$) and small for gestational age (aOR 1.18, 95% CI 1.10 to 1.27, $P < 0.001$), independently from the effect of endometriosis. Risk of pre-eclampsia, placental abruption or congenital malformations was not increased with ART.

Conclusion: Endometriosis is an independent risk factor for mother and child morbidities. Maternal morbidity and perinatal morbidity were significantly increased by ART in addition to endometriosis; however, some perinatal and maternal morbidity risks were increasingly linked to pathologies related to infertility.

KEYWORDS: endometriosis, assisted reproductive techniques, maternal and perinatal morbidity, pregnancy induced hypertension disorders, premature birth

<A>Introduction

Pregnancies achieved after assisted reproductive technologies (ART) are associated with increased risks of adverse obstetrical and perinatal outcomes compared with pregnancies that are spontaneously conceived (Qin *et al.*, 2017; Pinborg, 2019h). Notably, significantly higher rates of maternal complications, such as gestational diabetes mellitus, venous thrombosis, gestational hypertensive disorders and perinatal complications (placenta previa, placental abruption, premature rupture of membranes, premature birth, postpartum haemorrhage) were reported after IVF and fresh embryo transfer compared with spontaneous conception (Lei *et al.*, 2019; Pessione *et al.*, 2020). Concerning neonatal effects, babies conceived after fresh IVF cycles have a significantly higher risk of preterm birth, low and very low birthweight, and neonatal morbidity compared with spontaneous conceptions (Koivurova *et al.*, 2002; Pessione *et al.*, 2020). Moreover, children born after ART are at increased risk of birth defects (Hansen *et al.*, 2005; Davies *et al.*, 2012; Wen *et al.*, 2012), and ART pregnancies have also been associated with higher rates of congenital anomalies, imprinting disorders and neurodevelopmental disorders (Strömberg *et al.*, 2002; Lehti *et al.*, 2013; Vermeiden and Bernardus, 2013).

Overall, in all studies of increased maternal and neonatal risks after ART, the question is that of considering the respective share of responsibility of ART and the underlying cause of infertility itself. Among the female pathologies that constitute indications of ART, endometriosis seems to be a potential candidate because its individualization in all its clinical manifestations can be objectivized.

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrial-like tissue outside the uterus in pelvic and extra-pelvic locations (Eskenazi and Warner, 1997). The prevalence of endometriosis is 1–2% of all women of reproductive age and 3–11% of infertile women (Eskenazi and Warner, 1997).

Modifications or complications of a pre-existing endometriosis during pregnancy have been recently described, with consequences on obstetric and perinatal outcomes depending on a number of mechanisms, including endometriosis-related chronic inflammation (Petraglia *et al.*, 2012; Vannuccini *et al.*, 2016), bleeding from endometriotic implants (Brosens *et al.*, 2012), functional abnormalities of the endometrium (Brosens *et al.*, 2013) and defective deep placentation (Leone Roberti Maggiore *et al.*, 2017). In spontaneous conceptions, higher rates of miscarriage, preterm delivery, placental abruption and caesarean section have been reported in cases of endometriosis (Porpora *et al.*, 2020), and a meta-analysis of 24 studies reported an increased risk of placenta previa, pre-term delivery and small for gestational age (SGA) newborns (Zullo *et al.*, 2017). Moreover, the relationship between endometriosis and hypertensive disorders, of which pre-eclampsia is an example, is still in question (Lalani *et al.*, 2018).

Endometriosis may compromise the physiological course of pregnancy; however, it has rarely been targeted as partly responsible for increased maternal and perinatal morbidity when it is the indication of ART. Most studies have compared the effect of endometriosis with other causes of infertility in ART, but not the effect of ART in endometriosis. Little is known about the risk of endometriosis-related symptoms progressing during ART. Endometriosis-related pain symptoms during ART might be modulated by many factors, such as the endometriosis phenotype or the intensity of ovarian response during ovarian stimulation. Among the scarce

data available, a prospective, controlled, observational cohort study comparing 102 women with endometriosis and 104 disease-free patients undergoing ART investigated whether ART affected pain by means of a visual analogue scale during ART and quality of life assessment (Santulli *et al.*, 2016). After multiple linear regression, no worsening of pain was observed between patients with or without endometriosis, and quality of life was similar between the two groups.

The aim of this cohort study was to investigate whether endometriosis causes a higher prevalence of obstetric and neonatal complications, and whether ART results in an additional risk of maternal or fetal morbidity.

<A>Materials and methods

A nationwide cohort study of singleton births compared the risks of maternal and perinatal morbidities of endometriosis alone and in association with ART compared with spontaneous conceptions without diagnosed endometriosis.

Population and data sources

The large French National Health System database (Système National des Données de Santé-SNDS), in which all hospitalizations (in any public hospital and private clinic) are registered, was used. This contains information on patient characteristics, diagnoses and treatments. All data were anonymized at data entry through a specific software making it impossible to retrieve patient identity but allowing information to be linked through anonymized codes. Access to data was legally approved. From this database, all singleton births (deliveries ≥ 22 weeks of gestation, > 500 g of birthweight, or both) that occurred in France over a 6-year period (2013–2018), were selected. Pregnancies resulting from

spontaneous conception and from fresh embryo transfer were included, and those resulting from frozen embryo transfer were excluded. The diagnosis of endometriosis was recorded if reported in previous hospitalizations since 2008. The pregnancies were classified as pregnancies resulting from spontaneous conceptions with endometriosis, from IVF and fresh embryo transfers (conventional IVF or with intracytoplasmic sperm injection) with endometriosis, or spontaneous conceptions without endometriosis (control group).

Deliveries after ART but without endometriosis were excluded from the analysis because the identification of the causes of infertility was unavailable. In that previous group, the risk of morbidity would not only have been related to ART treatment but also to various other diseases causing infertility, some of which, male or female, were shown to have an increased or decreased risk of morbidity regardless of ART.

Patient characteristics available in the hospital database were as follows: parity, maternal age, active smoking during pregnancy, obesity, history of diabetes (type 1 or 2) and hypertensive disorders, mode of conception, term, neonatal weight, sex and typology of malformation, if any.

The main identified maternal morbidity indicators were as follows: venous thrombosis, gestational diabetes mellitus, hypertensive disorders (pre-eclampsia or gestational hypertensive disorders), placenta previa and placental abruption, identified by specific codes in the hospitalization records during the index pregnancy. The main identified perinatal morbidity indicators were as follows: premature birth (<37 weeks' gestation), SGA (<10th percentile adjusted for gestational age and sex) and major congenital

malformations (according to the recommendations of the European register EUROCAT) and recorded at birth or until 2018.

Statistical analysis

The risks related to endometriosis alone were estimated by comparing spontaneous deliveries with and without endometriosis. Risks related to ART in patients with endometriosis were estimated by comparing deliveries with endometriosis with and without ART. Univariate and multivariate analyses were conducted using logistic regression models. The effect of endometriosis and ART conception on maternal and perinatal morbidities were estimated after adjusting for maternal age, smoking, obesity, parity and history of diabetes and hypertensive disorders with adjusted odds ratios and their 95% confidence index. The interaction between variables was tested and considered if $P < 0.05$.

<A>Results

The study included 4,121,767 single deliveries occurring between 2013 and 2018. A total of 4,083,732 were cases of spontaneous conceptions without endometriosis and 38,035 (0.92%) were women with diagnosed endometriosis, among which 31,101 were natural conceptions and 6934 were assisted.

The description of maternal characteristics is presented in **Table 1**. In the spontaneous conception group, the mean maternal age was lower compared with the endometriosis groups (30.0 ± 5.3 years for spontaneous conception versus 31.7 ± 4.8 for spontaneous conceptions with endometriosis and 33.1 ± 4.0 for ART pregnancies with endometriosis, respectively, $P < 0.0001$). Similar lower results were observed for primiparity (39.58% versus 47.37% and 76.71%, respectively, $P < 0.0001$), and history of hypertensive disorder

rates (0.85% versus 1.14% and 0.96%, respectively, $P < 0.0001$). The risk of obesity and smoking dependency, however, was higher in the spontaneous conception group compared with the spontaneous group with endometriosis and ART pregnancies with endometriosis groups (4.89% versus 3.87% and 3.10%, respectively, $P < 0.0001$ for obesity and 4.65% versus 3.74% and 2.37%, respectively, $P < 0.0001$ for smoking dependency). No difference was found between groups for history of diabetes mellitus ($P = 0.18$). Obstetrical and perinatal risks according to mode of conception and diagnosis of endometriosis are presented in univariate and multivariate analysis in **Table 2** and **Table 3**.

In spontaneous conceptions, endometriosis significantly increased the risk of venous thrombosis (0.21% versus 0.13%, adjusted OR (aOR) 1.51, 95% CI 1.18 to 1.94), pre-eclampsia (2.18% versus 1.57%, aOR 1.29, 95% CI 1.19 to 1.39], placenta previa (1.67% versus 0.56%, aOR 2.62, 95% CI 2.40 to 2.86), placental abruption (0.65% versus 0.41%, aOR 1.54, 95% CI 1.34 to 1.77), premature birth (7.70% versus 5.60%, aOR 1.37, 95% CI 1.31 to 1.43), SGA (12.2% versus 11.4%, aOR 1.05, 95% CI 1.02 to 1.08) and neonatal malformations (3.75% versus 3.52% , aOR 1.06, 95% CI 1.00 to 1.13), in univariate and multivariate analysis. The risk of gestational diabetes was not increased in the endometriosis group.

In endometriosis groups, ART compared with spontaneous pregnancy increased the risks of placenta previa (4.76% versus 1.67%, aOR 2.43, 95% CI 2.10 to 2.82), premature birth (11.0% versus 7.66%, aOR 1.42, 95% CI 1.29 to 1.55), and SGA (16.0% versus 12.2%, aOR 1.18, 95% CI 1.10 to 1.27). Women undergoing ART with diagnosed endometriosis did not result in additional risk for gestational diabetes, pre-eclampsia, placental abruption

and congenital malformations. The low number of thrombosis did not allow statistical analysis.

<A>Discussion

These large national recent cohort data provide evidence for an independent role of endometriosis in the increased adjusted risk of most maternal and perinatal morbidities in spontaneous deliveries of singletons, and for a role of ART as an associated risk added to complications related to endometriosis.

Endometriosis-related risk

Our results demonstrate in univariate and multivariate analysis that endometriosis significantly increases maternal risks such as venous thrombosis (aOR 1.51, $P < 0.001$), pre-eclampsia (aOR 1.29, $P < 0.001$), placenta previa (aOR 2.62, $P < 0.001$) and placental abruption (aOR 1.54, $P < 0.001$), as well as neonatal risks such as premature birth (aOR 1.37, $P < 0.001$), SGA (aOR 1.05, $P < 0.001$) and malformations (aOR 1.06, $P = 0.049$), compared with spontaneous pregnancies without endometriosis.

These results are consistent with published research. Indeed, an increased risk of placenta previa in cases of endometriosis was found in a meta-analysis by Zullo *et al.* (2017) of 24 studies including 1,924,114 women, of which 52,111 (2.7%) had endometriosis and 1,872,003 (97.3%) controls did not have endometriosis (OR 3.03, 95% CI 1.50 to 6.13). This is similar to the prospective cohort study by Harada *et al.* (2019) after adjusting for the confounding influence of ART (aOR 2.87) and the study by Mannini *et al.* (2017) in spontaneous pregnancies ($P < 0.05$). In line with our results, many of these studies also found significantly higher preterm birth rates in women with endometriosis compared with controls

without endometriosis (Mannini *et al.*, 2017; Zullo *et al.*, 2017; Bruun *et al.*, 2018; Harada *et al.*, 2019; Porpora *et al.*, 2020). Porpora *et al.* (2020) compared spontaneous pregnancies in women with endometriosis ($n = 145$) and controls ($n = 280$), and identified endometriosis as significantly associated with an increased risk of late preterm births. A hypothesis could be that, in the case of endometriosis and adenomyosis, progesterone resistance and altered contractility could lead to deferred implantation, causing miscarriage, recurrent pregnancy loss and placenta previa, and defective placentation, which could play a role in intrauterine growth retardation. Adenomyosis by itself could not be treated in our study as its presence was not distinguishable from that of endometriosis in our database. Alterations in uterine junctional zone and inflammation could also induce a shallow invasion playing a role in the genesis of pre-eclampsia and premature birth.

Data on pre-eclampsia, however, are discrepant. It has been suggested that alterations in the inner myometrium in women with endometriosis, such as defective remodelling of myometrial from the onset of decidualization, might induce vascular disorders (Leone Roberti Maggiore *et al.*, 2017). As such, our data are consistent with that of Glavind *et al.* (2017), showing an increased risk of pre-eclampsia among women with endometriosis (aOR 1.37, 95% CI 1.06 to 1.77, $P < 0.05$), and Porpora *et al.* (2020), showing a significant correlation with pregnancy-induced hypertension and pre-eclampsia in the presence of adenomyosis. Conversely, the meta-analysis by Zullo *et al.* (2017) of 24 studies found no difference in the incidence of gestational hypertensive disorders and pre-eclampsia. Discrepancies in results may be attributed to the difference in the criteria used to select patients with endometriosis. For instance, similar to Glavind *et al.* (2017), the present study included all types and stages of endometriosis, and endometriosis was addressed as one

disease entity, whereas, in the meta-analysis by Zullo *et al.* (2017), studies with and without ART were included and subgroup analyses without ART could not be conducted.

Furthermore, concerning neonatal outcomes, the meta-analysis by Zullo *et al.* (2017) also reported higher rates of SGA in case of endometriosis (OR 1.27, 95% CI 1.03 to 1.57), which was also the case in the meta-analysis by Pérez-López *et al.* (2018) of nine cohort studies including 13,798 pregnant women with endometriosis whose conception was either spontaneous or assisted compared with patients who did not have endometriosis (OR 1.16, 95% CI 1.05 to 1.28), and the meta-analysis by Bruun *et al.* (2018) of 13 studies (OR 1.26, 95% CI 1.04 to 1.549). In the present study, the increased risk of SGA was significant, but low (aOR 1.05, $P = 0.0003$).

Finally, to the best of our knowledge, the present study is the first to report that the presence of endometriosis significantly increased the rate of congenital malformations in spontaneous pregnancies, although this increase was small (aOR 1.06, $P = 0.049$). Indeed, studies so far have only focused on the risk of malformations in pregnancies generally obtained with ART (Liang *et al.*, 2019).

****Risks related to assisted reproductive technologies

Our findings also highlight that ART in the endometriosis group had an independent effect from endometriosis with an exacerbation of some major maternal and perinatal morbidities. Indeed, in patients with endometriosis, ART compared with spontaneous pregnancy increased the risk of placenta previa (4.76% versus 1.67%, aOR 2.43, 95% CI 2.10 to 2.82), premature birth (11.0% versus 7.7%, aOR 1.42, 95% CI 1.29 to 1.55), and SGA (16.0% versus 12.2%, aOR 1.18, 95% CI 1.10 to 1.27).

The effect of ART techniques on the increased risks of adverse obstetrical and perinatal outcomes compared with spontaneous pregnancies has previously been demonstrated (Qin *et al.*, 2017; Pinborg, 2019). Concerning the interaction between endometriosis and ART, studies so far have focused on whether the presence of endometriosis has led to increased maternal and perinatal complications in pregnancies obtained by ART, compared with the other causes of infertility and indications of ART. The question in these studies is whether endometriosis is more of a risk than other indications in ART, whereas our objective was to determine whether ART was an additional risk compared with the risk related to endometriosis. Few have treated the potential additional effect of ART compared with spontaneous pregnancies in patients with endometriosis, as was the objective of our study.

Among the existing data, the meta-analysis by Pérez-López *et al.* (2018) found an increased risk of preterm birth in women with endometriosis, as the preterm birth risk was significantly increased in both spontaneous conceptions (OR 1.59, 95% CI 1.32 to 1.90) and ART (OR 1.43, 95% CI 1.14 to 1.79). Similarly, in a recent systematic review and meta-analysis (Lalani *et al.*, 2018), the presence of endometriosis was found to be associated with placenta previa ($n = 8$ studies, OR 3.33, 96% CI 1.52 to 7.30) and preterm birth ($n = 10$ studies, OR 1.27 95% CI 1.04 to 1.55 among the subgroup of women who conceived with ART). As we deliberately chose, in the present study, to compare the two subgroups of pregnant women with endometriosis according to spontaneous conception or ART (and not pregnant women after ART according to indication of ART), we cannot compare our results to these studies, which had different objectives.

****Non-additional risk in assisted reproductive technologies

In the present study, no evidence was found of an additional effect of IVF treatment on the risk of other adverse obstetric and perinatal outcomes, such as pre-eclampsia, placental abruption and congenital malformation. In any case, our number of cases in the IVF and fresh embryo transfer with endometriosis group was too low ($n = 7$) to interpret the statistical test for the additional risk of venous thrombosis. Concerning gestational diabetes mellitus, no increased risk of IVF in pregnancies with endometriosis was observed.

The risk of pre-eclampsia after ART in endometriosis was low despite a fairly large number. Otherwise, the estimated risk of placental abruption was 1.19 ($P = 0.27$), but with a non-significant confidence interval, which could be explained by a lack of test power owing to limited numbers in spontaneous conception and ART conceptions ($n = 202$ and 58, respectively) for this relatively rare morbidity.

Hence, the increased risk of vascular disorders usually observed in ART could be explained by the risks associated with pathologies at risk of infertility or the characteristics of the populations (as a higher frequency of primiparity). It is the same for the risk of malformation in children. Conversely, a recent study comparing patients with endometriosis ($n = 1495$) and without endometriosis ($n = 27,105$) suggested that, after ART and frozen-thawed embryo transfer, a 1.6-fold risk of congenital birth defects occurred in cases of severe maternal endometriosis (aOR 1.66, 95% CI 1.03 to 2.35) (Liang *et al.*, 2019). An explanation for this could be that the study only included patients with severe forms of endometriosis (stages III-IV) diagnosed through laparotomy or laparoscopy, and introduces the potential risk related to embryo freezing and thawing. Again, this study analyses the consequences of endometriosis compared with other indications of ART, whereas we aimed to determine the responsibility of ART (and fresh transfer) and endometriosis in the compared risks.

To the best of our knowledge, the present study is the largest national cohort exploring the underlying causes of the excess of morbidity in mother and child after ART, while considering one of the most frequent causes of infertility, i.e. endometriosis. The strengths of the present study rely on the method of analyses, and which was conducted among a large and exhaustive cohort of women who gave birth to singletons during the recent years and ensured the presence or absence of ART and fresh transfer as mode of conception, as well as diagnosed endometriosis. Nevertheless, our analysis is limited by the methodology itself, as data were extracted from a national health registry that did not enable us to explore some data as those concerning different stages of endometriosis (regarding adenomyosis, endometriomas, or hormonal treatment before or after surgery), or details of ART techniques (IVF or intracytoplasmic sperm injection or embryo stage at transfer). This absence of differentiation could influence the results in the IVF and fresh embryo transfer with endometriosis group, which is probably not always pure endometriosis, and be a potential bias. Nevertheless, despite these restrictions, this group remains an informative group compared with groups who have conceived spontaneously, because of the weight of the diagnosis of endometriosis and the persistence of results in multivariate analysis after adjustment for six maternal confounding factors.

Furthermore, we did not investigate the rare specific complications of severe specific endometriotic disease, such as intestinal perforation and gestational digestive bleeding (in case of digestive localization) or upper urinary tract complications (in case of ureteral lesions) because they could not be compared with spontaneous pregnancies without endometriosis, nor between the two endometriosis groups given the small number of these complications during pregnancy described in published research (Zullo *et al.*, 2017; Porpora *et al.*, 2020).

The pros and cons of our decision not to present a group of patients having undergone ART without endometriosis, i.e. including all other indications of ART, were weighed carefully. The main aim was to analyse the effect of endometriosis on maternal–fetal morbidities in spontaneous conceptions and the additional risk when ART is associated with endometriosis, including an IVF and fresh embryo transfer without endometriosis group, and inclusion of other indications of ART would have deviated us away from our focus. Furthermore, recent research highlights the extreme heterogeneity of the indications of ART, and the specific effect of the different causes of infertility on obstetric complications and perinatal complications in ART pregnancies. For example, studies from the Massachusetts Outcomes Study of Assisted Reproductive evaluated birth outcomes by infertility diagnosis and concluded that, although the infant outcomes of low birth weight, SGA and large for gestational age were generally similar across diagnosis groups, specific diagnoses had greater risks for prematurity, gestational diabetes, prenatal hospital utilization and primary caesarean delivery (Luke *et al.*, 2015). From the same group, strong evidence was provided for a significant role of underlying infertility-related diagnosis as a major contributing factor to increases in adverse pregnancy and obstetric outcomes of ART deliveries (Stern *et al.*, 2015). In a systematic review and meta-analysis, authors demonstrated that polycystic ovary syndrome led to increased risk of adverse pregnancy and neonatal complications (Qin *et al.*, 2013). Another available study concluded that tubal factor was associated with an increased risk of miscarriage, preterm birth and low birth weight delivery compared with outcomes for couples with male factor infertility using ART (Kawwass *et al.*, 2013).

Overall, the findings from this large nationwide study comparing maternal and perinatal complications of single births resulting from spontaneous conceptions with endometriosis, ART and fresh transfer with endometriosis, or spontaneous conceptions without

endometriosis, prompt us to propose several conclusions. On one hand, it has been confirmed that endometriosis was an independent risk factor for several pregnancy and neonatal pathologies (risk of venous thrombosis, pre-eclampsia, placenta previa, placental abruption, premature birth and malformations) compared with spontaneous pregnancies, in univariate and multivariate analysis. On the other hand, our findings have also highlighted that ART additionally affected endometriosis by increasing the risk of placenta previa, prematurity and SGA.

Finally, the increased risk in some maternal or perinatal pathologies (pre-eclampsia, placental abruption and congenital malformation), usually attributed to ART, was not seen in this study, and was more probably related to pathologies at risk of infertility that led to the indication of ART. These data should assist ART physicians in providing the best information to their patients, candidates for ART, and those who are, or who are not, suffering from endometriosis.

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Declaration

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TABLE 1 MATERNAL CHARACTERISTICS IN SINGLETON DELIVERIES ACCORDING TO MODE OF CONCEPTION AND DIAGNOSIS OF MATERNAL ENDOMETRIOSIS

	Spontaneous conception without endometriosis (n = 4,083,732)		Spontaneous conception with endometriosis (n = 31101)		ART conception with endometriosis (n = 6934)		P-value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Age (mean ± SD)	30.0 ± 5.3		31.7 ± 4.8		33.1 ± 4.0		<0.0001
Obesity	200,070	4.90	1203	3.87	215	3.10	<0.0001
Smoking during pregnancy	189,811	4.65	1164	3.74	164	2.37	<0.0001
Primiparity	1,616,434	39.58	14,739	47.39	5319	76.71	<0.0001
History of hypertension	34,656	0.85	353	1.14	69	1.00	<0.0001
History of diabetes	35,851	0.88	297	0.95	52	0.75	0.18

TABLE 2 RISK OF MATERNAL AND PERINATAL MORBIDITY ACCORDING TO MODE OF CONCEPTION AND DIAGNOSIS OF MATERNAL ENDOMETRIOSIS

	Spontaneous conception without endometriosis (<i>n</i> = 4,083,732)		Spontaneous conception with endometriosis (<i>n</i> = 31,101)		ART conception with endometriosis (<i>n</i> = 6934)		<i>P</i> -value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Gestational diabetes	365,130	8.94	2969	9.55	641	9.24	<0.0001
Venous thrombosis	5392	0.13	64	0.21	7	0.10	0.0035
Pre-eclampsia	64,288	1.57	679	2.18	164	2.37	<0.0001
Placenta previa	23,002	0.56	520	1.67	330	4.76	<0.0001
Placental abruption	16,661	0.41	202	0.65	58	0.84	<0.0001
Premature birth	229,224	5.60	2382	7.66	761	11.0	<0.0001
Small for gestational age	463,776	11.4	3802	12.2	1111	16.0	<0.0001
Congenital malformation	143,932	3.52	1166	3.75	290	4.18	<0.0001

TABLE 3 RISKS OF MATERNAL AND PERINATAL MORBIDITIES IN MULTIVARIATE ANALYSIS ACCORDING TO MODE OF CONCEPTION AND DIAGNOSIS OF MATERNAL ENDOMETRIOSIS

	Spontaneous conception with endometriosis versus spontaneous conception without endometriosis			ART conception with endometriosis versus spontaneous conception without endometriosis			ART conception with endometriosis versus spontaneous conception with endometriosis		
	Adjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Gestational diabetes	1.01	0.97 to 1.05	0.63	0.95	0.88 to 1.03	0.24	0.94	0.8-1.04	0.22
Venous thrombosis	1.51	1.18 to 1.94	<0.001	^a	–	–	^a	–	–
Pre-eclampsia	1.29	1.19 to 1.39	<0.001	1.11	0.95 to 1.30	0.06	0.91	0.76 to 1.09	0.29
Placenta previa	2.62	2.40 to 2.86	<0.001	6.51	5.82 to 7.28	<0.001	2.43	2.10 to 2.82	<0.001
Placental abruption	1.54	1.34 to 1.77	<0.001	1.87	1.44 to 2.42	<0.001	1.19	0.87 to 1.61	0.27
Preterm birth	1.37	1.31 to 1.43	<0.001	1.92	1.78 to 2.07	<0,001	1.42	1.29 to 1.55	<0.001
Small for gestational age	1.05	1.02 to 1.08	<0.001	1.25	1.18 to 1.32	<0.001	1.18	1.10 to 1.27	<0.001
Malformation	1.06	1.06 to 1.13	0.049	1.18	1.04 to 1.32	<0.01	1.04	0.88 to 1.23	0.67

^aNumber of cases not sufficient for a statistical test.

ART, assisted reproductive technology.