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GENERAL GYNECOLOGY

New adverse obstetrics outcomes associated with endometriosis: a retrospective cohort study

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Abstract
Purpose The main aim of this study was to evaluate the incidence of endometriosis and intrahepatic cholestasis (ICP) and induction of labor in pregnant women with endometriosis compared with women without endometriosis. The secondary aim was to confirm increased incidence of already known endometriosis-related pregnancy complications in these patients.
Methods This is a retrospective cohort study performed at a tertiary hospital between January 2009 and December 2014 to compare obstetrics outcome between women with endometriosis and women without endometriosis. Pregnant patients with endometriosis were included in the study group. Patients were divided in the following subgroups: patients with deep infiltrating endometriosis (DIE subgroup) and patients without deep infiltrating endometriosis (non-DIE subgroup); patients with singleton pregnancy and spontaneous conception (subgroup A) and patients with multiple pregnancy and/or patients who underwent assisted reproductive technology (subgroup B). To form a control group, for each patient with endometriosis, two patients without endometriosis were selected as the control group by means of matched sample.
Results The study population included 262 pregnant women with endometriosis and 524 controls. Patients of the study population had significantly increased risks of placenta praevia ($p < 0.05$), ICP ($p < 0.01$), induction of labor ($p < 0.01$) and preterm birth ($p < 0.01$). DIE patients had a significantly higher percentage only of preterm birth ($p < 0.01$), while in non-DIE group all complications had a higher incidence except for placenta praevia, which did not differ with control. Subgroup A had a statistically higher incidence of placenta praevia ($p < 0.01$), ICP ($p < 0.01$), induction of labor ($p < 0.01$) and preterm birth ($p < 0.01$) compared to its control subgroup. There was no difference in distribution of pregnancy complications between subgroup B and control subgroup.
Conclusions Our results showed for the first time that women with endometriosis are at higher risk of developing ICP and experiencing an induced labor. Further studies are warranted to clarify whether the history of endometriosis might be taken into account in the antenatal care of these patients.

Keywords Endometriosis · Pregnancy outcome · Intrahepatic cholestasis · Induction of labor

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Introduction

Endometriosis is a common chronic disease of the reproductive years and is associated with pelvic pain and infertility. The prevalence of endometriosis in the general population is still unknown, though it has been reported that almost a quarter of women of reproductive age suffers of this disease [1].

Endometriosis is an enigmatic disease, defined as the presence of hormonally responsive endometrial glands and

stroma outside the uterine cavity [2]. Nevertheless, today it could be said that endometriosis is a disease with different clinical profiles [3]. It causes alterations of the local uterine environments, such as abnormal local estrogen production and altered endometrial response to progesterone, increase in oxidative stress, inflammatory process, impaired uterine contractility and structural changes in the uterine junctional zone (JZ) [4–6]. These modifications might cause defects during implantation period and consequently pregnancy adverse outcomes.

A recent review on endometriosis and pregnancy has reported an increased incidence of miscarriage, hypertensive disorders and preeclampsia, placenta praevia, obstetric hemorrhages, preterm birth and uterine rupture in patients with endometriosis [7]. Nevertheless, we hypothesized that aberrant hormonal milieu, chronic inflammation, impaired endomyometrium, and deficient immunologic response in endometriosis patients might lead to an higher incidence of other unstudied variables in these women, i.e., intrahepatic cholestasis (ICP) and induction of labor.

The main aim of this study was to evaluate the association between pregnant women with endometriosis and unstudied pregnancy complications in our cohort of patients. The secondary aim was to confirm increased incidence of already known endometriosis-related pregnancy complications in these patients.

Methods

This is a retrospective cohort study performed at a tertiary hospital between January 2009 and December 2014 to compare obstetrics outcome between pregnant women with endometriosis and women without endometriosis. Pregnant patients with endometriosis who delivered in our hospital were included in the study group. The inclusion criteria were: women treated surgically for deep infiltrating endometriosis (DIE) and non-deep infiltrating endometriosis (non-DIE) who had undergone previous surgical evaluation for endometriosis together with a pathological diagnosis of endometriosis. Data on whether or not there was disease left after surgery was not available for all patients. Consequently, the variable "disease left" was not assessed in the analysis. The exclusion criteria were: women with biochemical pregnancies (defined as transient increase in human chorionic gonadotropin (HCG) levels in serum with no signs of intrauterine or ectopic pregnancy at pelvic ultrasound scan), ectopic pregnancies, or missing data. Moreover, to clarify the effect of endometriosis on pregnancy, patients of the study were analyzed as a whole group and as subgroups. First, patients were divided on the basis of anatomical distribution of endometriosis in DIE subgroup and in non-DIE subgroup. Patients of the study subgroup without DIE were patients with ovarian endometrioma and/or peritoneal endometriosis. Second, patients were divided considering the mode of conception and number of fetus in: patients with singleton pregnancy and spontaneous conception (subgroup A) and patients with multiple pregnancy and/or patients who underwent assisted reproductive technology (ART) (subgroup B).

This investigation was a 1:2 retrospective cohort study, and consequently for each patient with endometriosis, two patients without endometriosis were selected as the control group by means of matched sample. Patient without endometriosis was defined as patient who did not have a previous clinical or surgical diagnosis of endometriosis, and who did not have any imaging sign of endometriosis. Additionally, we compared DIE-subgroup with non-DIE subgroup in endometriosis cohort of patients.

The following data was obtained for each patients: (1) demographics [age, body mass index (BMI)]; (2) previous obstetrical history (number of previous pregnancy, previous miscarriages, previous cesarean section); (3) mode of conception (spontaneous, ART); (4) pregnancy complications [multiple pregnancies, preterm labor, pregnancy-induced hypertension disorders (PIH), ICP, placenta praevia, fetal growth restriction (FGR), gestational diabetes, post partum hemorrhage], (5) route of delivery [vaginal delivery or cesarean section (CS)], (6) type of labor (spontaneous or induced).

The following definition were used: preterm labor was the delivery before 37 weeks of gestation; PIH was used for pregnancy-induced hypertension (defined as values persistently above 140/90 mmHg in a formerly normotensive patient after 20 weeks of gestation in the absence of proteinuria or other diagnostic features of preeclampsia) and preeclampsia (defined as PIH with either proteinuria ($\geq$300 mg/24 h) or end-organ dysfunction); ICP was presence of pruritus in the absence of a skin rush with abnormal liver function tests, neither of which had an alternative cause and both of which resolved after birth; placenta praevia was the presence of placental tissue that reached or extended over the internal cervical os and the diagnosis was confirmed within 2 weeks prior to cesarean section with a transvaginal ultrasound; FGR was an estimated fetal weight below the tenth percentile for gestational age and sex; gestational diabetes was a positive 75-g 2-h oral glucose tolerance test in a formerly non-diabetic woman after 16 weeks of pregnancy; post partum hemorrhage was maternal blood loss at delivery >500 ml.

Statistical analysis was performed using SPSS 19 and PRISM 6.0 g. Categorical variables were assessed using Chi-square Test of Pearson and the Fisher's exact test; continuous variables were analyzed by the Mann–Whitney *U* test. A *p* value less than 0.05 was considered significant. The study was approved by the local ethical committee.

Results

The study population included 262 pregnant women with endometriosis and the control group comprised 524 women. Among the study group, 40 (15.3 %) women had DIE (DIE group), whereas 222 (84.7 %) patients had ovarian and/or peritoneal endometriosis (non-DIE group). Considering the mode of conception and number of fetus, 188 (71.8 %) and 74 (28.2 %) women were included, respectively, in group A and in group B. Baseline characteristics of groups and subgroups are shown in Tables 1, 2 and 3.

The comparison of the case group with control group and DIE, non-DIE and A subgroups with the respective control subgroups showed no significant differences in terms of age and BMI, whereas there was a significant higher incidence of ART ($p < 0.001$) and twin pregnancies ($p < 0.001$) among cases compared with controls. On the contrary, subgroup B had a significant lower average age compared with its control subgroup (38.39 vs 40.27 years, respectively, $p < 0.05$). The percentage of nulliparous women was statistically higher in the study group comparing with the control group ($p < 0.01$), as well as between cases and controls in the following subgroups: DIE subgroup ($p < 0.05$), non-DIE subgroup ($p < 0.01$), subgroup A ($p < 0.01$). The proportion of patients in the control group who had had a previous miscarriage was significantly higher than in the study group ($p < 0.01$), although, among subgroups, the subgroup A had no statistically fewer miscarriages compared with controls.

Distribution of pregnancy complications, mode of delivery and type of labor between the study population and controls are reported in Table 1. Patients of the study population had a higher incidence of placenta praevia ($p < 0.05$), ICP ($p < 0.01$), induction of labor ($p < 0.01$) and preterm birth ($p < 0.01$). Considering each study subgroup, DIE patients had a significantly higher percentage only of preterm birth; in non-DIE group all pregnancy complications had a higher incidence except for placenta praevia, which did not differ with control. Subgroup A had a statistically higher incidence of placenta praevia ($p < 0.01$), ICP ($p < 0.01$), induction of labor ($p < 0.01$) and preterm birth ($p < 0.01$) compared to its control subgroup. On the contrary, there was no difference in distribution of pregnancy complications between subgroup B and control subgroup. No significant difference in rates of FGR, PIH, gestational diabetes, obstetrics hemorrhage and CS was registered in all the case–control group and subgroups.

Concerning the localization of endometriosis lesions, there were no significant differences in pregnancy complications between DIE subgroup and non-DIE subgroup (Table 4).

Discussion

In the recent years, research has focused on the consequences of endometriosis for pregnancy outcome, namely on endometrial environment, and on the structural and molecular features of the endomyometrium; we believe that some of our results could be explained in this manner.

The endomyometrial modifications in endometriosis have been reported to be responsible for several adverse pregnancy outcomes such as miscarriages, FGR, placenta praevia, PIH and preterm birth [7]. Processes of implantation and decidualization are complex and compulsory for a successful pregnancy [8]. Endometrial receptivity, decidualization and remodeling of uterine spiral vessels have been reported to be dysregulated in patients with endometriosis, leading to the increased incidence of pregnancy complications.

Endometrial receptivity is impaired for several reasons. First, it has been reported that patients with endometriosis have progesterone resistance and inadequate uterine contractility, which is connected with miscarriages and placenta praevia [9]. Moreover, several studies have reported that decidualization in women with endometriosis is compromised. One mechanism of impaired decidualization is the abnormal interplay of transcriptional factors, cytokines, cell-cycle regulators and signaling pathways [9]. Indeed, in humans the process of decidualization is induced by the expression of several genes necessary for a successful decidualization. Therefore, endometriosis might be seen as a genetic disease and many studies have demonstrated that aberrations in the molecular signaling are due to epigenetic changes in eutopic endometrium of endometriotic patients [9–12]. Furthermore, the conversion of uterine spiral arteries into utero-placental vessels is abnormal in endometriosis and it is due to inflammatory mediators, oxidative stress and alteration in the uterine junctional zone (JZ) [13]. Results of defective decidualization and pathological utero-placental vascularization are preeclampsia and preterm birth. In addition, there is evidence that endometriosis is associated with free radical metabolism and inflammation in the eutopic endometrium, both of these may cause miscarriages, preeclampsia and preterm birth [13–15]. Ota el al [16] reported an increase in the expression of many enzymes involved in the accumulation of free radicals in patients with endometriosis. Indeed, different studies have found a link between endometriosis and increased white cells, macrophages activation, cytokines production in endometriosis patients [17–19]. Hence, it could be said that endometriosis is a disease with different independent clinical profiles [3]: not only the presence of functional endometrial-like tissue outside the uterus, but also an aberrant endomyometrial environment.

Table 1 Patients characteristics in the study group compared with the controls group

	Cases group	Controls group	*p* OR IC		Cases group	Controls group	*p* OR IC
Age				Delivery, *n* (%)			
Mean (SD)	36.89 (±0.27)	36.88 (±0.19)	0.98	Vaginal	113 (43.1)	334 (63.7)	0.07
			–	Cs	149 (56.9)	190 (36.3)	0.75
			–				0.55–1.00
BMI				Induction, *n* (%)			
Mean (SD)	22.18 (±0.21)	22.38 (±0.16)	0.48	No induction	189 (72.1)	442 (84.4)	<0.001
			–	Induction	73 (27.9)	82 (15.6)	0.05
			–				0.34–0.69
Previous pregnancy, *n* (%)				PP, *n* (%)			
0	181 (69.1)	283 (54.0)	<0.01	No PP	252 (96.2)	518 (98.9)	0.03
≥1	81 (30.9)	241 (46.0)	1.90	PP	10 (3.8)	6 (1.1)	0.29
			1.40–2.60				0.10–0.81
Previous miscarriages, *n* (%)				FGR, *n* (%)			
0	211 (80.5)	376 (71.8)	<0.001	No FGR	243 (92.7)	499 (25.2)	0.20
≥1	51 (19.5)	148 (28.2)	0.10	FGR	19 (7.3)	25 (4.8)	0.64
			0.07–0.14				0.35–1.20
Previous CS, *n* (%)				PIH, *n* (%)			
0	236 (90.1)	453 (86.5)	0.18	No PIH	251 (95.8)	510 (97.3)	0.35
≥1	26 (9.9)	71 (13.5)	1.40	PIH	11 (4.2)	14 (2.7)	0.63
			0.88–2.30				0.28–1.40
Conception, *n* (%)				GD, *n* (%)			
Spontaneous	194 (74.0)	471 (89.9)	<0.001	No GD	206 78.6)	436 (83.2)	0.14
ART	68 (26.0)	53 (10.1)	0.32	GD	56 (21.4)	88 (16.8)	0.74
			0.22–0.48				0.51–1.10
Number of fetus, *n* (%)				ICP, *n* (%)			
1	235 (89.7)	515 (98.3)	<0.001	No ICP	248 (94.7)	518 (98.9)	0.001
≥2	27 (10.3)	9 (1.7)	0.15	ICP	14 (5.3)	6 (1.1)	0.21
			0.07–0.33				0.08–0.54
				Preterm birth, *n* (%)			
				No pret. birth	218 (83.2)	492 (93.9)	<0.001
				Pret. birth	44 (16.8)	32 (6.1)	0.32
							0.20–0.52
				PPH, *n* (%)			
				No PPH	240 (91.6)	475 (90.6)	0.76
				PPH	22 (8.4)	49 (9.4)	1.10
							0.66–1.90

Pregnancy outcomes and complications in the study groups compared with the controls groups

OR odds ratio, *IC* confidence interval, *BMI* body max index, *CS* cesarean section, *ART* assisted reproductive technology, *PP* placenta praevia, *FGR* fetal growth restriction, *PIH* pregnancy-induced hypertension disorders, *GD* gestational diabetes, *ICP* intrahepatic cholestasis, *PPH* post partum hemorrhage

Our study reported, for the first time in literature, an increase incidence of ICP and induction of labor in pregnant patients with previously documented endometriosis.

The available data shown that the placenta plays a pivotal role in ICP pathogenesis, although the etiology of ICP is still elusive [20–22]. Du et al. published a study on placental gene-expression profiles in ICP, showing that genes associated with immune response were up-regulated in mild ICP and further up-regulated in severe ICP. Moreover, the study reported that placentas from mild ICP had more T cells and B cells aggregation, and placentas from severe ICP displayed massive leukocytes infiltration

Table 2 Patients characteristics in the study groups compared with the controls groups

	Subgroup DIE, *n*	Subgroup controls of DIE, *n*	*p* OR IC	Subgroup non-DIE, *n*	Subgroup controls of non-DIE, *n*		Subgroup DIE, *n* (%)	Subgroup controls of DIE, *n* (%)	*p* OR IC	Subgroup non-DIE, *n* (%)	Subgroup controls of non-DIE, *n* (%)	*p* OR IC
Age						Delivery, *n* (%)						
Mean (SD)	36.82 (±0.49)	36.88 (±0.38)	0.92 – –	36.98 (±0.30)	36.73 (±0.22)	Vaginal	22 (55.0)	57 (71.3)	0.12	126 (56.8)	281 (63.3)	0.12
						Cs	18 (45.0)	23 (28.7)	0.49 0.22–1.10	96 (43.2)	163 (36.7)	0.76 0.55–1.10
BMI						Induction, *n* (%)						
Mean (SD)	22.55 (±0.63)	22.90 (±0.45)	0.66 – –	22.11 (±0.23)	22.49 (±0.17)	No induction	28 (70.0)	69 (86.3)	0.06	159 (71.6)	373 (84.0)	<0.001
						Induction	12 (30.0)	11 (13.7)	0.37 0.15–0.94	63 (28.4)	71 (16.0)	0.48 0.33–0.71
Previous pregnancy, *n* (%)						PP, *n* (%)						
0	23 (57.5)	26 (32.5)	0.02	121 (54.5)	166 (37.4)	No PP	38 (95.0)	80 (100)	0.20	214 (96.4)	438 (98.6)	0.10
≥1	17 (42.5)	54 (67.5)	2.80 1.30–6.10	101 (45.5)	278 (62.6)	PP	2 (5.0)	0 (0)	0.10 0.01–2.00	8 (3.6)	6 (1.4)	0.37 0.13–1.10
Previous miscarriages, *n* (%)						FGR, *n* (%)						
0	33 (82.5)	49 (61. 3)	0.03	178 (80.2)	320 (72.1)	No FGR	38 (95.0)	80 (100)	0.20	205 (92.3)	422 (95.0)	0.22
≥1	7 (17.5)	31 (38.7)	3.00 1.20–7.60	44 (19.8)	124 (27.9)	FGR	2 (5.0)	0 (0)	0.10 0.01–2.00	17 (7.7)	22 (5.0)	0.63 0.33–1.20
Previous CS, *n* (%)						PIH, *n* (%)						
0	34 (85.0)	73 (91.3)	0.47	202 (91.0)	383 (86.3)	No PIH	39 (97.5)	78 (97.5)	0.50	213 (96.0)	434 (97.8)	0.28
≥1	6 (15.0)	7 (8.7)	0.54 0.17–1.70	20 (9.0)	61 (13.7)	PIH	1 (2.5)	2 (2.5)	1.00 0.09–11.00	9 (4.0)	10 (2.2)	0.55 0.22–1.40
Conception, *n* (%)						GD, *n* (%)						
Spontaneous	33 (82.5)	49 (61.3)	0.03	164 (73.9)	397 (89.4)	No GD	34 (85.0)	69 (86.3)	0.90	173 (77.9)	366 (82.4)	0.20
ART	7 (27.5)	31 (38.8)	0.29 0.10–0.83	58 (26.1)	47 (10.6)	GD	6 (15.0)	11 (13.7)	0.90 0.31–2.70	49 (22.1)	78 (17.6)	0.75 0.50–1.10

Table 2 continued

	Subgroup DIE, *n*	Subgroup controls of DIE, *n*	*p* OR IC	Subgroup non-DIE, *n*	Subgroup controls of non-DIE, *n*		Subgroup DIE, *n* (%)	Subgroup controls of DIE, *n* (%)	*p* OR IC	Subgroup non-DIE, *n* (%)	Subgroup controls of non-DIE, *n* (%)	*p* OR IC
Number of fetus, *n* (%)						ICP, *n* (%)						
1	37 (92.5)	79 (98.8)	0.20	198 (89.2)	438 (99.5)	No ICP	37 (92.5)	80 (100)	0.06	211 (95.0)	439 (98.9)	0.006
≥2	3 (7.5)	1 (1.2)	0.16	24 (10.8)	6 (0.5)	ICP	3 (7.5)	0 (0)	0.07	11 (5.0)	5 (1.1)	0.22
			0.16–1.60						0.01–1.30			0.08–0.64
						Preterm birth, *n* (%)						
						No pret. birth	30 (75.0)	79 (98.8)	<0.001	212 (95.5)	443 (99.8)	<0.001
						Pret. birth	10 (25.0)	1 (1.2)	0.038	10 (4.5)	1 (0.2)	0.048
									0.01–0.03			0.01–0.38
						PPH, *n* (%)						
						No PPH	38 (95.0)	71 (88.0)	0.43	202 (91.0)	403 (90.8)	0.96
						PPH	2 (5.0)	9 (12.0)	2.40	20 (9.0)	41 (9.2)	1.00
									0.49–12.00			0.59–1.80

Pregnancy outcomes and complications in the study groups compared with the controls groups

OR odds ratio, *IC* confidence interval, *BMI* body max index, *CS* cesarean section, *ART* assisted reproductive technology, *PP* placenta praevia, *FGR* fetal growth restriction, *PIH* pregnancy-induced hypertension disorders, *GD* gestational diabetes, *ICP* intrahepatic cholestasis, *PPH* post partum hemorrhage

Table 3 Patients characteristics in the study groups compared with the controls groups

	Subgroup A, *n*	Subgroup controls of A, *n*	*p* OR IC	Subgroup B, *n*	Subgroup control of B, *n*	*p* OR IC		Subgroup A, *n* (%)	Subgroup control of A, *n* (%)	*p* OR IC	Subgroup B, *n* (%)	Subgroup control of B, *n* (%)	*p* OR IC
Age							Delivery, *n* (%)						
Mean (SD)	36.30 (±0.31)	36.45 (±0.19)	0.69	38.39 (±0.48)	40.27 (±0.63)	0.02	Vaginal	118 (62.8)	311 (66.7)	0.38	31 (41.9)	59 (39.9)	0.88
			–			–	Cs	70 (38.2)	155 (33.3)	0.84	43 (58.1)	89 (60.1)	1.10
			–			–				0.59–1.20			0.75–1.50
BMI							Induction, *n* (%)						
Mean (SD)	22.07 (±0.26)	22.27 (±0.18)	0.54	22.47 (±0.38)	22.72 (±0.44)	0.67	No induction	135 (71.8)	391 (83.9)	<0.001	54 (63.0)	18 (12.2)	<0.001
			–			–	Induction	53 (29.2)	75 (16.1)	0.49	20 (37.0)	130 (88.8)	20.00
			–			–				0.33–0.73			9.6–40.00
Previous pregnancy, *n* (%)							PP, *n* (%)						
0	93 (49.5)	169 (36.3)	<0.01	52 (70.3)	77 (52)	0.01	No PP	180 (95.7)	461 (98.9)	0.02	72 (97.3)	145 (98.0)	0.87
≥1	95 (50.5)	297 (63.7)	1.70	22 (29.7)	71 (48)	0.46	PP	8 (4.3)	5 (1.1)	0.24	2 (2.7)	3 (2.0)	0.74
			1.20–2.40			0.25–0.83				0.08-0.76			0.12–4.60
Previous miscarriages, *n* (%)							FGR, *n* (%)						
0	148 (78.7)	338 (72.5)	0.12	64 (86.5)	99 (66.9)	0.003	No FGR	176 (93.6)	444 (95.3)	0.50	67 (90.5)	140 (94.6)	0.39
≥1	40 (21.3)	128 (27.5)	1.40	10 (13.5)	49 (33.1)	0.32	FGR	12 (6.4)	22 (4.7)	0.73	7 (9.5)	8(5.4)	0.55
			0.94–2.10			0.15–0.67				0.35–1.50			0.19–1.60
Previous CS, *n* (%)							PIH, *n* (%)						
0	168 (89.4)	402 (86.3)	0.35	69 (93.2)	133 (89.9)	0.56	No PIH	181 (96.3)	454 (97.4)	0.59	70 (94.6)	128 (86.5)	0.11
≥1	20 (10.6)	64 (13.7)	1.30	5 (6.8)	15 (10.1)	0.64	PIH	7 (3.7)	12 (2.6)	0.68	4 (5.4)	20 (13.5)	2.70
			0.78–2.30			0.22–1.80				0.26–1.80			0.90–8.30
Conception, *n* (%)							GD, *n* (%)						
Spontaneous	188 (100)	466 (100)		6 (8.1)	3 (2.0)	0.07	No GD	149 (79.3)	387 (83.0)	0.30	57 (77.0)	125 (84.5)	0.24
ART	0 (0)	0 (0)		68 (91.9)	145 (98.0)	4.30	GD	39 (20.7)	79 (17.0)	0.78	17 (23.0)	23 (15.5)	0.62
						1.00–1.80				0.51–1.20			0.31–1.20

Table 3 continued

	Subgroup A, *n*	Subgroup controls of A, *n*	*p* OR IC	Subgroup B, *n*	Subgroup control of B, *n*	*p* OR IC		Subgroup A, *n* (%)	Subgroup control of A, *n* (%)	*p* OR IC	Subgroup B, *n* (%)	Subgroup control of B, *n* (%)	*p* OR IC
Number of fetus, *n* (%)							ICP, *n* (%)						
1	188 (100)	466 (100)		47 (63.5)	139 (93.9)	<0.001	No ICP	180 (95.7)	461 (98.9)	0.02	68 (91.9)	145 (98.0)	0.01
≥2	0 (0)	0 (0)		27 (36.5)	9 (6.1)	0.11	ICP	8 (4.3)	5 (1.1)	0.24	6 (8.1)	3 (2.0)	0.17
						0.049–0.26				0.08–0.76			0.05–0.66
							Preterm birth, *n* (%)						
							No pret. birth	168 (89.4)	448 (96.1)	0.002	50 (67.6)	112 (75.7)	0.26
								20 (10.6)	18 (3.9)	0.34	24 (32.4)	36 (24.3)	0.67
							Pret. birth			0.17–0.65			0.36–1.2
							PPH, *n* (%)						
							No PPH	174 (92.6)	421 (90.3)	0.46	66 (89.2)	138(93.2)	0.43
							PPH	14 (7.4)	45 (9.7)	1.30	8 (10.8)	10 (6.8)	0.60
										0.71–2.50			0.23–1.60

Pregnancy outcomes and complications in the study groups compared with the controls groups

OR odds ratio, *IC* confidence interval, *BMI* body max index, *CS* cesarean section, *ART* assisted reproductive technology, *PP* placenta praevia, *FGR* fetal growth restriction, *PIH* pregnancy-induced hypertension disorders, *GD* gestational diabetes, *ICP* intrahepatic cholestasis, *PPH* post partum hemorrhage

Table 4 Pregnancy outcomes and complications in the study group DIE compared with the study group non-DIE

	Subgroup DIE, *n* (%)	Subgroup non-DIE, *n* (%)	*p* OR IC
Delivery, *n* (%)			
Vaginal	22 (55.0)	126 (56.8)	0.97
Cs	18 (45.0)	96 (43.2)	0.93 0.47–1.80
Induction, *n* (%)			
No induction	28 (70.0)	159 (71.6)	0.99
Induction	12 (30.0)	63 (28.4)	0.92 0.44–1.90
PP, *n* (%)			
No PP	38 (95.0)	214 (96.4)	0.98
PP	2 (5.0)	8 (3.6)	0.71 0.15–3.50
FGR, *n* (%)			
No FGR	38 (95.0)	205 (92.3)	0.79
FGR	2 (5.0)	17 (7.7)	1.60 0.35–7.10
PIH, *n* (%)			
No PIH	39 (97.5)	213 (96.0)	0.98
PIH	1 (2.5)	9 (4.0)	1.60 0.20–13.00
GD, *n* (%)			
No GD	34 (85.0)	173 (77.9)	0.42
GD	6 (15.0)	49 (22.1)	1.60 0.64–4.00
ICP, *n* (%)			
No ICP	37 (92.5)	211 (95.0)	0.78
ICP	3 (7.5)	11 (5.0)	0.64 0.17–2.40
Preterm birth, *n* (%)			
No pret. birth	30 (75.0)	212 (95.5)	<0.001
Pret. Birth	10 (25)	10 (4.5)	0.14 0.05–0.37
PPH, *n* (%)			
No PPH	38 (95)	202 (91.0)	0.59
PPH	2 (5.0)	20 (9.0)	1.90 0.42–8.40

OR odds ratio, *IC* confidence interval, *CS* cesarian section, *PP* placenta praevia, *FGR* fetal grow restriction, *PIH* pregnancy-induced hypertension, *GD* gestational diabetes, *ICP* intrahepatic cholestasis, *PPH* post partum hemorrhage

[21]. The role of immune system in ICP was described in several studies [23, 24]. Another study found dysregulated expression of several proteins, including heat shock proteins and chaperons, in placentas of patients with ICP [25]. Given the fact that endometriosis is associated with increased oxidative stress and inflammation in the endometrium, it is tempting to postulate that the unfavorable endometrial environment might be an additional factor for the development of ICP in predispose patients.

The higher frequency of induction of labor in the study group might be associated with structural and molecular abnormalities of JZ in patients with endometriosis. Moreover, the progesterone resistance responsible for the reduced endometrial receptivity might interfere with the

complex molecular steps that lead to the withdrawal of progesterone's functions, which is needed to allow the labor [26].

Moreover, our analysis showed a correlation between endometriosis and some already reported pregnancy complications: nulliparity, placenta praevia and preterm labor.

The proportion of nulliparity was significantly higher in the following subgroups: DIE, non-DIE and A. These results on nulliparity are in agreement on literature evidence of subfertility associated with endometriosis. The reduction of fertility in women with endometriosis is linked not only to mechanical factors, like distortion of the tubes, or reduce egg quality due to inflammatory processes in the ovary and peritoneal fluid, but also to impaired endomyometrial environment.

Different studies have investigated the possible linkage between placenta praevia and endometriosis, and a higher incidence of placenta praevia has been demonstrated. However, most of the available data is on patients with endometriosis and ART pregnancies [27–29]. Interestingly, in our study, placenta praevia was significantly more frequent only in study group and in subgroup A, whereas all the other subgroups did not have. We believe that subgroup B and its control subgroup had similar incidence of placenta praevia for two possible reasons. One explanation is that the strength of ART as risk factor for placenta praevia might be greater than the endometriosis one. The other is that the average age among the controls of subgroup B is significantly higher and maternal age is one of the risk factor for placenta praevia.

Concerning placenta praevia and localization of endometriosis, Vercellini et al. have published a retrospective study on pregnancy outcomes in patients with spontaneous pregnancy after surgery for different sites of endometriosis [30]. Authors found that patients with ovarian endometriomas had no occurrence of placenta praevia, while women with DIE had a sixfold increase in risk when compared with all women with ovarian and peritoneal lesions. In our series, there was no significant difference in pregnancy outcomes between DIE and non-DIE subgroups and their relative controls. The different result in our study can be explained with the small number of DIE group ($n = 40$) compared with a wider subgroup of non-DIE ($n = 222$).

Finally, some retrospective studies have reported a correlation between endometriosis and preterm birth [27, 31]. Nevertheless, most of the studies that showed an increase incidence of preterm birth in endometriosis patients had subjects with both endometriosis and ART. A retrospective study on patients with diagnosis of endometriosis who conceived naturally reported no difference in the rate of preterm birth comparing with patients with no disease. On the contrary, Stern et al. found an increased incidence of preterm birth in patients with endometriosis without ART, while there was no increase rate in the endometriosis ART group [32].

This study has some limitations. First, the sample size was relatively small, especially in subgroups analysis. Second, data was collected retrospectively and there might be unforeseen bias. Finally, we were unable to ascertain data on factors, such as therapy during pregnancy for preterm birth, luteal support in the first trimester or prophylactic therapy to reduce the incidence of FGR e preeclampsia, which can influence adverse outcomes. Conversely, the strength of this study lies in the large numbers of variables studied. Moreover, we study separately the subgroup of women with ART pregnancies and/or twin pregnancies, leading to a clear understanding of the role of these confounding factors. Indeed, given that subgroup A had higher incidence of placenta praevia, ICP, induction of labor and preterm birth compared to its control subgroup, it could be said that endometriosis alone contributes significantly to these pregnancy complications. On the contrary, there was no difference in distribution of pregnancy complications between subgroup B and control subgroup. Lastly, there were no statistical differences in BMI and age between case–control groups and subgroup, removing confounding factors.

In conclusion, our results showed for the first time that women with endometriosis are at higher risk of developing ICP and experiencing an induced labor. Moreover, our study reported a higher incidence of placenta praevia, preterm delivery, nulliparity and previous miscarriages in patients with endometriosis. Interestingly our analysis did not register significant difference in the incidence of FGR, PIH, gestational diabetes, obstetrics hemorrhage and CS between case–control group and subgroups. Further studies are needed not only to assess the causes of these two new endometriosis associated complications and the reason underlying the wide variation in adverse pregnancy outcomes described in different studies, but also to clarify whether the history of endometriosis might be taken into account in the antenatal care of these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest. Authors state that they have had full control of all primary data and that they agree to allow the Journal to review their data if requested.

Research involving human participants and/or animals Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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