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# Pregnancy outcomes after in vitro fertilization for moderate and severe endometriosis. A case-control study

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## A B S T R A C T

**Introduction:** Previous international studies showed that endometriosis could have a link with obstetrical complications, as an increased risk of preterm birth, gestational diabetes mellitus, and cesarean section. However, the results are difficult to interpret because biases are common, such as heterogeneity in the severity of the endometriosis cases included. That's why some complications as risk of miscarriage and post-partum hemorrhage are still debated. Our objective was to study pregnancy outcome after In Vitro Fertilization (IVF) in women suffering from rAFS stage III and IV endometriosis.

**Methods:** We conducted a case-control study between 2009 and 2019. We compared pregnancy outcomes after IVF in two groups of women matched by age, body mass index and smoking in two hospital centers. Group A was constituted by singleton pregnancies following ART for moderate and severe endometriosis (rAFS stage III and IV endometriosis). Group B was composed of singleton pregnancies in women with no endometriosis following ART for another reproductive disease. All women achieved pregnancy after 22 weeks.

**Results:** A total of 240 pregnant women were included: 80 singleton IVF pregnancies (group A) were compared with 160 singleton IVF pregnancies (group B). We observed an increased risk of placenta previa (12.5% Vs 1.9%;  $p = 0,001$ ), and cesarean section (49.4% ( $n = 39$ ) Vs 29.6% ( $n = 47$ )  $p = 0,004$ ). Rate of postpartum hemorrhage was not significantly different in endometriosis group (11.2% Vs 7.5%  $p = 0.47$ ).

**Conclusion:** Despite conflicting results in literature due to a lot of confounding variables, the impact of endometriosis on pregnancy is still debated in women suffering from rAFS III and IV endometriosis. In our study, we observed statistically higher rates of placenta previa and cesarean section but not an increased risk of postpartum hemorrhage. Further larger series are needed to confirm our findings and a possible link with other obstetrical complications. However, we think that an ART pregnancy in a context of severe endometriosis should be considered at risk of adverse obstetrical outcomes.

## Keywords:

Endometriosis  
Assisted reproductive technologies  
In vitro fertilization  
Pregnancy outcome  
Postpartum hemorrhage

## Introduction

Endometriosis is a pelvic disease that affects 6 to 15% of women worldwide [1]. Endometriosis is defined by ectopic endometrial tissue and is often responsible of pelvic pain and infertility. The eutopic endometrium of women with endometriosis has shown molecular and cellular alterations that are believed to alter pregnancy outcome in these women [2]. All ART pregnancies could be considered at higher risk of adverse outcome [3].

Moreover, some studies have reported an increasing risk of unfavorable pregnancy outcome in women with endometriosis such as preterm birth, small for gestational age (SGA), preeclampsia and cesarean section rate [4,5]. In contrast, some other studies did not show higher risk of preterm birth even with a significant sample size [2]. These observations confirm difficulty to obtain homogeneous population and reproducible results. If endometriosis seems to be associated with more obstetrical complications, it is unclear if obstetrical complications depend of endometriosis stage. In most studies, all endometriosis stages are included, leading to heterogeneity of the studied population. Some studies compared pregnancy outcomes of women with endometriosis conceived by ART with those who conceived naturally.

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In endometriosis, chronic inflammation leads to a rise of inflammatory cytokines like interleukins (IL) and tumor necrosis factor alpha (TNF $\alpha$ ) in peritoneal tissue. IL1 and TNF $\alpha$  have an effect on myometrium receptors and could induce uterine contractions [6,7]. This situation may explain more threatened preterm labor in pregnant women with endometriosis [8]. Likewise, more women suffering from several endometriosis may have increased internal bleeding. Endometriosis located at the level of the uterine isthmus may weaken the posterior uterine wall, predisposing it to uterine rupture during pregnancy or postpartum hemorrhage [9]. Most studies support the idea that dysfunctional critical uterine changes during implantation process can trigger a defective process of decidualization and placentation, with a cascade of events resulting in defective remodeling of the spiral arteries [10].

The main objective of our study was to assess obstetrical complications, in women with stage III and IV endometriosis who conceived following IVF.

## Materials and methods

### Studied population

In our study, only stages III and IV endometriosis were included, according to the revised American Society for Reproductive Medicine (rASRM) classification of 1997 [11]. Women's data concerning IVF pregnancy and neonatal outcome were collected retrospectively from medical database between 2009 and 2019 in two Departments of Gynecology-Obstetric and Reproductive Medicine of two Public Hospitals. Two groups of pregnant women between 18 and 42 years with a history of infertility > 12 months and pregnant after IVF or ICSI were constituted: group A was constituted by women pregnant following IVF for rASRM stage III and IV endometriosis Vs Group B of IVF pregnant women with no endometriosis. We also excluded ART pregnant women after intra-uterine inseminations, gametes donation, and embryo transfer from vitrified oocytes. Twin pregnancies were excluded. A personal phone call was performed to every woman in order to collect their oral and written consent to participate to the study and to complete obstetrical or neonatal information when needed. We excluded all women who didn't consent to participate to the study and women who didn't understand French well enough to give their consent.

For group A, diagnosis of endometriosis was established during a laparoscopic exploration and/or Magnetic resonance imaging (MRI), as previously described [12]. Data from MRI were available for most women in order to determine deep infiltrating endometriosis combined (DIE)). Group B was the control group composed by women without endometriosis and who underwent IVF during the same period as women from group A. For each group, we included both pregnancies obtained after fresh embryo transfer (ET) and those obtained after frozen-thawed embryo transfer (FET). Transferred embryos were 2, 3 or 5 days embryos. All supernumerary good quality embryos were frozen with a slow-freezing program at Day 2, 3 or 5. Among pregnancies of more than 22 weeks of gestation, groups A and B were paired 1:2 for exploration of pregnancy outcomes.

### Studied parameters

Concerning women's clinical characteristics, we collected age, body mass index (BMI) and smoking status. Smoking status was considered as an active smoking status for one or more cigarettes per day. IVF or ICSI was decided according to sperm parameters. Abnormal sperm parameters included oligospermia (<39 million spermatozoa per ml of semen), asthenozoospermia (<50% of mobile sperm), and teratozoospermia (<4% with normal morphology). We defined a positive pregnant test as a positive level of hCG 14 days after ET. A clinical ongoing pregnancy was defined by an embryo with a cardiac

activity at 8 weeks of gestation (WG). Secondly, we collected obstetrical diseases during pregnancy after 22 weeks of gestation: placenta previa, placental abruption.

Placenta previa was defined by a placenta implant in the lower segment of the uterus unless 20 mm of cervix. Concerning obstetrical and neonatal outcomes, we collected gestational age at delivery (gestational weeks), rate of postpartum hemorrhage (PPH) (defined as bleeding < 500 mL after delivery), rate of cesarean section, birth weight and neonatal hospital admission for each baby.

### Outcome measures

Primary outcome measure was all obstetrical complications at delivery considered together (PPH, placenta previa, placental abruption and cesarian section). Secondary outcomes were rate of postpartum hemorrhage, rate of placenta praevia, rate of cesarian section, gestational age at delivery and neonatal hospitalization rate.

### Statistical methods

Descriptive data were expressed as counts and percentages for qualitative variables, and as means and standard deviations (SD) for continuous variables. The search for association between two independent variables was done using the  $\chi^2$  test for homogeneity, the FISHER's exact test for qualitative variables, the Student's *t*-test for two independent groups for the comparison of continuous variables, with the determination of significance thresholds at 0.05.

We performed univariate and multivariable analyses. Variables in the univariate analysis with  $p < 0.20$  were introduced in the multivariable regression model. A backward selection method was performed with an alpha significance level of 0.05 (both for entry and retention). The results are shown as odds ratios (ORs) with 95% confidence intervals (CIs). The matching of case and control cases was performed using greedy matching (1:2 nearest neighbor) [13] from three criteria: age, BMI and smoking status. The statistical analysis was performed using the software IBM SPSS Statistics V20.0.0. Bergstralh, EJ and Kosanke JL (1995); Section of Biostatistics Technical Report 56. Mayo Foundation.

### Ethics statement

This study was approved by the Ethical Committee of Aix-Marseille University (2017-05-04-005).

## Results

### Study population

We included 240 women who achieved pregnancy after IVF or ICSI: 80 singleton pregnant women after IVF for severe endometriosis (group A) were compared with 160 IVF singleton pregnancies in women with no endometriosis (group B). The two groups were comparable in terms of age, BMI and smoking status and rates of fresh or frozen embryo transfers were comparable among the two groups, and so were gestational age at delivery and birth weight (Table 1). All women achieved pregnancy after 22 WG. Concerning type of ART, 66 women received IVF (82.5%) in group A Vs 88 women (55%) in group B ( $p < 0.001$ ). Conversely, more group B women had undergone ICSI ( $n = 72$ , 45%) than patients suffering from endometriosis ( $n = 14$ , 17.5%). Moreover, we observed no difference between fresh and frozen ET in the two groups ( $p = 0.42$ ) (Table 1).

### Endometriosis features

In population with several stages of endometriosis, 65 (81.2%) women underwent surgery in order to diagnose or treat peritoneal

**Table 1**  
Pregnancy outcomes after IVF for moderate and severe endometriosis: women's characteristics.

	Group A IVF for severe endometriosis n = 80	Group B IVF without endometriosis n = 160	p-Value
Age (years)	32.8 ± 3.8	32.8 ± 3.8	1.00
BMI (kg/m <sup>2</sup> )	21.9 ± 3.6	21.9 ± 3.6	0.98
Active smoking habits (%)	30 (37.5)	60 (37.5)	1.00
Type of ART	66 (82.5)	88 (55.0)	<0.001
- IVF (%)	14 (17.5)	72 (45.0)	
- ICSI (%)			
- Fresh embryo transfer (%)	64 (80.0)	120 (75.0)	0.42
- Frozen embryo transfer (%)	16 (20.0)	40 (25.0)	
Gestational age at delivery (WG)	39.0 ± 2.6	39.1 ± 2.1	0.94
Birth weight (g)	3050.6 ± 641.4	3114.3 ± 559.9	0.43

Values are presented as Mean ± SD or numbers (%). P-value less than or equal to 0.05 was considered as statistically significant. BMI, body mass index; WG, weeks' gestation. ART, assisted reproductive technology. IVF, In vitro fertilization. ICSI, intra cytoplasmic sperm injection.

and ovarian lesions of endometriosis. Surgical managements included resection, ablation or drainage of ovarian endometrioma, deep infiltrating endometriosis ablation and bowel surgery. Although rASRM classification is defined by a laparoscopic assay, we considered that the MRI evaluation is effective for diagnosing severe endometriosis when performed by experienced radiologists [14].

#### Obstetrical outcomes after 22 WG

Analysis of primary outcomes showed that postpartum hemorrhage rate was not higher in endometriosis group (11.2% (n = 9) versus 7.5% (n = 12), p = 0.47) (Table 2). Group A had an increased risk of placenta praevia with 12.5% (n = 10) Vs 1.9% (n = 3), in group B (p < 0.001) (Table 2). The cesarean section rate was increased in group A (49.4% (n = 39)) Vs group B 2 (9.6% (n = 47)) (p = 0.004). Neonatal hospitalization rate was similar in group A (22.1% (n = 17)) and in group B (14.7% (n = 21), (p = 0.19)) (Table 2). Multivariate analysis of risk factors associated to all obstetrical outcomes considered together (PPH, placental abruption (RPH), PP and cesarean section), were endometriosis ([adjusted OR] 2.47, CI95% [1.38–4.44], p-value 0.002), BMI ([OR] 1.15, CI95% [1.06–1.25], p-value < 0.001) and gestational age at delivery ([OR] 0.78, CI95% [0.68–0.90], p-value 0.001) (Table 3).

#### Discussion

In our study, 80 singleton IVF pregnancies (group A) were compared with 160 singleton IVF pregnancies (group B). We observed an increased risk of placenta praevia (12.5% Vs 1.9%; p = 0,001), and

cesarean section (49.4% (n = 39) Vs 29.6% (n = 47) p = 0,004). Rate of postpartum hemorrhage was not significantly different in endometriosis group (11.2% Vs 7.5% p = 0.47).

Decreased fertility observed in women suffering from endometriosis has been suggested to be due to several pathogenic consequences of this gynecological disease: e.g., mechanical defects, chronic inflammation and ovarian dysfunction [15,16]. Moreover, structural changes in the junctional zone including abnormal remodeling of spiral arteries may cause deficient deep placentation, therefore increasing risk of adverse pregnancy outcomes [15]. In our retrospective cohort study, we decided to only include women with moderate and severe endometriosis (rASRM stage III and IV) who was matched by age, BMI and smoking statue to control group (Table 1). We excluded twin pregnancies that are associated with their own adverse pregnancy outcomes, as compared to single pregnancies [17]. We observed a higher rate of adverse obstetrical outcomes in singleton IVF pregnancy in women with moderate and severe endometriosis, namely placenta praevia and cesarean section (Table 2). In agreement, the meta-analysis of Breintoft *et al.* also reported evidence highlighting the association of endometriosis and placenta praevia, cesarean section but also preeclampsia, gravidic hypertension, placental abruption, and stillbirth [18]. Interestingly, in agreement with our findings, results of this meta-analysis didn't show a significant risk of PPH. However, our study presents two major limitations: with a retrospective study of a small sample size. Moreover, we acknowledge the fact that it cannot be excluded that patients in the control group may have had asymptomatic endometriosis; they did not undergo MRI. Nevertheless, the precise potential biological mechanisms underlying any differences between symptomatic and asymptomatic endometriosis, remain poorly characterized [19].

Our study presents several strengths: we only included stages III and IV endometriosis and our two study groups were matched according to maternal characteristics in order to assure comparability. In an effort to study association of obstetrical outcomes with endometriosis as an independent factor not influenced by ART, we compared IVF-pregnancies with or without endometriosis. Importantly, our results agree with previously published data.

Several mother-child morbidities associated with endometriosis are still subject to debate, mainly due to heterogeneity in the design and populations of these studies. For instance, an increased rate of miscarriage in deep and ovarian endometriosis group has been reported, but authors didn't compare miscarriage rate to a control group without endometriosis [20]. While, Santulli *et al.* also found an increased rate of spontaneous miscarriages in endometriosis women [21], a recent retrospective cohort study of 1006 women with endometriosis, showed that the risk of miscarriage did not statistically increase in women with endometriosis who achieved pregnancy through IVF fresh cycles. The miscarriage rate between women with and without endometriosis was similar [22]. These observations showed that the difficulties to conclude on links between endometriosis and obstetrical morbidity.

Previous studies have reported impact of endometriosis on late pregnancy outcome, and have often described an increased risk of premature birth. However, this outcome also remains controversial.

**Table 2**  
Obstetric and neonatal outcomes after IVF for moderate and severe endometriosis: main results.

	Group A IVF for severe endometriosis (n = 80)	Group B IVF without endometriosis (n = 160)	p-value	Odds ratio	95% CI
Placenta praevia	10 (12.5)	3 (1.9)	<b>0.001</b>	7.4	1.9–28.0
Placenta abruption	2 (2.5)	3 (1.9)	1.00	1.3	0.2–8.2
Postpartum hemorrhage	9 (11.2)	12 (7.5)	0.47	1.5	0.6–3.9
Cesarean section	39 (49.4)	47 (29.6)	<b>0.004</b>	2.3	1.3–4.0
Neonatal hospitalization	17 (22.1)	21 (14.7)	0.19	1.6	0.8–3.3
Complications (PPH, PP, RPH, CS)	44 (5.0)	57 (35.6)	0.004	2.2	1.27–3.81

Values are presented as numbers (%). P-value less than or equal to 0.05 was considered as statistically significant.

**Table 3**  
IVF for moderate and severe endometriosis: risk factors of adverse obstetrical outcome.

Variable	Univariate			Multivariate		
	Complication yes	Complication no	p-value	p value	Adjusted Odds ratio	95% CI
Endometriosis	44 (55.0)	57 (35.6)	0.004	0.002	2.47	1.38 - 4.44
Tobacco	40 (39.6)	50 (36.0)	0.5	–	–	–
IVF	66 (65.3)	88 (63.3)	0.7	–	–	–
Maternal age (years)	33.14±3.59	32.62 ± 3.97	0.29	–	–	–
BMI (kg/m <sup>2</sup> )	23.32±4.18	21.68±3.02	0.001	< 0.001	1.15	1.06 - 1.25
Gestational age at delivery (WG)	38.48 ± 3.05	39.51 ± 1.53	0.002	0.001	0.78	0.68 - 0.90
Birth weight (g)	3080.53± 759.84	3102.46±419.62	0.79	–	–	–

Values are presented as Mean ± SD or numbers (%). IVF, in vitro fertilization; BMI, body mass index; WG, weeks' gestation.

During our study, in accordance with the retrospective study of Benaglia *et al.* [2] we didn't observe a higher risk of preterm delivery < 37 weeks of gestation (Table 1). Conversely, the national Swedish cohort study of Stephansson *et al.*, including 1 442 675 singleton live-births with 13 090 singletons born from 8 922 women diagnosed with endometriosis found a higher risk of preterm birth, antenatal bleeding, preeclampsia and cesarian section [23]. After having stratified their statistical analysis, they found that the risk of preterm birth was lower among ART-pregnancies Vs spontaneous pregnancies. Other studies have also reported an increased risk of preterm birth in singleton ART pregnancies obtained in women with endometriosis [18,5]. Two studies have addressed the relationship between adenomyosis and pregnancy outcome. Adenomyosis could be associated with an increased risk of preterm birth and premature rupture of membranes [24,25]. However, to our knowledge, no studies have yet considered association between endometriosis and adenomyosis as a possible confounding factor. Despite placental complications seem more frequently observed in pregnancies with endometriosis, several studies didn't find a relationship between endometriosis and preeclampsia [26,27].

In most studies, placenta previa would be more frequent in endometriosis pregnancies. Vercellini *et al.* reported an influence of deep infiltrative endometriosis on obstetrical outcome. They observed most placenta previa when endometriosis was located at the level of the uterine isthmus [20]. Several retrospective cohort studies reported that endometriosis increased risks of placenta previa [2] and preterm labor [26]. The prospective cohort study of Harada *et al.* found an increased risk of placenta praevia and PROM [28] among 330 women with history of endometriosis but only 29 women had received ART therapy with 16 IVF and 13 ICSI, making it difficult to conclude. The retrospective cohort study of Fujii *et al.* also suggested a correlation between endometriosis stages and adverse outcomes during the second and third trimester of ART- pregnancies. They found a high risk of preterm birth and placenta previa in women with endometriosis rASRM stage IV [29]. Also, the retrospective cohort study of Farella *et al.* reported that placenta previa was associated with history of stage III and IV endometriosis in ART-conceived pregnancies [30]. Concerning neonatal morbidity associated to endometriosis, Fernando and *al.* reported that preterm birth and SGA rates were increased in case of endometriomas [4]. Stern and *al.* observed only a higher rate of prenatal hospitalizations and not a higher rate of preterm delivery or SGA in endometriosis with ART group [3]. Conversely, two authors didn't observe a significant risk of obstetrical complications in pregnant women with endometriomas [31,32]. In our study, there was no difference between fresh and frozen ET in the two groups ( $p = 0.42$ ). However, in a large Nordic Study, Wennerholm *et al.* (2013) showed that singletons conceived after frozen ET had reduced low birth weight, more preterm birth, and SGA [33]. Despite the absence of any suitable randomized trials without bias, a systematic review of observational studies suggested that singleton pregnancies resulting from frozen ET were associated with lower obstetric and perinatal morbidity. The meta-analysis of Maheshwari

*et al.* showed that singleton pregnancies after transfer of frozen embryos were associated with better perinatal outcomes compared with those after fresh IVF embryos [34]. The study of Rombauts *et al.* showed that perinatal outcome wasn't linked to the type of embryo transfer (fresh/frozen) but to the type of endometrial preparation, and suggested that the risk of placenta praevia in ART could be reduced by considering an elective frozen embryo transfer in a natural cycle, supported by growing evidence that this may provide several maternal and neonatal benefits [35].

Recently, the French longitudinal national study of Epelboin *et al.* showed that endometriosis is an independent risk factor for several obstetrical and neonatal pathologies, for which ART may additionally affect endometriosis by increasing risk of placenta previa, prematurity and small for gestational age [36]. Our study, contributes to the understanding of pregnancy complications in this population of women with endometriosis. Our results seem to confirm that women with moderate and severe endometriosis have increased adverse pregnancy outcomes like placenta previa and cesarean section even if we didn't find a higher rate of PPH in endometriosis group. It would be interesting to explore specific endometriosis risk factors and outcomes by conducting a large cohort prospective study taking into account rASRM stage and endometriosis localization, but also ART characteristics (fresh or frozen ET, Day 2–3 or blastocyst stage).

#### Author's roles

E.R. and B.C. have conceived and designed the study. E.R., J.P., J.B., B.C. and A.A. made substantial contributions to acquisition, analysis and interpretation of data, in addition to drafting the article, reviewing the content and final manuscript approval. J.B. performed the analysis and interpretation of data, revising it critically for content and final approval of the version to be published.

#### Ethics statement

Study was approved by Ethical Committee of Aix-Marseille University (2017–05–04–005).

#### Study funding/competing interest(s)

The authors have no competing interests to declare.

#### Declaration of competing interest

None declared.

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