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REVIEW

Placenta previa and placental abruption after assisted reproductive technology in patients with endometriosis: a systematic review and meta-analysis

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Abstract

Introduction Recent evidence suggests that assisted reproductive technology (ART) increases the risk of adverse pregnancy outcomes, including placental disorders. Similarly, endometriosis resulted detrimental on placenta previa. However, up to 50% of women with endometriosis suffer from infertility, thus requiring ART. The aim of our metanalysis is to compare women with and without endometriosis undergoing ART in terms of placenta disorders events, to establish if ART itself or endometriosis, as an indication to ART, increases the risk of placenta previa.

Methods Literature searches were conducted in January 2018 using electronic databases (PubMed, Medline, Scopus, Embase, Science Direct, and the Cochrane Library Scopus). Series comparing pregnancy outcome after ART in women with and without endometriosis were screened and data on placenta previa and placental abruption were extracted.

Results Five retrospective case–control studies met the inclusion criteria. The meta-analysis revealed that endometriosis is associated with an increased risk of placenta previa in pregnancies achieved through ART (OR 2.96 (95% CI 1.25–7.03); $p=0.01$, $I^2=69\%$, random-effect model). No differences in placental abruption incidence were found (OR 0.44 (95% CI 0.10–1.87); $p=0.26$, $I^2=0\%$, fixed-effect model).

Conclusion Patients with endometriosis undergoing ART may have additional risk of placenta previa. Despite the inability to determine if endometriosis alone or endometriosis plus ART increase the risk, physicians should be aware of the potential additional risk that endometriosis patients undergoing ART harbor.

Keywords Placental abruption · Placenta previa · Assisted reproduction · Endometriosis · Adverse pregnancy outcome

Introduction

Endometriosis is a benign chronic condition affecting approximately 10% of women worldwide [1, 2]. Up to 50% of women with infertility are affected by endometriosis [2]. With such strong association with infertility, the affected patients often require assisted reproductive technology (ART) to conceive. Pregnancies achieved through ART have a higher prevalence of adverse perinatal outcomes compared with those achieved naturally, such as preterm delivery, low birth weight and small for gestational age (American College of Obstetricians and Gynecologists bulletin 671) [3]. Recently, a meta-analysis showed that ART procedures are a risk factor for placenta previa [4].

Although the influence of pregnancy on endometriosis is historically accepted [5], the impact of endometriosis on pregnancy remains controversial [6–23]. Some authors suggest that endometriosis may be responsible for an increased incidence of obstetric complications [24–26]. Women with endometriosis have functional endometrial-like tissue outside the uterus as well as an aberrant endometrial environment. The inflammatory and metabolic environment associated with endometriosis affects the endometrial receptivity, decidualization and remodeling of the uterine spiral vessels after embryo implantation [27]. The deregulated endometrial

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receptivity of women affected by endometriosis is associated with progesterone resistance and inadequate uterine contractility. The impaired decidualization in women with endometriosis may result from the abnormal interplay of transcriptional factors, cytokines, and signaling pathways. The inflammatory mediators, oxidative stress and alterations in the uterine junctional zone of patients with endometriosis lead to an abnormal conversion of the uterine spiral arteries into uteroplacental vessels. These subsequent suboptimal endometrial functions, defective decidualization, and pathological vascularization may be responsible for an increase in pregnancy complications, including placental disorders.

Whether ART itself or the underlying reproductive disorder (endometriosis) underpinning ART is responsible for an increase in placental disorders and, therefore, predisposes a poor pregnancy outcome, remains an unanswered question. The aim of this meta-analysis is to compare the incidence of placental disorders in women with and without endometriosis achieving pregnancy through ART, thereby shedding light on this issue.

Methods

Data identification and selection

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. On January 2018, a systematic literature search was carried out. All eligible studies were included without restriction on publication year. Papers were identified using the electronic databases (PubMed, Medline, Scopus, Embase, Science Direct, and the Cochrane Library) using the search terms "assisted reproductive technology" and "endometriosis" and "adverse pregnancy outcome" and "placental disorders" and "placenta previa" and "placental; abruption". All English-language original reports evaluating the incidence of placenta previa and placental abruption in pregnant women with and without endometriosis were included. Only studies reporting pregnancies achieved through ART, including in vitro fertilization (IVF) and intra-cytoplasmatic sperm injection (ICSI) were assessed. Only studies comparing pregnant women with and without endometriosis were included in the meta-analysis. To reduce selection biases, and all the studies were matched for at least three of the following factors: first pregnancy, singleton pregnancy, smoking status and maternal age. Reference lists of already published reviews and original reports were also analyzed to identify potential studies. A diagnosis of endometriosis by US and/or MRI, or histology was accepted. Review articles, case reports, video articles and letters were excluded.

Outcomes

The outcomes considered in our study were placenta previa (PP) and placental abruption (PA). Placenta previa was defined as the pathologic condition in which the placenta completely or partially covered the internal cervical os; PA was defined as the pathological separation of the placenta from its site of implantation prior to delivery.

Statistical analysis

The PP and PA events after ART in women with endometriosis compared with women without endometriosis were stratified by studies. Pooled odds ratio (OR) or risk ratio (RR) were calculated using fixed- or a random-effects models. The I^2 value was used to quantify the inconsistency across studies. It was calculated to describe the proportion variability in effect estimating resulting from heterogeneity rather than sampling error. A naive categorisation of values for I^2 would not be appropriate for all circumstances, although we would tentatively assign adjectives of I^2 as follows: I^2 value ranking from between 0 to 40% was not relevant, 30–60% represented moderate heterogeneity, 50–90% represented substantial heterogeneity, and 75–100% considerable heterogeneity. Graphical representation of each study and pooled analysis are displayed by forest plots. The contribution of each study in the meta-analysis is graphically reported by squares of different sizes. Confidence intervals (CIs) for each study are presented as a horizontal line passing through the square. The pooled OR or RR are shown as a lozenge in the forest plot where the size corresponds to the 95% CI of the OR or RR. A p value of ≤ 0.05 was considered significant. Statistical analysis was performed using Review Manager 5.3 (http://www.cochrane.org).

Results

Five studies met the inclusion criteria (Fig. 1) and were evaluated [9, 11, 16, 19, 26]. A total of 8007 patients undergoing ART were included, of which 1719 (21%) had a diagnosis of endometriosis. Table 1 summarizes the characteristics of the included studies.

Placenta previa (PP)

In the comparison of women with and without endometriosis having undergone ART, the analysis of pooled data showed a significantly higher incidence in PP events in patients

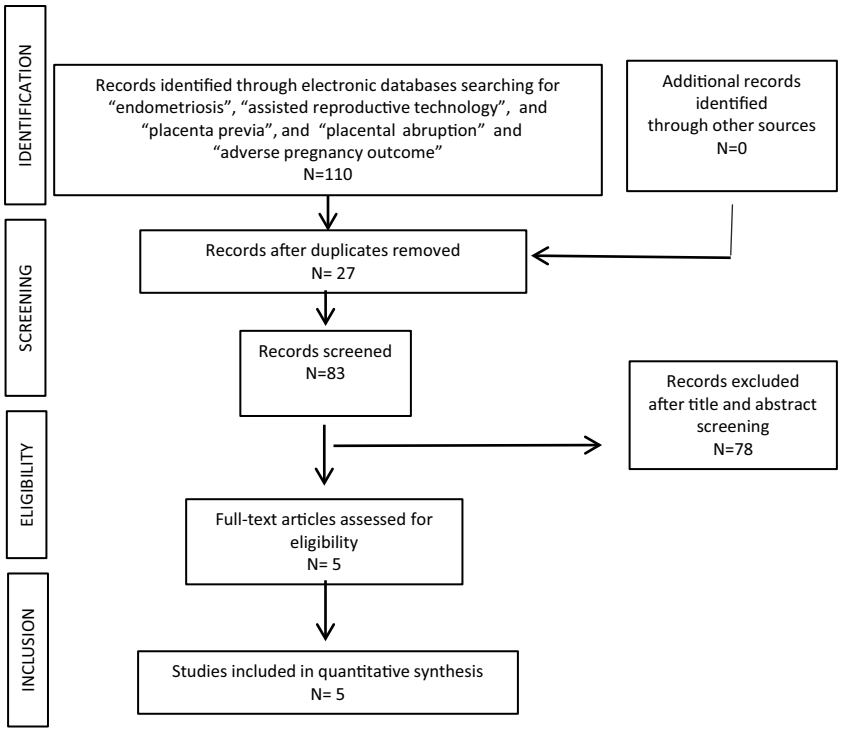

Fig. 1 PRISMA flow diagram on the meta-analysis process

with endometriosis (OR 2.96 (95% CI 1.25–7.03); $p=0.01$, $I^2=69\%$, random-effect model) (Fig. 2).

Placental abruption (PA)

In the comparison of women with and without endometriosis having undergone ART, the pooled analysis data showed no differences in PA events between the two groups (OR 0.44 (95% CI 0.10–1.87); $p=0.26$, $I^2=0\%$, fixed-effect model) (Fig. 3).

Discussion

In this meta-analysis evaluating pregnancy outcomes following ART, we found that the risk of PP after ART in endometriosis patients was threefold higher than those without endometriosis and this difference was statistically significant. No difference was found in the incidence of PA between the two groups. ART itself has been associated with an increased risk of pregnancy complications in non-randomized studies and found to be associated with a sixfold increased risk of PP [28–30]. The American College of Obstetricians and Gynecologists (ACOG) recently released recommendations on the management of these risks [31]. The present meta-analysis highlights that this risk is greater still when ART is performed in patients with endometriosis, suggesting that endometriosis is an additional and potentially independent risk factor of PP.

A recent meta-analysis examined the influence of endometriosis on the ART outcome of live births [32]. This study found a lower pregnancy rate among women with severe endometriosis. More recently, in women with endometriosis, the preterm birth risk was significantly increased in both spontaneous conception (OR 1.59, 95% CI 1.32–1.90) and ART (OR 1.43, 95% CI 1.14–1.79) [33]. Both the meta-analyses did not investigate the impact of endometriosis after ART on PP.

Known risk factors for PP are previous cesarean deliveries, maternal age, multiple pregnancy, multiparity, smoking, drug use and previous termination of pregnancy [34]. The mechanisms accounting for a higher risk of PP in women with endometriosis are largely unknown. This may be due to anomalous blastocyst implantation in the lower segment due to dysperistalsis and abnormal frequency and amplitude of uterine contractions observed in women with endometriosis [35]. Another explanation proposed previously is pelvic adhesions, secondary to peritoneal endometriosis, which may cause a fixed uterus leading to abnormal placental implantation. Placenta previa can also be a consequence of the profound structural and functional alterations observed in the endo-myometrium of women with endometriosis. Some already described differences in the endometrium of women with endometriosis include lower peak endometrial thickness, progesterone resistance, altered local estrogen production and oxidative stress response as well as differences in cytokines, inflammatory mediators and apoptotic markers [36–39]. It has been shown that various hormone therapies,

Table 1 Characteristics of the included studies

References	Study design	ART center	Number of participants		Study group diagnostic procedures (%)	Endometriosis site and/or ASRM stage	Nulliparas (%)			Outcomes considered
			Case study	Control group			Case study	Control group	*p* value	
Healy et al. [28]	Multicentric retrospective cohort study	Melbourne University, Australia Monash University, Australia	1265	5465	n/a	n/a	5253/6730 (78)[a]			APH, PP, PA, PPH
Kuivasaari-Pirinen et al. [16]	Retrospective case–control study	University Hospital of Kuopio, Finland	49	206[b]	The etiology of infertility was defined by laparoscopy, ultrasonography, and laboratory parameters (when appropriate); unclear what kind of surgery was performed	n/a	41 (83.7)	152 (73.8)	$p > 0.05$	PE, PP, PA, PTD, GDM, SGA, NICU
Takemura et al. [23]	Retrospective case–control study	University of Tokyo Hospital, Tokyo, Japan	53	265	Endometriosis was diagnosed by histopathology on surgery (47/53) or MRI (6/53); unclear what kind of surgery was performed	n/a	The parity has been only compared between women with and without placenta previa ($p > 0.05$). Data on parity in patients with and without endometriosis cannot be extracted			PP
Benaglia et al. [7]	Retrospective case–control study	Fondazione Cà Granda, Ospedale Maggiore Policlinico of Milan, Italy	239	239	History of surgery for endometriosis in 186 (78%) patients. Sonographic diagnosis of ovarian endometriosis in 53 (22%) patients	DIE: 77 (41%) Ovarian: 134 (72%)	216 (90)	202 (84)	$p = 0.07$	PIH, PE, PP, PA, GDM, pPROM, PTD, SB, CD, SGA, L6A, NICU

Table 1 (continued)

References	Study design	ART center	Number of participants		Study group diagnostic procedures (%)	Endometriosis site and/or ASRM stage	Nulliparas (%)			Outcomes considered
			Case study	Control group			Case study	Control group	*p* value	
Jacques et al. [14]	Retrospective case–control study	Nantes University Hospital, France	113	113	Endometriosis surgically diagnosed in 101 (78.3%) patients. For the other patients diagnosis via clinical examination and MRI	I: 27(20.9%) II: 36 (27.9%) III: 26 (20.2%) IV: 35 (27.1%) Ovarian: 77 (59.7%) DIE: 56 (43.4%) Peritoneal: 53 (41.1%) Adenomyosis: 12 (9.3%)	64 (56.6)	65 (57.5)	$p > 0.05$	First trimester bleeding, PE, PP, PTD, pPROM, IUGR, CD, GDM, GC, pelvic pains, PPH

APH antepartum hemorrhage, *ART* assisted reproductive technology, *n/a* not available, *ASRM* American Society for Reproductive Medicine, *PIH* pregnancy-induced hypertension, *PE* pre-eclampsia, *PPH* primary postpartum hemorrhage, *PP* placenta previa, *PA* placental abruption, *pPROM* preterm premature rupture of membranes, *PTD* preterm delivery, *PPH* postpartum hemorrhage, *IUGR* intra-uterine growth restriction, *SGA* small for gestational age, *CD* Cesarean delivery, *GC* gestational cholestasis, *SB* spontaneous birth, *NICU* neonatal intensive care unit admission, *GDM* gestational diabetes mellitus

[a]Data not presented separately in the two groups

[b]The control group in this study was women with spontaneous singleton pregnancies in the general population during 1996–2007 at the University Hospital of Kuopio. However, this could have included women with endometriosis. That is why for the current meta-analysis only women with pregnancy after ART and infertility reason other than endometriosis were considered as control group

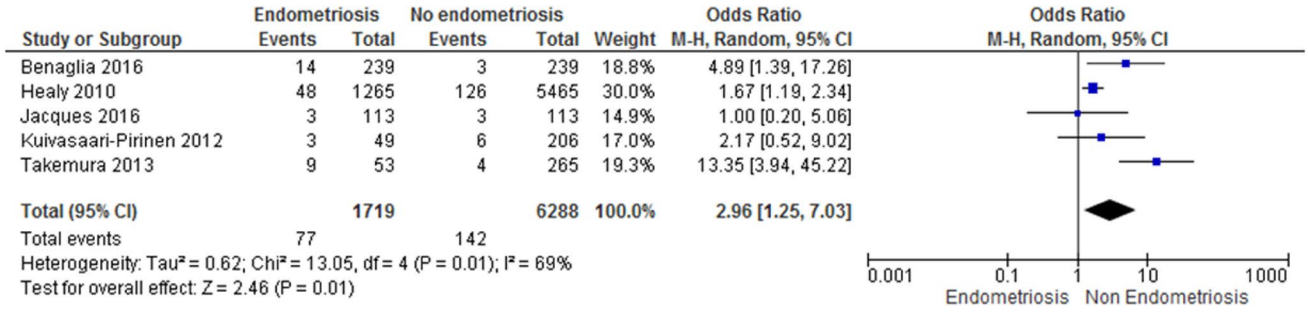

Fig. 2 Placenta previa in women with and without endometriosis after ART

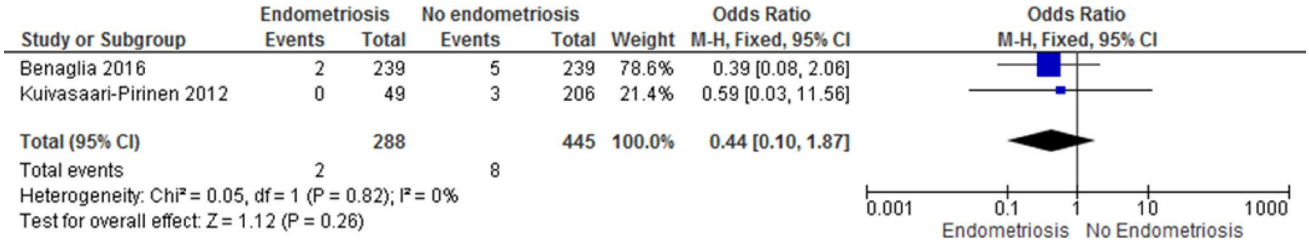

Fig. 3 Placental abruption in women with and without endometriosis after ART

such as progestins and GnRHa, may reduce cytokine concentration and inflammation in patients with endometriosis, thereby also suppressing the pathogenesis of the disease [40–42]. It remains to be determined whether such therapy used prior to ART is also influential in reducing the risk of PP in ART pregnancies. It is also unclear whether these patients would benefit from surgical pretreatment. Studies examining possible correlations between PP and the stage and type of endometriosis may also help to clarify possible links. Certainly, without these data, the performance of any form of prophylactic medical or surgical treatment to reduce the risk of PP would not be justified. The current study only demonstrates association and not causality between endometriosis and PP. Given the paucity of data currently available, a definitive evidence-based strategy for the management of endometriosis before ART cannot be determined.

In the general population of women with endometriosis with or without ART, the data considering PA are variable and do not allow clear conclusions to be drawn [10, 15, 17, 20]. Moreover, there do not appear to be differences between patients undergoing ART with and without endometriosis.

The association between endometriosis and other placental diseases, such as placenta accreta could not be examined due to a paucity of existing data. However, an association would not be surprising since placenta accreta is known to be correlated with PP [43].

The limitations of this meta-analysis also require consideration. First, the relatively high heterogeneity in the PP outcome, which is related to the design of the studies included and by the magnitude and direction of effects. Unfortunately, subgroup analysis was not possible to investigate the impact of stage and type of endometriosis or previous cesarean deliveries because the details were not always provided. However, because systematic reviews bring together studies that are diverse both clinically and methodologically, a certain degree of heterogeneity is expected [44]. Indeed, the distribution of observed values of I^2 derived from 509 meta-analyses in the Cochrane Database of Systematic Reviews revealed that about a quarter of the meta-analyses have I^2 values over 50% [45]. Furthermore, biases that may impact on the final set of included studies may also include publication bias given the tendency to submit or accept manuscripts for publication based on the direction or strength of the study findings [46].

There are also inherent limitations in drawing conclusions from retrospective studies. However, the lack of prospective trials comparing pregnancy outcome between women with and without endometriosis means that meta-analysis of retrospective studies remains the best available level of evidence.

The selection of the controls in the studies we assessed did not always require the exclusion of a diagnosis of endometriosis based on histology/surgery. However, this possible bias may be of limited relevance since the indication to ART in most of the patients in the control groups was male infertility. Nevertheless, the inclusion of even a small proportion of patients with endometriosis in the control groups would represent a selection bias and affect the results concerning

the level of differentiation between the two groups. Limitations also include lack of information regarding the method of diagnosis in one study [28].

The lack of detailed data on previous cesarean deliveries should also be noted. Due to the well-established correlation between previous cesarean delivery and PP, a higher number of previous cesarean deliveries, and not endometriosis, may be the reason for a higher incidence of PP among endometriosis patients. However, the case and control groups included a similar number of nulliparas in most of the included studies; it is, therefore, unlikely that a history of a previous cesarean section may have significantly biased our results. Of note, Takemura et al. reported no PP after a history of previous cesarean delivery [23].

Many of the limitations outlined above are intrinsic limitations to controlled observation studies, and as previously stated, this remains the only available evidence to conduct this analysis.

In conclusion, the present meta-analysis suggests that endometriosis is associated with an increased risk of PP in pregnancies resulting after ART. Despite the inability to determine if endometriosis alone or endometriosis plus ART results in placental outcomes, physicians should be aware of the potential additional risk that endometriosis patients undergoing ART harbor. Patients with endometriosis undergoing ART should be counseled accordingly.

Author contributions MLG was responsible for the conceptualization, literature search, data extraction, and statistical analysis. The paper was equally drafted by MLG, KN, and KT. MM and AP performed the final revision.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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