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ENDOMETRIOSIS: ORIGINAL ARTICLE

Endometriosis Increases the Risk of Placenta Previa in Both IVF Pregnancies and the General Obstetric Population

Eider Gómez-Pereira[1] · Jorge Burgos[2] · Rosario Mendoza[1] · Irantzu Pérez-Ruiz[1] · Fátima Olaso[1] · David García[1] · Iker Malaina[3] · Roberto Matorras[1,4]

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Abstract

Is there a relationship between endometriosis and placenta previa (PP)? To investigate if there is a relationship between endometriosis and PP, a retrospective study was carried out, using prospectively recorded data from two different databases from Cruces University Hospital. Two different populations were included in the study. The ART (assisted reproduction techniques) population consisted of 246 cesarean sections (CS), from a total of 1170 deliveries, and the obstetric population consisted of 7045 CS, from a total of 50,298 deliveries. A representative subset from the obstetric population was established selecting 4 CS without PP for each CS with PP. In our ART population, the PP rate was 1.71% among all deliveries and 8.13% among CS. In our general obstetric population, the PP rate was 0.34% among all deliveries and 2.41% among the CS. Among the CS in ART pregnancies, the PP rate was 20% in the women with endometriosis vs 5.47% in women without endometriosis (OR = 4.32; 95% CI = 1.67–11.17), while considering all ART deliveries, the PP rates were 6.43% and 1.07%, respectively (OR = 6.36; 95% CI = 2.59–15.65). In the CS-obstetric population, the rate of PP was 9.61% among women with endometriosis vs 2.19% among women without endometriosis (OR = 4.74; 95% CI = 2.91–7.73). Considering all deliveries, the PP rate was 1.35% among women with endometriosis vs 0.30% in women without endometriosis. Differences persisted when adjusting for age, IVF, multiplicity, and previous deliveries. In the CS-obstetric population with PP, mean surgical time and hospital stay were significantly higher in women with endometriosis. Endometriosis is associated with a higher risk of PP even after adjusting for other parameters.

Keywords ART · Cesarean section · Endometriosis · Placenta previa · Risk factors

Introduction

Endometriosis is an enigmatic disease which affects 4.5–33% of the infertile population [1–3]. Its main symptoms are pelvic pain, dysmenorrhea, and infertility, but a notable proportion of women with endometriosis is asymptomatic [4]. Although data are controversial, a number of autoimmune diseases have been linked to endometriosis, such as systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, rheumatoid arthritis, thyroid disorders, celiac disease, and inflammatory bowel disease [5–7].

In recent years, a number of authors have reported a new association, that of endometriosis with placenta previa (PP). PP is found in 0.4–0.5% of deliveries and is an important cause of antepartum/intrapartum hemorrhage with a risk of severe morbidity for the mother and fetus [8, 9]

Previous studies on the association of PP with endometriosis are based on national registers [10, 11] or self-complete questionnaires [10], or are retrospective studies of women with endometriosis who underwent surgery [12–16], or surgery or medical treatment [17, 18] IVF [19–22] or are focused on deep endometriosis [23, 24]. A number of these studies excluded multiple pregnancies [12, 14, 15, 19–21, 25]. PP was studied within the set of perinatal problems [10, 12, 13, 15–18, 22–25], but, as far as we know, no studies

✉ Irantzu Pérez-Ruiz
irantzuperez0@gmail.com

1 Reproduction Unit, Cruces Hospital, Biocruces Health Research Institute, Vizcaya, Spain

2 Obstetrics Service, Cruces Hospital, Biocruces Health Research Institute, Vizcaya, Spain

3 Applied Mathematics, Statistics, and Operative Research Department, University of the Basque Country, Biocruces Health Research Institute, Vizcaya, Spain

4 IVI, IVIRMA, Bilbao, Vizcaya, Spain

have focused exclusively on this problem. Indeed, the definition of PP was not explicitly established in a number of the aforementioned studies [10, 13, 18, 20, 21, 25]. One author included only completely occlusive PP [12, 15], while other studies included both totally and partially occlusive PP [16, 22–24]. Additionally, one study also included marginal placenta [25] and another low-lying placenta [14].

Since cases of low-lying and marginal PP in which vaginal delivery is possible are of little relevance, we have focused our study on PP requiring CS (that is, totally and partially occlusive PP and marginal PP requiring CS). Moreover, focusing our study on the CS population allowed us to perform a more efficient search and also to avoid a number of confounding factors related to both CS and PP such as age [20], multiparity [26], multiple pregnancy [20], and IVF [20, 27]. In the present study, we sought to investigate the association of endometriosis with PP, in the CS population, by two different approaches: (1) considering the ART population from our IVF center, the only public IVF center in our geographic area, and (2) considering the obstetric population from our Obstetrics and Gynecology Department. In addition, we analyzed the surgical outcome of the CS of women with PP with and without endometriosis, which previously had received little attention.

Material and Methods

We retrospectively analyzed two prospectively maintained databases to assess the frequency of PP in women diagnosed with endometriosis, compared with those not diagnosed with this condition. This study was carried out at the Human Reproduction Unit of Cruces University Hospital. Our Human Reproduction Unit was the only public ART Unit for a catchment population of about 2,200,000 until 2015, and from 2016 for 1,500,000. Our Obstetrics Department is the largest in our area, handling nearly 5000 deliveries every year, with a low CS rate [28].

The study sample is composed of two subgroups: the ART subgroup and the obstetric subgroup. The ART subgroup was made up of all the women who became pregnant by means of IVF (both fresh and frozen embryo transfers) at our unit and who subsequently had a CS (regardless of the center where it was performed), from 2010 to 2018 ($n = 255$). The obstetric subgroup was made up of all the women who had a CS managed by the Obstetrics and Gynecology Department between 2010 and 2018 ($n = 7045$). Data reported in databases corresponded to cesarean sections/deliveries. Thus in some cases, there was more that 1 delivery/cesarean section per woman ($n =$ not available).

The study project was approved by the Clinical Research Ethics Committee (CEIC) of Cruces University Hospital on 25 February 2020, with CEIC code E20/11.

ART Subgroup

Data were extracted from the ART database. This database is curated by a single biologist (RM), who prospectively enters, for each IVF cycle, the main clinical parameters (obtained directly from the medical history) as well as perinatal outcomes (obtained either directly from the obstetric charts from our hospital or from obstetric reports submitted by the patients, if the delivery took place in another center). The main indications for IVF were as follows: male factor infertility (54.4%), idiopathic infertility (16.2%), tubal factor (12.1%), endometriosis (9.1%), and ovulatory disorder (2.8%). The following indications represented < 1.5% each: low ovarian reserve, oocyte donation, recurrent miscarriage, medical condition in the mother, previous perinatal death, and vitrified oocytes.

In the ART subgroup, 1170 records were screened, corresponding to all the women (1030 without endometriosis and 140 with endometriosis) who became pregnant by assisted reproductive techniques who subsequently had a delivery of (at least) one infant > 24 gestational weeks between the years 2010 and 2018. Of them, the 255 histories corresponding to all the ART pregnancies who subsequently had a CS during the study period were reviewed by one researcher (EGP) (Fig. 1).

The diagnosis of endometriosis was established by laparoscopy in 80% (112/140) of cases. The endometriosis was staged in accordance with American Society for Reproductive Medicine guidelines [29]. Deep endometriosis was defined as invasion > 5 mm in depth. In the other 20% (28/140) of cases, the diagnosis of endometriosis was made by vaginal ultrasound according to established criteria [30], and it was required that the condition be documented on at least two occasions at least two menstrual cycles apart. Ureter, bladder, and bowel involvement was investigated by additional imaging if there was a suspicion based on history or physical examination of deep endometriosis [31]. Imaging usually started with ultrasonography [32] and was followed by magnetic resonance imaging (MRI). Adenomyosis was not considered a type of endometriosis. All control patients had at least two vaginal ultrasounds including those with no suspicion of endometriosis. In control patients with pelvic pain/severe dysmenorrhea, endometriosis was ruled out by laparoscopy.

For the purpose of the study, endometriosis diagnosed by ultrasound was considered advanced in the presence of endometriomas > 5 cm in diameter.

The diagnosis of PP was confirmed by transvaginal ultrasound in the 24–72 h immediately before CS. The 2014 PP classification was used, PP being diagnosed when the placenta totally or partially covered the internal os or just reached the margin of the internal os [33]. Cases

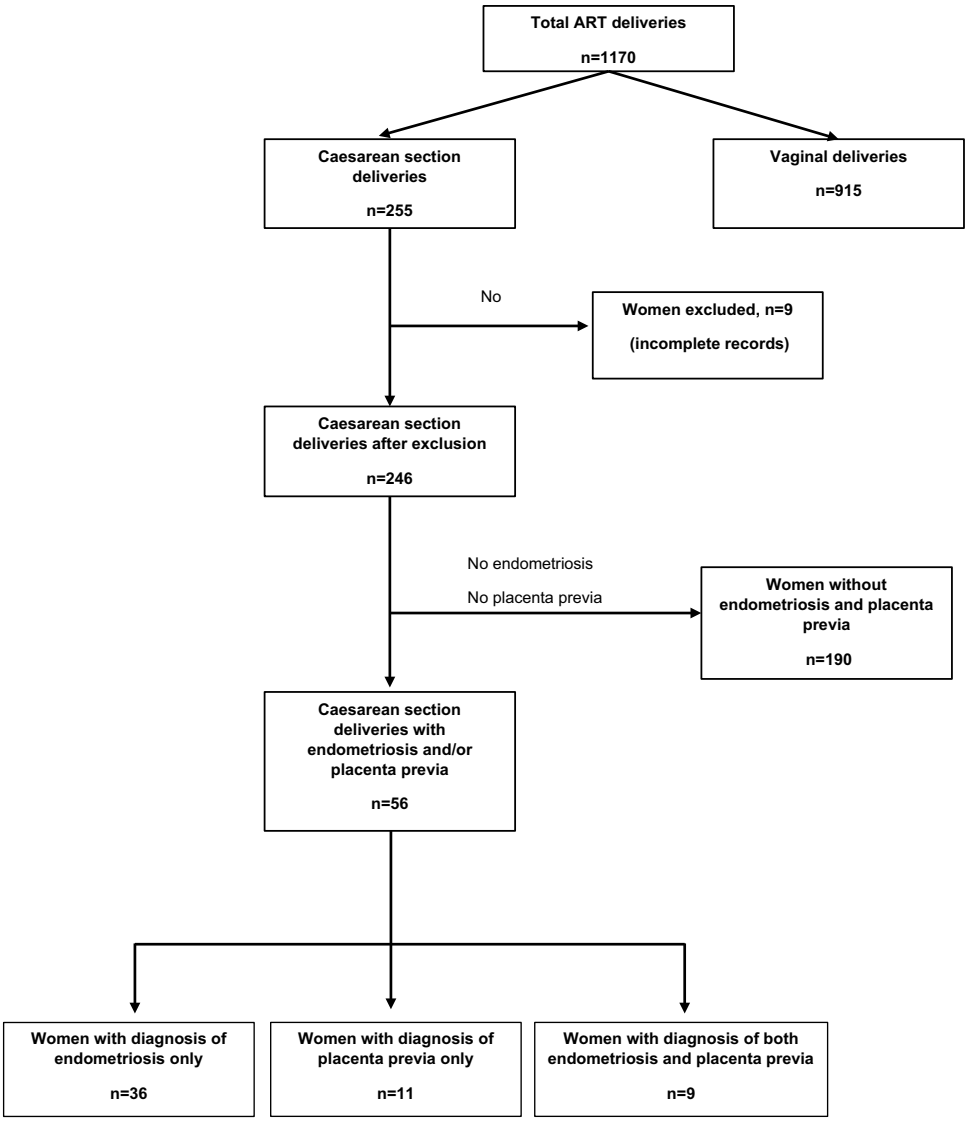

Fig. 1 Flowchart of the composition of the ART population

where the placenta edge was within 2 cm of the internal os were defined as low-lying placenta, and hence not included in our study [33]. Further, cases with a placental edge between 11 and 20 mm from the internal os in which the woman had a successful trial of labor were also excluded from the study.

The following data were collected for each of the patients: woman's age; presence of endometriosis, its stage, and whether deep endometriosis was observed; presence of PP, and if so, whether it was occlusive (total or partial) or marginal; previous pregnancies; the number of fetuses; and the birth weight and gestational age of the newborn.

The main characteristics of the ART CS population were mean maternal age 34.86 ± 3.29 years, 18.29% had a previous pregnancy, 3.25% had a previous CS, none of them by PP, and 21.1% were smokers.

Obstetric Subgroup

The obstetric subgroup was formed by the 50,298 deliveries that took place at Cruces Hospital's Obstetrics and Gynecology Service between 2010 and 2018. Data are entered into the obstetric database by the administrative personnel, after extracting specific numerical data from the electronic medical record as well as certain diagnostic codes. Coding and data entry are supervised by a staff gynecologist (JB).

Among these cases, we extracted all the 7045 that corresponded to women who underwent a CS during the study period (Fig. 2). This group was split according to whether the woman had PP or not. The PP group contained 170 women, and the other 6875 formed the control group. A representative subgroup in the control group was identified for manual review of the data. This subgroup was established by record number, selecting four controls not diagnosed with

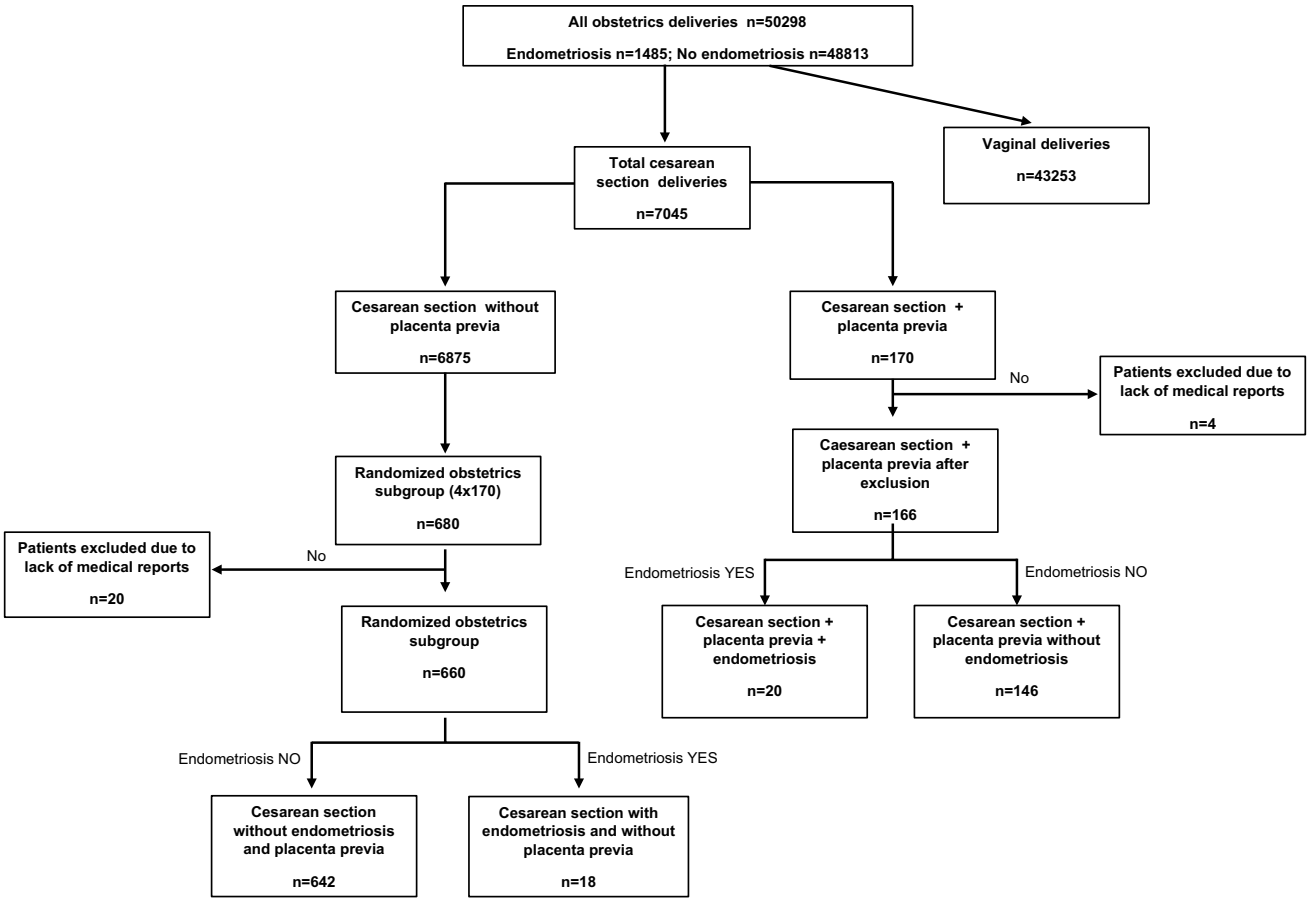

Fig. 2 Flowchart of the composition of the Obstetrics Department population

PP for each woman with PP (the two preceding and the two following each case of PP); the resulting control group contained $170 \times 4 = 680$ women. As in the ART subgroup, cases of low-lying placenta were excluded. Endometriosis stage was taken from our hospital records or from medical records from other centers. Patients were contacted in case additional medical reports were needed. The same types of data were collected from these records as in the ART subgroup. There were 29 cases which were included in both databases: 5 had endometriosis and PP, 3 had only endometriosis without PP, 4 developed only PP without endometriosis, and the other 17 had no diagnosis of either endometriosis or PP.

The main characteristics of the obstetric CS population were mean maternal age 32.53 ± 4.50 years, 35.69% had a previous pregnancy, 5.2% had a previous CS, none of them by PP, and 24.2% were smokers.

Endometriosis Management

Endometriosis management was not uniform during the study period. The management was different in the infertile population and pelvic pain population. In the infertile population, stages I–II did not receive excisional surgery and only adhesiolysis was performed. In the pelvic pain population, stages I–II were diagnosed by laparoscopy performed for this reason. In these cases, excision and adhesiolysis were performed.

In the infertile population, stages III–IV endometriosis were subjected to surgery only in case of endometriomas > 5 cm or/and if there was associated pain. Hydrosalpinges were excised. In the pelvic pain population, stages III–IV endometriosis were subjected to laparoscopic surgery. In our series, only five cases of deep endometriosis were treated with surgery.

Statistical Analysis

The quantitative variables were analyzed by comparing their means, with Student's *t* test and the analysis of variance. The possible association between the conditions under study was explored by calculating odds ratios (ORs) with their corresponding confidence intervals (CIs). The qualitative variables were analyzed with the χ^2 test. Stratified analysis

was performed to ascertain if PP and endometriosis were dependent parameters.

Results

Prevalence of PP

In our ART population, the PP rate was 1.71% (20/1170) among all deliveries and 8.13% (20/246) in the CS population. In our general obstetric population, the PP rate was 0.34% (170/50,298) among all deliveries and 2.41% (170/7045) in the CS population. The prevalence of PP was significantly higher in the ART population than the obstetric population, both in the CS subgroup (OR = 3.58; CI = 2.21–5.79) and among all deliveries (OR = 5.13; CI = 3.21–8.18) (Table 1). There were no cases of stillbirth associated with PP.

Endometriosis Staging

There were 45 cases of endometriosis (3 stage I, 4 stage II, 22 stage III, 16 stage IV, of which 9 were deep endometriosis) in the ART population and 38 (respectively, 3, 2, 16, and 17, of which 8 were deep endometriosis) in the obstetric population (20 in the CS + PP group based on the whole population and 18 in the randomized subset). There were 8 cases included in both databases. Deep infiltrating endometriosis ($n = 15$) was located in the rectum/sigmoid/pouch of Douglas in 7 cases, in the vaginal fornix in 4 cases, in the uterosacral ligament in 4 cases, and in the anterior compartment in 3 cases. Three of the cases presented more than 1 location.

Type of PP

Overall, 44.1% (82/186) of cases of PP were classified as totally occlusive, 21.5% (40/186) as partially occlusive, and 21.5% (40/186) as marginal. In 12.9% (24/186), the type was not documented.

Endometriosis and PP in the ART Group

Among the cases of CS in ART pregnancies, the PP rate in women with endometriosis was 20% (9/45) versus 5.47% (11/201) among those without endometriosis. The differences were statistically significant (OR = 4. 32; 95% CI = 1.67–11.17; $p = 0.0026$) (Table 1).

Considering all ART deliveries, the PP rate was 6.43% (9/140) in the endometriosis ART population vs 1.07% (11/1030) in the non-endometriosis ART population. The difference was again statistically significant (OR = 6.36; 95% CI = 2.59–15.65) ($p = 0.0001$).

In the CS population, the comparison of the main demographic and reproductive data in women with and without endometriosis and with and without PP is shown in Table 2. There were no statistically significant differences between any of the groups. The multiple pregnancy rate in women with endometriosis who had PP was 0% (0/9) whereas in those with endometriosis who did not have PP, it was 47.2%

Table 1 Prevalence of placenta previa in women with endometriosis in the ART population and the general obstetric population

	ART population			Obstetrics population		*p* value OR CI
PP rate/total number of deliveries	1.71% (20/1170)			0.34% (170/50,298)		$p < 0.0001$ OR = 5.13 CI = 3.21–8.18
PP rate/total number of CS	8.13% (20/246)			2.41% (170/7045)		$p < 0.001$ OR = 3.58 CI = 2.21–5.79
	Endometriosis	No endometriosis	*p* value OR CI	Endometriosis	No endometriosis	
PP rate/total number of deliveries	6.43% (9/140)	1.07% (11/1030)	$p = 0.0001$ OR = 6.36 CI = 2.59–15.65	1.35% (20/1485)	0.3% (146/48,813)	$p < 0.0001$ OR = 4.55 CI = 2.84–7.28
PP rate/total number of CS a	20% (9/45)	5.47% (11/201)	$p = 0.0026$ OR = 4. 32 CI = 1.67–11.17	9.61% (20/208)	2.19% (150/6837)	$p < 0.001$ OR = 4.74; CI = 2.91–7.73

CI confidence interval, *OR* = odds ratio

[a]For the obstetric population, denominators are based on total cesarean sections with placenta previa ($n = 170$) and those extrapolated assuming that the rate of endometriosis in the subgroup of cesarean sections without placenta and without endometriosis ($n = 660$) was the same as in the total population of cesarean sections without placenta previa and without endometriosis ($n = 7045$)

Table 2 ART population: demographic characteristics of women undergoing cesarean section by the presence/absence of placenta previa and/or endometriosis

	Placenta previa with endometriosis ($n=9$) (A)	Placenta previa without endometriosis ($n=11$) (B)	No placenta previa with endometriosis ($n=36$) (C)	No placenta previa, no endometriosis ($n=190$) (D)	p value (A vs. B)	p value (C vs. D)	p value (A vs. C)	p value (B vs. D)
Age (years) (mean ± SD)	34.00 ± 3.35	35.00 ± 3.49	34.08 ± 2.53	34.91 ± 3.42	0.53	0.09	0.95	0.94
Previous pregnancy (%)	11.11	9.09	19.44	18.95	0.88	0.95	0.56	0.41
Newborn weight (g) (mean ± SD)	2882.50 ± 316.58	2710.90 ± 554.37	2670.91 ± 674.18	2787.62 ± 773.98	0.41	0.36	0.19	0.67
Multiple pregnancy (%)	0	27.27	47.2	41.05	0.09	0.41	0.057	0.36
Gestational age at birth (weeks) (mean ± SD)	37.56 ± 1.33	36.54 ± 2.66	37.56 ± 2.86	37.28 ± 3.42	0.29	0.61	1	0.40

(17/36) ($p=0.057$). Given the small number of cases, we were unable to perform multivariate or regression analysis to isolate the effect of multiple pregnancy.

Endometriosis and PP in the Obstetric Group

In the CS population, the PP rate was 9.61% (20/208) among women with endometriosis and 2.19% (1504/6837) among women without endometriosis. The differences were statistically significant (OR = 4.74; 95% CI = 2.91–7.73) ($p<0.001$) (Table 1).

Considering all the deliveries, the PP rate was 1.35% (20/1485) among women with endometriosis vs 0.3% (146/48,813) in women without endometriosis.

In the CS population, the comparison of the main demographic and reproductive data in women with and without PP showed that in cases of PP, the mean age of the woman was higher, while newborn weight and gestational age were lower (Table 3). The percentage of women who had had a child was similar in the two populations.

Among CS in women with PP, the percentage of women who had had a previous pregnancy was significantly lower in the endometriosis group (19.0 vs 44.8%) compared with the no endometriosis group. The same occurred among the CS in women without PP (11.1% vs 36.5%) ($p=0.03$). The other parameters, including multiple pregnancy rate, were very similar.

Table 3 Obstetric population: demographic characteristics of women undergoing cesarean section by the presence/absence of placenta previa and/or endometriosis

	Cesarean section with placenta previa	Cesarean section without placenta previa [a]		Cesarean sections with placenta previa			Cesarean section without placenta previa		
	$n=166$	$n=660$	p value	Endometriosis ($n=20$)	No endometriosis ($n=146$)	p value	Endometriosis ($n=18$)	No endometriosis ($n=631$)	p value
Age (years) (mean ± SD)	36.33 ± 4.02	34.96 ± 4.62	0.0002	36.095 ± 5.195	36.365 ± 3.843	0.82	35.556 ± 3.535	34.94 ± 4.644	0.48
Previous pregnancy (%)	41.6	35.7	0.16	20.0	44.5	0.04	11.1	36.5	0.03
Newborn weight (g) (mean ± SD)	2877.41 ± 618.92	3094.29 ± 829.88	0.0002	3022.38 ± 604.09	2856.41 ± 620.27	0.25	2995 ± 498.38	3097.13 ± 837.48	0.41
Multiple pregnancy (%)	9.0	13.6	0.12	10	8.9	0.87	22.2	13.3	0.28
Gestational age at birth (weeks) (mean ± SD)	36.86 ± 2.49	38.28 ± 3.11	< 0.0001	37.523 ± 2.562	36.766 ± 2.47	0.21	38.833 ± 1.505	38.267 ± 3.145	0.15

[a]A randomized subgroup of four cesarean sections without placenta previa per cesarean section with placenta previa selected from the total obstetric population

Stratified analysis showed that a history of pregnancy and PP were independent parameters ($\chi^2 = 1.92$; $p = 0.1657$). The same analysis showed that PP and endometriosis were dependent parameters ($\chi^2 = 28.30$, $p < 0.00001$).

Surgical Outcome of Women Undergoing Cesarean Section for PP With and Without Endometriosis (Obstetric Group) (Table 4)

The mean operative time was significantly longer in CSs performed by PP in women with endometriosis (47.8 ± 9.6 min) compared to those performed in women without endometriosis (41.3 ± 8.5 min). Among surgical complications, only one case was reported, corresponding to a bladder injury requiring 10-day bladder catheterization, which occurred in a woman with endometriosis. There were no cases of hysterectomy in either population. The frequency of intraoperative hemorrhage, defined as such by the gynecologist who performed the CS, was 15.0% in women with endometriosis vs. 4.1% in women without endometriosis ($p = 0.06$). The proportion of women with a hospital stay of more than 4 days was significantly higher in the endometriosis population (20.0 vs 4.8%) ($p = 0.02$).

Severity of the Endometriosis and PP Rate

In the ART group, the PP rate was 0% (0/7) in stages I–II vs 23.68% (9/38) in stages III–IV. The OR was 0.20 (CI = 0.01–3.97) ($p = 0.29$). The PP rate in deep endometriosis was (44.44%, 4/9) compared with 13.89% (5/36) in non-deep endometriosis (OR = 4.96; CI = 0.98–25.04) ($p = 0.053$).

In the obstetric group, the PP rate was 60% (3/5) in stages I–II vs 51.52% (17/33) in stages III–IV. The OR was 1.41 (CI = 0.20–9.58) ($p = 0.77$).

The rate of PP in deep endometriosis was 25.0% compared with 60% (18/30) in non-deep endometriosis (OR = 0.22; CI = 0.04–1.29) ($p = 0.09$).

Discussion

PP, a condition present in 0.4–0.5% of deliveries [8, 9], is associated with a number of complications, among them, hemorrhage, CS, emergency hysterectomy, disseminated intravascular coagulation, placenta accreta, and massive bleeding. PP has also been associated with brain damage and cerebral palsy in the fetus [8, 34]. The classical risk factors for PP include uterine surgery, a history of CS, multiple pregnancy, IVF, multiparity, and a history of PP [35].

In recent years, a number of reports have indicated an association between PP and endometriosis. Previously reported ORs range from 1.6 [14] to 13.3 [36] and 15.1 [22]. In a meta-analysis, the OR was 6.8 for naturally conceived pregnancies, 3.33 for ART pregnancies, and 3.31 for combined natural conception and assisted reproduction [37]. In another meta-analysis, the unadjusted OR was 3.63 and the adjusted OR was 3.17 [38].

The difficulty of assessing the exact prevalence of PP has been highlighted previously [9]. On the one hand, until 2014, the definition of PP included low-lying placenta. Nonetheless, this condition was often not included, as it usually does not have major obstetric implications. On the one hand, facility-based studies may overestimate PP rate because of referral patterns [9]. On the other hand, population-based studies are more likely to lack detailed information on the grade of the PP, and many of them restrict the denominator to live births, excluding cases of stillbirth in the presence of PP [9].

Our study has some strengths. First of all, we employed two different databases, the general database of the Obstetrics Department and one for women undergoing ART, the relative risks obtained in each of them being very similar. Secondly, the definition used for PP was the same for all the populations studied. Moreover, all the data were reviewed by the same researcher. Finally, we have performed our study in the CS population since delivery is by CS in almost all cases of clinically relevant PP. In this way, cases of low-lying placenta, which do not have major obstetric implications, do not distort the results. On the other hand, selecting only

Table 4 Surgical outcome of women undergoing cesarean section for placenta previa with and without endometriosis

Cesarean section	Placenta previa with endometriosis ($n = 20$)	Placenta previa without endometriosis ($n = 146$)	p	OR (95% CI)
Surgical time (min) (mean ± SD)	47.8 ± 9.6	41.3 ± 8.5	0.002	nc
Intrapartum hemorrhage (%)	15.0 (3/20)	4.1 (6/146)	0.06	4.12 (0.94–17.99)
Transfusion (%)	5.0 (1/20)	2.7 (4/146)	0.58	1.87 (0.20–17.60)
Bladder injury (%)	5.0 (1/20)	0.0 (0/146)	0.06	22.54 (0.89–572.82)
Hospitalization time > 4 days (%)	20.0 (4/20)	4.8 (7/146)	0.02	4.96 (1.31–18.83)

nc not calculable

CS allowed us to perform a more efficient search of patient characteristics in the databases. Stages I–II of endometriosis were managed differently in the fertile and infertile population, and this could represent a weakness in the inclusion criteria. However, since this criterion was the same for PP and non-PP populations, it should not differentially affect the results.

Unlike most previous studies, our study focused specifically on PP and endometriosis, and several parameters were analyzed in detail, such as type of PP, stage of endometriosis, age of patients, performance of ART, newborn weight, gestational age, multiple pregnancy, previous pregnancies, and surgical outcome.

The prevalence of PP was much higher in the ART group than in the obstetric group, both when considering only CS and when including all deliveries. This is in agreement with ART being a risk factor for PP, as previously published [20, 27].

Nonetheless, when considering only the ART-CS subgroup, the prevalence of PP was much higher in endometriosis patients than in women without endometriosis (OR = 4.32; 95% CI = 1.67–11.17). Notably, considering all deliveries, the pattern was similar, the OR being even higher (OR = 6.36; CI = 2.59–15.65).

Further, analyzing the obstetric subgroup, a similar pattern was observed. The OR for PP among women with endometriosis was 4.89 (CI = 2.52–9. 4) in the CS population and 3.9 (CI = 2.45–6.23) considering all deliveries.

Our multivariate analysis in the obstetric population showed that the PP-endometriosis association was not explained by confounding factors considered, namely, age, multiple pregnancy, previous pregnancies, gestational age, and newborn weight. Moreover, in the ART group, the analysis of the mentioned parameters did not differ significantly between women with and without endometriosis or PP. Further, we did not find the PP rate to be associated with the stage of endometriosis, unlike other authors [12, 15, 18, 22]. Nonetheless, we cannot rule out their influence given the relatively small number of cases in each stage. The association of PP with deep endometriosis has been previously reported [23, 24]. In our study, the comparison of PP rates with the other stages of endometriosis was hampered by the relatively small number of deep endometriosis cases. Our study did not take into account the presence of adenomyosis, which can be associated to endometriosis [39, 40]. However, in three previous studies, adenomyosis was not reported as a risk factor of PP [41–43]. In one of them, PP was found to be associated with endometriosis but not with adenomyosis [44].

In our study in the ART population, all the control pregnancies and all the endometriosis pregnancies resulted from IVF treatment. Thus, it was concluded that in the ART population, endometriosis was a PP risk factor independent from ART. However, the obstetrical population included both ART and non-ART pregnancies, and from our data, it was not possible to ascertain the risk of PP associated to endometriosis in the women achieving pregnancy without ART.

A number of mechanisms could be responsible for the higher prevalence of PP in women with endometriosis. Some are related to differences in the endometrium between women with endometriosis and healthy women regarding invasiveness, apoptosis, genes and proteins involved in cell proliferation and differentiation, and steroid and cytokine production [44–47]. Further, women with endometriosis have been reported to have impaired development of uterine spiral vessels [7] and increased uterine contractility [48] that could also play a role in the higher PP rate. The peritoneal microenvironment contains immune cells, endometrial cells, and red blood cells, which produce and secrete growth factors, angiogenic factors, adhesion molecules, extracellular matrix metalloproteinases, and cytokines [49, 50] that may promote conditions for differentiation, adhesion, proliferation, and survival of ectopic endometrial cells, pivotal in the pathogenesis of endometriosis [51, 52]. In addition, a different pattern in proinflammatory and profibrotic macrophages has been reported in advanced-stage endometriosis [53]. Moreover, several reports have described a different microbiome pattern in women with endometriosis, which could, in turn, modulate the immune response [54, 55]. New theories on the pathogenesis of endometriosis have proposed that many of the above conditions could play a role in it [53, 54, 56]. In our opinion, they may also affect endometrial implantation and alter the development of the placental vascular framework. We suggest an additional mechanism, related to uterine position. Notably, in endometriosis, uterine retroversion is a common finding [4]. Therefore, it can be speculated that such distorted uterine anatomy leads to a higher rate of abnormal implantation. In a recent report employing magnetic resonance imaging, a high rate of retroverted cervix was observed in PP, especially when there were posterior adhesions [57].

Complications of labor in patients with endometriosis have received little attention. A recent meta-analysis reported that there was no study that examined the surgical outcomes of patients with endometriosis developing PP [38]. A study of 28 women with deeply infiltrating endometriosis undergoing CS (including 7 with PP) reported a 7.1% rate of hysterectomy and hemoperitoneum and a 7.1% rate of bladder injury [23]. Similar rates of postpartum hemorrhage after CS in women with endometriosis undergoing CS (with and without PP) have been reported in one study [11]. In another study while univariate analysis showed an increased risk of postpartum hemorrhage for women with endometriosis, such increased risk disappeared in the multivariate analysis [17].

In our study, the mean operative time was significantly longer in PP with endometriosis compared to those

without endometriosis. Postoperative length of stay was also significantly longer. Two non-exclusive mechanisms can be proposed: (i) PP with endometriosis could be more adherent or pose more surgical difficulties and (ii) compared to women without endometriosis, the higher rate of pelvic and parietal adhesions could lengthen surgery. The tendency to a higher rate of surgical bleeding could speak in favor of the first mechanism, while the tendency to a higher rate of surgical injury to the second.

We conclude that endometriosis is a notable risk factor for PP, which is independent of IVF, age, previous pregnancies, and multiplicity. It was not possible to ascertain whether the aforementioned risk was due to endometriosis itself, to the conditions prompting the development of endometriosis in a woman, or to the treatments applied against endometriosis or to confounding not considered in our study (such as adenomyosis). The absolute risk for PP in ART pregnancies in women with endometriosis was around 6%, and it should be borne in mind in the follow-up of ART pregnancies in women with endometriosis. On the other hand, women with PP who underwent CS and had endometriosis had a longer surgical time and a longer hospital stay than those without endometriosis.

In the future, prospective studies should be designed to look for biomarkers that predict which patients with endometriosis are more likely to develop PP. Other fields to be explored would be the assessment of the impact of the release of periuterine adhesions as well as the possible periconceptional pharmacological approach.

Author Contribution E Gómez-Pereira: data collection and management, protocol development, data analysis, and manuscript writing. J Burgos: data collection and manuscript editing. R Mendoza: data collection and manuscript editing. I Pérez-Ruiz: data analysis and manuscript writing and editing. D García: data collection and management and manuscript editing. F Olaso: data collection and management and manuscript editing. I Malaina: data analysis and manuscript editing. R Matorras: protocol and project development and manuscript writing and editing.

Data Availability Available upon request.

Code Availability Not applicable.

Declarations

Ethics Approval The study project was approved by the Clinical Research Ethics Committee (CEIC) of Cruces University Hospital on 25 February 2020, with CEIC code E20/11.

Consent to Participate Informed consent was obtained from all patients for being included in the study (CEIC E20/11).

Consent for Publication As above.

Conflict of Interest The authors declare no competing interests.

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