# Endometriosis and *in vitro* fertilisation (Review)

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**Abstract.** The aim of the present review was to discuss a matter of concern in the clinical field of obstetrics/gynecology, namely the potency of *in vitro* fertilization (IVF) in the management of endometriosis-associated infertility. Endometriosis is a medical condition affecting one tenth of women in their fertile years, and accounts for up to 50% of infertile women. Thus, such high prevalence has established the necessity for investigating the effectiveness of available techniques in eradicating the disease and constraining infertility as well as the accompanying pain symptoms of endometriosis. The underlying mechanisms connecting endometriosis with low fecundity have been extensively studied, both in terms of genetic alterations and epigenetic events that contribute to the manifestation of an infertility phenotype in women with the disease. Several studies have dealt with the impact of IVF in pregnancy rates (PRs) on patients with endometriosis, particularly regarding women who wish to conceive. Results retrieved from studies and meta-analyses depict a diverse pattern of IVF success, underlining the involvement of individual parameters in the configuration of the final outcome. The ultimate decision on undergoing IVF treatment should be based on objective criteria and clinicians' experience, customized according to patients' individual needs.

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*Abbreviations:* ART, assisted reproduction treatment; COH, controlled ovarian hyperstimulation; DIE, deeply infiltrating endometriosis; FPT, fertility preservation technologies; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, *in vitro* fertilization; PR, pregnancy rate(s)

*Key words:* endometriosis, infertility, *in vitro* fertilization, assisted reproduction, pregnancy rates

**Contents**



## 1. Introduction: Endometriosis as a medical condition

*Definition, etiopathogenesis and clinical picture.* Endometriosis is a pathological entity characterized by the abnormal growth of endometrial tissue in ectopic sites, outside the endometrial cavity. Positions in the body where endometrial tissue can be found in the context of endometriosis include the ovaries, the rectovaginal fascia and the uterosacral ligament, the peritoneal cavity and the urinary bladder, the fallopian tubes, the colorectal tract, and even in the lungs (1). Endometrial glands and stroma can also be found in incisional scars, albeit in rare cases (2).

The frequency of endometriosis is not well defined in the general population, as available epidemiological data do not form a concrete picture. However, it is estimated that percentages rise from 2 to 10% in women belonging in the procreation age. Among infertile women, its prevalence is increased up to 50% (3). Moreover, assisted reproductive treatment is required in approximately 10 to 25% of women with endometriosis (4). The prevalence of endometriosis has been reported to be higher in women of Philippine, Indian, Japanese and Korean origin (5).

Three subcategories of endometriosis have been identified: i) superficial endometriosis (superficial peritoneal and ovarian implants); ii) ovarian endometrioma (ovarian cysts lined with endometrial mucosa) and iii) deeply infiltrating endometriosis (DIE), i.e., complex nodules consisting of endometrial, adipose and fibromuscular tissue (6). Deep infiltrating endometriosis is often multifocal, and can be roughly described as the presence of endometrial tissue that expands to a depth of more than 5 mm below the peritoneum. Uterine adenomyosis also exists, i.e., a benign condition characterized by presence of endometrial tissue within the myometrium.

Endometriosis is a multifactorial disease, generated by a combined action of genetic and environmental factors. Three theories are prevalent regarding the etiology of endometriosis: i) the Sampson's theory; ii) the Meyer's theory and iii) the Halban's theory. The Sampson's theory, describes that the

retrograde blood flux, namely the transferring of endometrial cells during menstruation via the fallopian tubes to the peritoneal cavity, causes endometriosis (7). On the other hand, Halban's theory explains that endometrial cells are transferred through the lymphatic system in distal areas, while Meyer's theory supports the idea that metaplasia occurs from visceral epithelium to endometrial (8). The eutopic endometrium of patients with endometriosis has been described to differ from that of healthy individuals in terms of a molecular and cellular level (9). These variations regard hormone responsiveness, immune alteration, angiogenesis and cell proliferation. Women with endometriosis possess a resilient endometrium to some progesterone actions, affecting implantation. It has been observed that immune response to endometriosis is abnormal, namely that phagocytes and cytotoxic are incapable of eliminating the ectopic endometrial tissue. In endometriosis, the immune system ceases to be resistant to endometrial antigens and this creates a chronic inflammatory response with release of toxic products and the formation of peritoneal adhesions (10). Integrins have also been reported to play a role in endometriosis (11). Recent findings have shown that the induction of oxidative stress favors the development of ectopic endometrium (12). Vitamin D has been suggested to partake in the pathogenesis of endometriosis, as it exhibits immune-modifying, anti-inflammatory and anti-proliferative traits, although this association remain to be confirmed (13). Syndecan-4 expression has been detected in elevated concentrations in patients with endometriosis compared to women with eutopic endometrium. Thus, the upregulation of syndecan-4 has been proposed as a pathophysiological mechanism provoking invasive cell growth (14). A genetic mechanism has also been suggested regarding the induction of endometriosis, as it has been found that the suppression of miR-183 expression favors the interception of apoptosis in endometrial cells, as well as intervenes in integrin β1 expression (15).

Exposure to several toxicants, such as organochlorines, may also affect the progression of endometriosis, in the presence of CYP gene polymorphisms (16). Recent data showed a positive association between decreased levels of serum EPA (eicosapentaenoic acid) and the manifestation of endometriosis (17).

Particular emphasis is attributed in the information below, considering the aggregate of mechanisms linking endometriosis to infertility provocation.

The symptoms manifesting with endometriosis are dependent on the site where the ectopic endometrial tissue is identified (18). The encountered symptoms include pelvic/abdominal/rectal pain, dysmenorrhea, dyspareunia, menorrhagia, bladder discomfort, ureteral obstruction, hematochezia, diarrhea and in case of thoracic lesions pneumothorax/hemothorax. Endometriosis presents a wide range of complications as well. It has been suggested that pregnant women with endometriosis are susceptible to developing preterm birth, antepartum hemorrhage, spontaneous hemoperitoneum (7), placental complications (19), pre-eclampsia and Caesarian section. Furthermore, endometriosis has a possible risk factor for ovarian cancer (5), albeit the causal association of endometriosis in ovarian cancer is not exhibited yet.

The American Society for Reproductive Medicine (ASMR) has provided a classification of endometriosis according to the extent of its progress. The criteria include size and depth of lesion, whether it is uni- or bilateral, ovarian intrusion and density of related adhesions. Minimal/mild disease is scored with 1-15 points, moderate belongs to 16-40˚, and over 40 points the disease is characterized as severe. It is important, however, to underline the fact that this scoring system has been entered into its utilization as a predictor for fertility results and it does not reflect the degree of symptoms (6).

*Diagnosis and therapeutic options of endometriosis*. Prompt and proper diagnosis should be the main target regarding management of endometriosis. Due to the broad range of symptoms encountered in endometriosis, a multi-disciplinary approach is often required. Laparoscopy currently is the gold-standard for the definitive diagnosis of endometriosis and histological biopsy confirms the diagnosis (20). Transvaginal ultrasound is also used for diagnostic purposes; currently, magnetic resonance has been presented as the optimal imaging tool for detecting small lesions and drawing the differentiation between benign and malignant tissue. Biomarkers for diagnosis have also been utilized, such as CA-125, although exhibiting low specificity. A new weapon in the arsenal regarding the diagnostic procedure of endometriosis has been added, in the context of molecular biomarkers, such as miRNA, the evaluation of the peritoneal fluid in terms of protein levels as well as the concertation of proinflammatory agents (21).

Therapeutic methods for endometriosis depend upon the symptoms, the patient's age and wish for childbearing, as well as the stage of disease. Medical treatment includes GnRH agonists/antagonists (e.g., deslorelin) (22), progestogens, oral contraceptives, PGs inhibitors, danazol and aromatase inhibitors. As knowledge regarding the underlying mechanisms of endometriosis improves and increases, new therapeutic options are examined. These treatments include novel NSAIDs, monoclonal antibodies, statins, antiangiogenic compounds and cannabinoids (23). Surgery is primarily indicated for pain alleviation. Considering surgical intervention, existing data suggest for minimal/mild endometriosis, the performance of laparoscopic ablation and adhesiolysis (24). Less lucid is the picture for stage III/IV endometriosis, as surgery is recommended according to ASRM. Nevertheless, an adequate number of randomized studies and meta-analyses are lacking and existing evidence is conflicting regarding pregnancy rates (PRs).

Superficial peritoneal endometriosis is an indication for laparoscopy, with subsequent ovarian stimulation ± intrauterine insemination (IUI). Surgical operation regarding DIE for pain attenuation presents satisfying PRs either spontaneously or in the context of ART, except for the cases where the digestive tract is involved. *In vitro* fertilization for DIE restrain offers good results and does not favor pathological recurrence. Little evidence exists to confirm the ascendency of IVF on surgery regarding the cases of DIE-related infertility. Thus, the ultimate decision should be individualized and based on specific context. The statement that surgery could be of benefit in patients with colorectal endometriosis in terms of fertility rates is supported by other studies as well (25), with particular emphasis on laparoscopy as a more effective treatment for the achievement of spontaneous pregnancy (26).

Microscopic foci of endometrial tissue cannot be resected through surgery; thus, hormonal therapy has been suggested

for the suppression of endometriosis and for the hindrance of its recurrence (24). However, in women with endometriosis-associated infertility, adjuvant hormonal therapy has not been suggested by the Guideline Development group (27) for the enhancement of spontaneous PR, as sufficient evidence is not available. It is noteworthy to underline that indicated is the administration of hormonal therapy to symptomatic women, in the time interval of waiting for surgical intervention or ART.

Treatment options that exist today in managing infertility associated with endometriosis include surgical intervention, as well as superovulation with IUI and IVF. Laparoscopic surgery has also been proposed as a tool for diagnosing and treating endometriosis. Especially in cases of minimal and mild endometriosis, laparoscopy has been reported to augment pregnancy rates (28). Laparoscopy, compared to open surgery, has also shown to be beneficial in the cases of colorectal endometriosis, positively affecting fertility (23). It has also been suggested as an option regarding women with severe endometriosis that have experienced repeated IVF implantation failures (29). Whether IVF is preferred over re-operation depends upon the clinical and histological picture, the patient's age and ovarian reserve. Superovulation with IUI is an effective first-line strategy for infertile women with early-stage endometriosis (30). According to ESHRE guidelines, clinicians should also consider performing laser vaporization, as enhanced spontaneous PR have been demonstrated (24). It is also known that the symptoms deriving from endometriosis can be alleviated during pregnancy (31). Therefore, pregnancy is deemed an additional therapeutic option of endometriosis.

Attention has been also given to the psychosocial dimension of patients with endometriosis, as the therapeutic approach has been proposed to take into consideration the patients' emotional wellbeing by specialists in holistic care centers (32).

## 2. Endometriosis-associated infertility

*Mechanisms leading to infertility*. The mechanisms inducing infertility in the context of endometriosis are orientated towards four main directions: i) mechanical obstruction due to pelvic adhesions; ii) local/systemic inflammatory processes accompanied by elevated cytokines in the peritoneal fluid; iii) altered hormonal profile and iv) genetic polymorphisms. The above suggested categorization of mechanisms is indicative, as at this point it should be mentioned that they do not comprise distinctive entities but rather demonstrate a pattern of interplay between them:

Ectopic endometrium demonstrates a similar behavior with the eutopic endometrium, which means that it can respond to hormonal stimulation by the ovaries. In distal sites, ectopic endometrium leads to pain, hemorrhage, adhesions and fibrous lesions. Local inflammation contributes to the formation of adhesions with re-triggering of inflammation, namely the onset of a vicious cycle. As ectopic endometrium may develop in any site lengthwise the reproductive tract (e.g., the Fallopian tubes), it is possible that mechanical obstruction occurs, hindering fertility (33).

Due to retrograde blood flow during menstruation in women with endometriosis, endometrial cells gain entrance in the peritoneal cavity where they interact with immune mechanisms. This initially starts through the activation of repairing mechanisms of the destroyed tissue. Macrophages, dendritic cells and mast cells release inflammation mediators responsible for vasodilation and increased endothelial permeability. Consequently, extravasation of white blood cells (neutrophils, monocytes) towards the tissue occurs. Several studies state that in endometriosis patients, elevated concentrations of macrophages, metalloproteinases, proteases, prostaglandins and cytokines can be detected in the peritoneal fluid (34,35). Cytokines include interleukins (IL)-1, -6, -7, -8, -17, -18, -33 (30), TNF-α, VEGF, HGF, SCGF-β (36), VCAM-1, RANTES, MCP1, SDF-1, ENA-78 and others (37). These factors create a rather hostile environment that intercepts folliculogenesis, spermatozoa transportation and transplantation (38). It has been observed that eutopic endometrium in women with endometriosis exhibits resistance towards the action of NK cells, compared to that of healthy women. A possible mechanism for this could be through the action of ICAM-1 (intracellular adhesion molecule-1) in stromal cells of the endometrium (32). Furthermore, elevated IL-6 in follicles in cases of endometriosis induces a decrease in the activation of aromatase via the MAPK signaling pathway, leading to lower conversion of androgens in estrogens and finally to reduced E2 levels.

Despite the fact that the number of macrophages in the peritoneal fluid is increased in endometriosis, these macrophages demonstrate a reduction in the expression and activation of metalloproteinase-9 (*MMP-9*). Moreover, CD-36 receptor exhibits a downregulation in the peritoneal macrophages, resulting in impaired phagocytic activity and decreased degradation of cellular debris that emerge due to the retrograde blood flow in menstruation occurring in endometriosis (35). In this manner, ectopic endometrial cells evade immune surveillance. Another way for achieving this is through the LFA1/ICAM-1 pathway (lymphocyte function-associated antigen-1/ICAM-1), where lymphocytes as well as NK cells are unable to identify endometrial cells.

Where pelvic endometriosis is present, macrophages become activated in the peritoneal cavity, stimulating the production of ROS, cytokines, growth factors and prostaglandins. The induced oxidative stress incites lipid hyperoxidation, whose degradation produces substances, such as malondialdehyde, which can be identified as foreign and provoke the production of antibodies. This procedure leads to destruction of red blood as well as endometrial cells found in the peritoneum, thus reinforcing this phenomenon. Through the systemic circulation, possible is the transport to the hypervascularised ovary, during the last stages of folicullogenesis, thus intervening in oocyte maturation (39). Oxidative stress may also cause lesions in mesothelial cells and further induce the presence of adhesions (40).

The elevated mRNA expression of the transcriptional factor Foxp3 has been observed. This expression is a specific surface factor for T-reg cells, which in turn play a primary role in transplantation (36).

Alterations in the peritoneal fluid in infertile patients with endometriosis can affect oocyte quality and maturation. Changes in the follicular fluid can also impact oocyte quality. The follicular fluid, produced from granular, endothelial and white cells, is a metabolically active micro-environment consisting of steroid hormones, growth factors, cytokines,

ROS and antioxidants. ROS normally play an important role in several functions of the reproductive tract, but when they are in increased levels they exert a negative impact on E1 levels, intercepting steroidogenesis, thus hindering oocyte maturation and ovulation (41). In a previous study, where the levels of oxidative stress markers in serum and follicular fluids of patients were under ICSI, higher levels of glutathione, superoxide dismutase and 8-hydroxy-2-deoxyguanosine (8OHdG) were found, as well as elevated vitamin E concentrations. These findings suggest the presence of systemic and follicular oxidative stress in patients with endometriosis, an event that is directly linked to reduced oocyte quality and infertility (42). A complementary study showed that the follicular fluid of patients with mild endometriosis negatively affects nuclear maturation and meiotic spindle of their oocytes, thus inducing meiotic abnormalities (43).

In women with endometriosis, the hormonal profile is altered through a range of mechanisms. To begin with, the function of the pituitary-ovarian axis has been observed to be hindered, compared to healthy individuals. Specifically, the duration of the follicular phase has been referred to be extended, and abnormalities in Luteinizing hormone (LH) secretion motif occur as the LH surge is delayed, while biphasic LH surges may also occur (44).

In endometriosis patients, the amount of preovulatory follicles, follicular development and estradiol levels within the follicle are lower. The follicular fluid in endometriosis has been described to entail altered hormone levels, with decreased estrogen, androgen and progesterone, while activin is augmented (44).

Uterine receptivity is also affected in these patients. The expression of integrin αvβ3 in endometriosis is impaired, while HOXA10, a transcription factor that stimulates αvβ3 expression is reported to be decreased, with its methylation also being modified (45). The expression of other transplantation factors is also affected in endometriosis, including glycodelin A (46), osteopontin (47), leukemia inhibitory factor (48) and lysophosphatidic receptors 2 and 4 (49).

Locally/systemically affected hormonal profile consists of increased estrogen levels and estradiol receptors, as well as higher steroeidogenic factor 1 in endometrial cells. Although steroidogenic factor 1 (SF1) is present in ectopic endometrial tissue, it is not found in the eutopic endometrium. This leads to the downregulation of nearby progesterone receptors, thus overturning the hormonal balance (50). The increased amount of estradiol observed in the peritoneal fluid of patients with endometriosis increases local cyclo-oxygenase-2 (COX2) activity, resulting in stimulation of prostaglandin E formation, which upregulates aromatase activity, resulting in additional estradiol to perpetuate the symptoms and lesions present in endometriosis (51). There is elevated expression of both estrogen receptor α and estrogen receptor β leading to a downregulation of progesterone receptors, ultimately causing the characteristic hormonal profile seen in endometriosis.

Endometriomas are related to the reduction of ovarian functionality. Various theories have been proposed regarding the decrease of the number of follicles. Hemolysis of trapped blood leads to augmentation of the Fe levels within the cyst, an event suggesting cytotoxic oxidative stress. Furthermore, primordial follicles are affected due to intense stretching of the cortex, constraining blood flow and causing ischemia. Another hypothesis is the disturbance in ovarian vascularization resulting in lower availability of gonadotropins and decreased stimulation for follicular growth (52).

A hypothesis has been stated that a relationship exists between endometriomas and diminished ovarian reserves, although not confirmed (53). Ovarian reserve reflects oocyte quantity; thus, conditions relevant to alterations in the peritoneal fluid (e.g., oxidative stress) and/or the follicular micro-environment, may affect fecundity in women with endometriosis. In cases of endometriomas, decreased levels of anti-Mullerian hormone subsequently to surgical resection are also linked to diminished ovarian reserve (54).

Notably, there is a synergy between the endocrine and immune system. Progesterone, during the secretory phase, normally displays an immune-modifying action, as it suppresses the action of NF-κB, a transcriptional nuclear factor with pro-inflammatory and anti-apoptotic function. Thus, it is evident that there is a direct interaction between the endocrine and immune system. Resistance to progesterone can be effectuated by genetic polymorphisms, alterations in microRNA expression and epigenetic modifications (exposure to toxins, resistance to retinoids). It has been stated that the enhanced progesterone signal forms a pro-inflammatory phenotype, while chronic inflammation induces progesterone resistance, underlying this bidirectional relationship (55).

Altered genetic expression and genetic polymorphisms also represent suggested mechanisms of endometriosis manifestation. As previously mentioned, genes responsible for the expression of pro-inflammatory cytokines and adhesion molecules are expressed at an augmented rate, including *CXCL1*, *CX3CL1*, *CXCL9*, *CXCL10*, *IL-32*, *CXCR2*, *IL-7R*, *ICAM-1* and *SELL*, respectively (56). It has also been observed that a reduced expression of *NOTCH1* and *NOTCH2* induces disruption in this signal pathway, affecting endometrium decidualization (36). Apart from previous gene-association studies, recent genome-wide association studies (GWAS) have identified 14 chromosomal regions as genetic risk factors for endometriosis thus far (57). Furthermore, whole exome sequencing (WES) is currently used extensively to detect rare causative gene mutations leading to endometriosis. In total, around 90 genes have been identified to present impaired expression in the eutopic endometrium of infertile women suffering from endometriosis. Oxidative stress in the peritoneal and follicular fluid, as well as epigenetic alterations in regional areas, either via DNA methylation or through histone modifications (58), and the expression of *CYP19A1* in cumulus cells has been reported to be decreased (59,60).

Various studies have described an association between gene polymorphisms and low fecundity in women with endometriosis. Genetic polymorphisms that have been reported to confirm this assumption include: i) *ESR1* rs9340799 SNP and *ESR2* (CA) n repeats polymorphism were suggested to contribute to a phenotype of infertility in endometriosis patients (61,62); ii) G-765C polymorphism in promoter region of *COX-2* gene, particularly linked to endometriosis stages III and IV-related infertility (63); iii) rs16826658 and rs3820280 polymorphisms in *WNT4* gene (64); iv) rs7582694 single nucleotide polymorphism of *STAT4* gene (65); v) *HSD17B1* 937G polymorphism, described as a risk factor for endometriosis

stages I and II (66); vi) Polymorphism in *FCL3_3*, reported to increase possibility for infertility in patients, independently of the disease stage (67) and vii) 460T/+405C haplotype in the *VEGF* gene, associated with lower promoter activity, has a lower frequency in women with endometriosis (68).

*In vitro fertilization technique and endometriosis*. As aforementioned, infertility is a problem that many patients with endometriosis encounter. Often, in the moiety of patients with developed endometriosis, and despite the various treatment options, disease-induced infertility does not constitute a priority.

General methods of achieving infertility management include surgical operation (laparoscopically or open surgery), ovulation stimulation ± IUI and ART. Fertility preservation technologies also include oocytic/embryonic freezing and ovarian tissue cryopreservation (69). In general, controlled ovarian hyperstimulation (COH), oocyte retrieval, IVF and embryo cryopreservation are the most established techniques. COH as an infertility-hindering technique contributes to the development of follicles and importantly increases estradiol plasma levels. Endometriosis is dependent on estrogens and the number of ovulatory events has been reported to play an important role in the formation of ovarian endometriomas. Factors that exert a positive effect in the success of IVF include young age, history of previous livebirth/pregnancy, short duration of infertility and infertility attributed to unknown factors but nevertheless presenting good prognostic potential (70).

An inquiry that emerges at this point is whether IVF should be preferred as a first-line treatment or as a resort. Clear IVF indications consist of infertility due to tubal bilaterality, advanced endometriosis stage that has led to tubal dysfunction, menopausal state requiring egg donation, preimplantation screening for genetically inherited pathologies and in case of severe male factor infertility (i.e., pathological spermogram) (27,71,72). In addition to those, IVF/ICSI represent the gold standard in the cases of severe male contribution to decreased fecundity. Hydrosalpinges stage ≥2 have been associated with low PR even after surgery; thus, IVF herein is a promising solution. It has been suggested that in women less than 35 years of age, there is a margin of a one-year waiting period postoperatively until they undergo IVF, while women older than 35 year should undergo surgery earlier, in a time interval of 6 months postoperatively. As far as the ovarian stimulation is concerned, administration of GnRH agonists/antagonists in women with healthy ovarian reserve is recommended (73).

By contrast, certain conditions exist, where IVF is not deemed a primary infertility management method. These conditions are unexplained infertility, endometriosis without tubal disease, unilateral tubal obstruction, diminished ovarian reserve and mild male infertility factor.

The argument regarding this issue concern the invasiveness that characterizes the IVF techniques, the clinician's personal adjustment and opinion, and the elevated costs required. In addition to these parameters, IVF exhibits certain complications: ovarian hyperstimulation syndrome, thromboembolic episodes, ectopic pregnancies, ovarian torsion and complications deriving from egg retrieval. For the above main reasons, it can be deduced that IVF in endometriosis plays a controversial role, not only by objective hindrances but also due to conflicting results that have been retrieved thus far from the existing literature.

To begin with, several studies have demonstrated the positive effect of IVF in the elimination of endometriosis-associated infertility, especially in women of procreation age. Thus, it has been proposed by Fadhlaoui *et al* (24) that, in patients with stage I/II endometriosis, IVF in combination with controlled ovarian stimulation (COS) may prove to be beneficial for PR increase. It is though unclear as to whether surgery for stage I/II prior to COS/IVF could further improve PR. That study also showed that medication for treatment purposes did not seem to improve spontaneous PR. Those findings are in agreement with Leung *et al* (74), where recommendation regarding minimal/mild endometriosis is the ovulation stimulation along with letrozole/clomiphene citrate administration for the enhancement of PR. It has been mentioned that the outcome of surgical intervention is enhanced when accompanied by IVF, particularly for pain relief and a diagnosis in ambivalent cases should be confirmed (6). However, according to Capelle *et al* (75), in the cases of DIE, surgery does not seem to improve PR prior to IVF. It is recommended that women with endometriosis stages II, III and IV should undergo treatment with one, two and three doses of GnRH-a depot, in order to improve IVF outcome after laparoscopy (76). A prospective multicenter study performed by Ballester *et al* (77), identified that intracytoplasmic sperm injection-IVF leads to an elevated cumulative pregnancy rate per patient in women with colorectal endometriosis, though factors including the presence of adenomyosis, levels of anti-Mullerian hormone in the serum and age, affect the final outcome. Serum anti-Mullerian hormone in particular can play a predictive role for ovarian responsiveness in women with endometriosis (78). According to a meta-analysis performed by Yang *et al* (79), it is underlined that ovarian responsiveness to stimulation did not present a significant statistical difference between women with endometriomas and control group. The efficiency of assisted reproductive technologies subsequently to colorectal surgical intervention has been underlined four years later by Ballester *et al* (80), in patients with endometriosis-induced infertility.

It has been stated that PR is improved when patients undergo surgery prior to IVF particularly in the early stages of endometriosis. PR are also enhanced if GnRH agonists are administered prior to IVF. Postoperative medical treatment does not seem to incite a rise in PR, in women aiming at spontaneous conception, while they also add an unwanted time delay (30,81). Opøien *et al* (82), have underlined the important role of surgery in eradicating macroscopic lesions. In the present study, it has been found that women belonging to stage I/II and undergoing IVF/ICSI had shorter time to pregnancy and achieved live-birth at higher rates. Mavrelos and Saridogan suggested surgery and subsequently a time interval prior to superovulation ± IUI in young women with I/II stage and good ovarian reserve as well as in women with less than 3 cm unilateral endometriomas (83). Considering older women with low ovarian reserve, it has been suggested that surgery may not be that beneficial, except for the cases where bulky lesions intercept access to the ovaries. Similarly Rizk *et al* (84), support the view that women of stage I/II should undergo surgical excision/ ablation of endometriosis as first

option, as it increases PR up to double. Indeed, according to Garcia-Velasco *et al* (4), the need for IVF is described as imperative; not only for time saving and economic sparing, but also for the constraint of unwanted surgery complications. It is also postulated that surgery should be considered only in cases of large lesions, malignancy and pain. Furthermore Dechanet *et al* (85), agree upon the combination of surgery and ART, targeting at increasing PR. Gn-RH agonists have been also reported to contribute in PR elevation, compared to GnRH antagonist (86).

A considerable number of studies have exhibited an independent association between IVF efficacy and endometriosis-related infertility. In addition, IVF has provided results in retrospective cohort studies independently of the main infertility factor, thus indicating promising results in endometriosis management (as it is revealed that endometriosis does not affect IVF outcome). Indeed, IVF has been described to be irrelevant to the state of endometriosis, or even additional infertility factors (87,88). Moreover, IVF potential has been described to be as effective as in women with any other cause of infertility (89). In accordance to that, further studies have drawn similar conclusions; in a systematic review and meta-analysis of retrospective and randomized control-trial studies, IVF/ICSI seems to demonstrate results independently of the cause of low fecundity. In that same study, it was identified that surgery for endometriosis does not affect IVF outcomes (90). Similarly, patients with endometriosis demonstrate comparable results regarding successful IVF rates, as with women with infertility due to tubal factors, irrelevant of endometriosis-induced lesions (91,92). The same study also stated that prior to IVF, and for the enhancement of successful IVF rates, aggressive COH, medical suppression of the pituitary gland (93) and surgical intervention are recommended. IVF has also been reported by several authors to not contribute to disease progression. Crochet *et al*, performed a retrospective case-control study, with the aim of investigating the progression of endometriosis after IVF treatment in women having previously undergone surgical intervention (94). The findings suggested that a non-important deviation was found in the results of the patients belonging to the IVF administration group compared to controls, further indicating that IVF is not responsible for aggravation of endometriosis (44). This statement agrees with the findings of Benaglia *et al* (95), as well as with the that PR in IVF are inversely linked with the severity of endometriosis (96). Particularly for COH, it has been displayed that PR, oocytes and embryonic functionality are not affected by the presence of endometrioma or in operation for that reason (97). IVF pregnancy rate has been demonstrated to be negatively associated with disease severity, with the optimal time for IVF performance being 7-25 months subsequently to surgical intervention, according to previous findings (98). Ovarian reserve status also seems not to affect the progression of endometriosis in patients who undergo IVF (99). Regarding risk of miscarriage when endometriosis is present, IVF seems to be an independent factor (100). In addition, the chance of women with endometriosis to conceive are similar to disease-free women, as identified in a previous study (101). It has been stated that women with endometriosis undergoing IVF exhibit aneuploidy percentages similar to healthy women of the IVF treatment group (102).

Attention should be also paid to the endometriosis fertility index (EFI), as it comprises a novel staging system and proves to be a useful tool in clinicians' hands (103). The EFI is used for the prediction of fertility subsequently to surgery. It is proposed that EFI presents better value in the estimation of IVF outcome, in comparison to r-AFS classification (104). Considering women that have undergone surgery, a subsequent estimation of EFI ≥5-12 months postoperatively, indicated is the implementation of IVF-ET (105). For the estimation of cumulative birth rates following IVF, competing risk has been used as a tool for evaluation (106).

Another issue occupying clinicians is the effect of IVF on pain symptoms. It has been shown by a recent study that IVF does not intensify endometriosis-related pain (15). In general, few data exist that give an indication on addressing this topic, as the impact of endometriosis on pregnancy is ambiguous.

However, several published studies describe a negative association between endometriosis and IVF outcome. Coccia *et al* (107) determined that the success rate of IVF is inversely correlated with endometriosis stage III/IV. This negative association has also been exhibited by Cohen *et al* (108), with the additional suggestion of GnRH administration prior to IVF for improving the final outcome. The limited effectiveness of IVF in endometriosis has been supported by other authors as well. Pallacks *et al* (109), state that endometriosis reduces the chance of conceiving, even after IVF/ICSI. Surgery for endometriomas alone does not enhance IVF, according to Polat *et al* (110). IVF can be effective under certain circumstances, which include the administration of GnRH and letrozole for the achievement of elevated PR. Weak outcomes from IVF even after surgery have also been reported by other studies (111,112). Cohen *et al* (108), performed a retrospective study by evaluating the results of IVF/ICSI cycle in young women with low ovarian reserve. It was found that these women presented decreased birth rates following an IVF/ICSI cycle and that elevated gonadotropin dose of onset could possibly be related to improved results.

Endometriosis is a frequently encountered pathology affecting women of reproductive age. Its symptomatology and complications impel clinical doctors to implement appropriate corrective or mitigating techniques, for pain alleviation and fecundity enhancement. Among them, IVF possesses a neuralgic place in the therapeutic arsenal. Previous studies have suggest the beneficial role of IVF in intercepting endometriosis-associated infertility, displaying an efficacy even equivalent to disease-free women. Nonetheless, a number of studies have identified a negative impact of IVF on PR augmentation. The vast majority of studies, however, agree upon the fact that individual patient factors play the most crucial role in the final outcome. Treatment choice depends upon patient's age, duration of infertility, disease level of progression and wish for childbearing.

Therefore, it can be deduced that the management of endometriosis-related infertility remains a matter of dispute. Thus, clinicians are advised to make an insightful decision for the optimal result, adjusting appropriately their scientific knowledge and experience in congruence with patients' individual needs.

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LV and MM conceived and designed the study. LV, MM, MIZ and CM researched the literature, performed analysis of data and drafted the manuscript. GNG drafted the manuscript. GNG, DAS and IM critically revised the article for important intellectual content.

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**Competing interests**

Demetrios A. Spandidos is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article.

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