Review

Endometriosis, Oocyte and Embryo Quality

Sania Latif and Ertan Saridogan *

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Endometriosis, Oocyte and Embryo Quality

Sania Latif [1,2] and Ertan Saridogan [1,2,*]

[1] Reproductive Medicine Unit, University College London Hospital
[2] Institute for Women's Health, University College London
* Correspondence: ertan.saridogan@nhs.net

Abstract: Endometriosis is a common finding among women with infertility and women who are diagnosed with endometriosis are almost twice as likely to experience infertility. Mechanisms by which endometriosis causes infertility remain poorly understood. In this review we evaluate the current literature on the impact of endometriosis on oocyte and embryo quality. The presence of endometriosis evidently reduces ovarian reserve, oocyte quality and embryo quality, however this does not appear to translate to a clear clinical impact. Analysis of data from large assisted reproduction technology registries has shown that women with endometriosis have a lower oocyte yield but no reduction in reproductive outcomes. There is a need for future studies in the form of well-designed randomised controlled trials to further evaluate the role of surgical and medical treatment options in women with endometriosis undergoing assisted conception.

Keywords: endometriosis; in vitro fertilization; oocytes; embryonic structures

Introduction

Endometriosis is a common finding among women with infertility and women who are diagnosed with endometriosis are almost twice as likely to experience infertility (Prescott et al., 2016). The three main subtypes of endometriosis include peritoneal, deep infiltrating, and ovarian, and these frequently coexist (Zondervan et al. 2020). Mechanisms by which endometriosis causes infertility remain poorly understood. Proposed theories include mechanical distortion of pelvic anatomy, impairment of gamete and embryo transport, impaired folliculogenesis, reduced oocyte quality and embryo quality, altered immune and endocrine function and dysregulation of hormonal and cell-mediated functions involved in endometrial receptivity. (Sung et al., 1997; Garcia-Velasco and Arici, 1999; Diaz et al., 2000, Pellicer et al., 2001, Garrido et al., 2002, Soares et al., 2008, Hauzman et al., 2013, Sanchez et al., 2017).

In vitro fertilisation (IVF) is an established management option for endometriosis-associated infertility (European Society for Human Reproduction and Embryology (ESHRE) Endometriosis guideline 2022, American Society for Reproductive Medicine (ASRM) practice committee opinion 2012). Several studies describe a negative effect of endometriosis on the reproductive outcomes of women undergoing IVF (Pellicer et al., 1995, Barnhart et al., 2002, Cossia et al., 2011, Somigliana et al., 2017) in contrast to others which show no difference in outcomes (Bukulmez et al., 2001, Al Fadhli et al, 2006, Opoien et al., 2011, Yang et al., 2015, Gonzalez-Comadran et al., 2017, Murta et a., 2018, RoyChoudhury et al., 2020). The reasons for these observed differences and whether endometriosis affects oocyte quality and embryo quality have not yet been clearly determined. In this review we evaluate the current literature on the impact of endometriosis on oocyte and embryo quality and management strategies which have been considered.

Oocyte and embryo quality assessment

In 2011, an expert panel convened to develop a set of recommendations to define the minimum criteria for grading oocytes and embryos (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Following scientific and technological advances in the

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field, these consensus points are currently undergoing review to provide updated recommendations. The development of the human embryo is directly influenced by nuclear and cytoplasmic maturation of the oocyte (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Oocyte morphology is a proposed marker of oocyte quality (van Blerkom and Henry, 1992) and its assessment is based on intracytoplasmic features of the oocyte such as the homogeneity of cytoplasm, presence of vacuoles, aggregation of smooth endoplasmic reticulum and extracytoplasmic features such as first polar body morphology, perivitelline space size, zona pellucida defects and shape anomalies (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011). Ideal oocyte morphology consists of a circular structure with a uniform zona pellucida, uniform translucent cytoplasm free of inclusions and a size-appropriate polar body (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011).

The assessment of embryo quality is based on its rate of development and morphological features evaluated by light microscopy. The ESHRE Atlas of Human Embryology provides reference images of oocyte and embryo development (Gianaroli et al., 2000). Consensus points in the scoring system for blastocysts include the stage of development of the embryo, the grade of the inner cell mass and the grade of the trophectoderm. A top-quality embryo comprises an expanded blastocyst, with an inner cell mass that is easily discernible having many cells that are compacted and tightly adhered together and a good trophectoderm with many cells forming a cohesive epithelium (Alpha Scientists in Reproductive Medicine and ESHRE Special Interest Group of Embryology, 2011).

Methods

We searched PUBMED for articles published in the English language between September 1991 and June 2022 using the following MeSH search terms: 'endometriosis' combined with 'oocytes' OR 'embryonic structures' OR 'in vitro fertilization' OR 'assisted' AND 'fertilization' with restriction to the human species, no other exclusions were applied. References of the selected articles were screened to identify relevant studies. Data were extracted independently by two investigators (SL and ES).

Oocyte quality in women with endometriosis

Oocyte quality is reflected by oocyte morphology and the ability of an oocyte to complete maturation and fertilisation. In a meta-analysis evaluating the potential effects of oocyte morphological abnormalities on IVF outcomes, fertilisation rate was found to be significantly associated with four oocyte morphological abnormalities: first polar body enlargement, perivitelline space enlargement and the presence of refractive bodies and intracytoplasmic vacuoles (Setti et al., 2011).

A systematic review of the literature showed that oocytes retrieved from women affected by endometriosis are more likely to fail in vitro maturation (IVM), have altered morphology and have a lower cytoplasmic mitochondrial content compared to women with other causes of infertility (Sanchez et al., 2017). A study evaluating oocytes that underwent IVM from women with and without endometriosis demonstrated that a significantly lower number of immature oocytes subjected to IVM reached metaphase II (MII) in the endometriosis group compared to controls (Goud et al., 2014). IVM oocytes from patients with endometriosis had a significantly higher incidence of cortical granule loss, spindle disruption and zona pellucida hardening, which could affect oocyte fertilisation (Goud et al., 2014). Similarly, a retrospective analysis of 1,568 mature oocytes in women with endometriosis compared to healthy controls showed a significant increase in morphological abnormalities of the cytoplasm, the zona pellucida and the first polar body (Kasapoglu et al., 2017).

Studies of IVF outcomes using donated oocytes from healthy women transferred to women with endometriosis have shown that recipients have implantation and pregnancy rates equivalent to patients without endometriosis, supporting the hypothesis that endometriosis is associated with poor oocyte quality (Simon et al.,1994, Sung et al., 1997, Diaz et al., 2000). In women whose donated oocytes came from women with Stage III and IV endometriosis, implantation rates were found to be significantly reduced (Simon et al.,1994). In view of the lower implantation and clinical pregnancy

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rates in women with endometriosis undergoing IVF using their own oocytes (Harb et al., 2013), these findings support the concept that women with endometriosis have lower oocyte quality and normal endometrial receptivity.

However, a number of publications suggest that there is no reduction in oocyte quality in women with endometriosis. In a large retrospective study of 596 women the presence of deep pelvic endometriosis lesions or endometriomas did not have an adverse impact on oocyte morphology (Robin et al., 2021), although women with endometriosis had fewer metaphase II oocytes retrieved, a lower total number of embryos and number of top-quality embryos and a lower cumulative clinical pregnancy rate, which the authors attributed to lower oocyte yield. A recent prospective cohort study of 503 IVF cycles comparing women with endometriosis to controls with tubal or unexplained infertility reported no difference in the mean fertilisation rate, independent of age and r-ASRM classification (Metzemaeker et al., 2020), findings that are consistent with several previous studies (Filippi et al., 2014, Yang et al., 2015, Demirel et al., 2016, Hamdan et al., 2015).

There are several mechanisms postulated for the possible lower oocyte quality in women with endometriosis. The presence of ovarian endometriosis is proposed to induce local pelvic inflammation and higher oxidative stress in the ovarian cortex, resulting in altered follicular and oocyte development and altered oocyte morphology (Matsuzaki et al., 2010, Kitajama et al., 2014). Reactive oxygen species (ROS) have been suggested to reduce oocyte quality by promoting meiotic abnormalities and chromosomal instability in women with endometriosis (Mansour et al., 2010). Moreover, the follicular milieu in infertile women with endometriosis is reported to show a lower antioxidant capacity and increased oxidative stress on mass spectrometry (Prieto et al., 2012, Regiani et al., 2015). Iron-mediated oxidative damage to the surrounding follicles has been associated with the presence of ovarian endometriosis, with higher levels of iron in the fluid of follicles developing adjacent to an endometriotic-cyst compared to contralateral healthy ovaries (Sanchez et al., 2014). In addition, RNA sequencing of oocytes in women with ovarian endometriosis and healthy oocytes has shown that women with endometriosis have a differential transcriptomic profile associated with lower oocyte quality (Ferrero et al., 2019). Affected pathways included those related to key biological processes such as steroid metabolism, response to oxidative stress and regulation of cell growth regulation, which could explain the reduction in oocyte quality (Ferrero et al., 2019).

The differing parameters used to assess oocyte quality make it challenging to compare findings between studies and may explain the conflicting data in the literature. The majority of studies have been conducted in small samples and each investigated a limited number of varying morphological abnormalities. Several studies in the literature provide an indirect assessment of the effect of endometriosis on oocyte quality, by studying granulosa cells or follicular fluid content of women with endometriosis. Others have used embryo quality as an indicator of oocyte quality, which is influenced by the male partner (Avedano et al., 2010, Anifandis et al., 2015).

Development of an updated consensus on oocyte and embryo quality assessment parameters aims to address this for future research studies. Current evidence suggests that the clinical impact of oocyte morphology on reproductive outcomes in women with endometriosis undergoing IVF is limited. Whilst there is evidence to suggest that impaired oocyte morphology in women with endometriosis may have an adverse impact on fertilisation rate, most studies have shown that there is no difference in embryo cleavage, implantation or clinical pregnancy rates following IVF, suggesting that once the oocyte is fertilised the chance of pregnancy is similar in women with and without endometriosis (Filippi et al., 2014, Yang et al., 2015, Demirel et al., 2016, Ashrafi et al. 2014, Metzemaeker et al., 2020, Robin et al., 2021).

Embryo quality in women with endometriosis

Several studies have examined the quality of embryos derived from oocytes of women with endometriosis to determine the impact of endometriosis on embryo quality, with conflicting results. A systematic review and meta-analysis evaluating the impact of endometriosis on embryo quality suggested that endometriosis does not compromise embryo quality from the perspective of

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morphology, with authors highlighting that there is a need for universal criteria and terminology for grading embryos to reduce the large heterogeneity between studies (Dongye et al., 2021).

A study of human oocytes exposed to endometriosis fluid from women with stage III/IV endometriosis reported a negative effect on the morphology of embryos with excess cellular fragmentation, proposing that increased cell fragmentation is implicated in impaired embryo development by inducing cell death in surrounding blastomeres or altering blastomere division (Paffoni et al., 2019). Pellicer and colleagues found that women with stage III/IV endometriosis had fewer blastomeres per embryo and a higher number of arrested embryos (Pellicer et al., 2001). Women with endometriosis have also been reported to have an increased incidence of aberrant development of embryos, with more prevalent nuclear and cytoplasmic impairment, cytoplasmic fragmentation and uneven cleavage in the endometriosis group (Brizek et al., 1995).

Conversely, whilst women with endometriomas undergoing IVF have been reported to have a significantly lower number of oocytes and number of MII oocytes retrieved compared to controls with tubal and male-factor infertility, there is no difference in their total number of embryos, number of top-quality embryos, clinical pregnancy rate, implantation rate or live birth rate (Alshehre, et al., 2020). Women operated for moderate/severe endometriosis are reported to have an equivalent number of cleavage embryos and good quality embryos compared to women without endometriosis (Sanchez et al., 2020). In a study evaluating the impact of endometriosis on embryonic aneuploidy, analysis of 25,000 blastocysts from women with and without endometriosis undergoing IVF with pre-implantation genetic screening (PGS) showed no difference in aneuploidy rates when stratified for age (Juneau et al., 2017).

Table 1. Summary of findings from studies examining the impact of endometriosis on oocyte and embryo quality.

Study author(s)	**Oocyte quality in women with endometriosis**	**Study author(s)**	**Embryo quality in women with endometriosis**
Sanchez et al., 2017	Reduced, as evidenced by: - Altered oocyte morphology - Increased likelihood of oocyte to fail in vitro maturation (IVM) - Lower cytoplasmic mitochondrial content	Brizek et al., 1995	Reduced, as evidenced by: Increased incidence of aberrant development of embryos (more prevalent nuclear and cytoplasmic impairment, cytoplasmic fragmentation, uneven cleavage)
Goud et al., 2014	Reduced, as evidenced by: - Increased likelihood of oocyte to fail in vitro maturation (IVM) - Altered oocyte morphology (higher incidence of cortical granule loss, spindle disruption zona pellucida hardening)	Pellicer et al., 2001	Reduced, as evidenced by: - Altered embryo morphology (fewer blastomeres per embryo, higher number of arrested embryos

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Kasopoglu et al., 2017	Reduced, as evidenced by: - Altered morphology (morphological abnormalities of the cytoplasm, zona pellucida and first polar body)	Paffoni et al., 2019	Reduced, as evidenced by: - Altered embryo morphology (excess cellular fragmentation, cell death in blastomeres and altered blastomere division
Simon et al., 1994, Sung et al., 1997, Diaz et al., 2000	Reduced, as evidenced by: - Lower implantation rates in donor oocytes from women with endometriosis - Equivalent implantation rates and pregnancy rates when women with endometriosis using donor oocytes from healthy women.	Alshehre, et al., 2020	Not reduced, as evidence - No difference in total number of embryos - No difference in number of top-quality embryos - No difference in clinical pregnancy rate, implantation rate or live birth rate
Ferrero et al., 2019	Reduced, as evidenced by: - Differential transcriptomic profile associated with lower oocyte quality.	Sanchez et al., 2020	Not reduced: - Equivalent number of cleavage embryos - Equivalent number of good quality embryos
Robin et al. 2021	Not reduced, as evidenced by: - Normal oocyte morphology - Lower number of top-quality embryos and a lower cumulative clinical pregnancy rate attributed to lower oocyte yield -	Dongye et al., 2021	Not reduced, as evidenced by: - Normal embryo morphology
Metzemaeker et al., 2020, Filippi et al., 2014, Yang et al., 2015, Demirel et al., 2016, Hamdan et al., 2015	Not reduced, as evidenced by: - Equivalent fertilisation rates	Juneau et al., 2017	Not reduced, as evidenced by: - No difference in aneuploidy rates

Endometriosis and IVF outcome

A large meta-analysis in women undergoing assisted conception for tubal-factor infertility reported that women with ASRM stage I/II endometriosis have reduced fertilization and implantation rates compared to women without endometriosis (Barnhart et al., 2002). Other IVF outcomes, including number of oocytes retrieved and fertilization rate were affected by the presence of endometriosis at all stages, suggesting that endometriosis affects fertility, oocyte and embryo quality and endometrial receptivity (Barnhart et al., 2002). This meta-analysis included articles published prior to 2000 when ART success rates were considerably lower than the current levels.

Another meta-analysis found that women with ASRM stage I/II endometriosis compared to women without endometriosis had lower fertilisation rates with no significant reduction in implantation, clinical pregnancy, or live birth rates (Harb et al., 2013). Women with stage III/IV endometriosis were found to have reduced implantation and clinical pregnancy rates but with no reduction in livebirth rate (Harb et al., 2013).

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A subsequent meta-analysis in women with endometriosis undergoing IVF compared to women without endometriosis similarly reported a reduction in mean number of oocytes retrieved per cycle and clinical pregnancy rate with no difference in live birth rate (Hamdan et al., 2015). Subgroup analysis showed that women with ASRM stage III/IV had lower clinical pregnancy rate and also lower live birth rate (Hamdan et al., 2015).

An analysis of 347,185 IVF cycles from the Society for Assisted Reproductive Technologies (SART) database evaluating the impact of endometriosis on reproductive outcomes also showed that women with endometriosis had a significantly lower oocyte yield, lower implantation rate and lower live birth rate following IVF treatment (Senapati, et al., 2016). Notably, in this study women with endometriosis had other co-existing infertility diagnoses. In the small number of women who had endometriosis alone, the live birth rate was reported to be similar or slightly higher than other infertility diagnoses.

A large retrospective study using data from the Latin American Data Registry in patients undergoing IVF showed that endometriosis does not affect the outcome of women having IVF (Murta, et al., 2018). Whilst women with endometriosis had a lower number of oocytes retrieved and higher cancellation rate, these findings did not translate to reduced pregnancy and live birth rates (Murta, et al., 2018), findings in keeping with several other meta-analyses (Barbosa et a., 2014, Yang et al., 2015, Alshehre et al., 2021, Qu et al., 2022).

Most recently, 13,614 IVF cycles were analysed using data from the Human Fertilization and Embryology Authority (HFEA) in women with endometriosis undergoing either donor oocyte recipient or autologous IVF cycles (Kamath et al., 2022). The authors reported no significant difference in live birth rate between the two groups in both fresh and frozen embryo transfer cycles, suggesting minimal or no effect of oocyte quality on IVF outcomes in women with endometriosis, though there was no information on the extent of endometriosis or number of oocytes retrieved.

Management options

There are limited studies evaluating medical management options to address the impact of endometriosis on oocyte and embryo quality.

In a Cochrane review evaluating the effect of medical ovarian suppression agents versus no treatment there was no significant difference in clinical pregnancy rate in women with endometriosis (Hughes et al al., 2007). Importantly, several patients included in this review had previously undergone surgical treatment, therefore recommendations on ovarian suppression and post-surgical ovarian suppression remain unclear (Hughes et al., 2007).

The effect of gonadotrophin-releasing hormone (GnRH) agonists on oocyte and embryo quality in women endometriosis has been investigated in a small number of studies. A retrospective cohort study comparing the administration of GnRH agonist alone or combined with the aromatase inhibitor letrozole prior to IVF in patients with endometriosis found no significant difference between groups in the number of oocytes, embryos and fertilization rates, though the mean percentage of mature oocytes was higher in the group treated with GnRH agonist alone (Kim et al., 2020). In contrast, in a similar study another research group observed a significantly higher number of oocytes, clinical pregnancy rate and live birth rate in patients with endometriosis treated with the combination of GnRH agonist and letrozole compared to patients treated with GnRH agonist alone (Cantor et al., 2019). However, this was a small study and further evaluation is needed. A Cochrane review evaluating the effectiveness of prolonged GnRH analogue use in women with endometriosis prior to IVF reported an uncertain effect on clinical pregnancy, live birth rate, number of oocytes retrieved and number of embryos due to low quality evidence, highlighting the need for more data (Georgiou et al., 2019).

A few studies have investigated the impact of dienogest on oocyte and embryo quality in women with endometriosis, with varying results. One study showed that women receiving dienogest had significantly higher clinical pregnancy (44.7% vs 16.7%) and live birth rate (36.8% vs 11.1%) compared to controls (Muller et al., 2017). Treatment with dienogest and the GnRH agonist triptorelin in patients after laparoscopic surgery and before ovarian stimulation in IVF cycles resulted in a

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significantly higher number of oocytes retrieved and good-quality embryos compared to women receiving no treatment (Muller et al., 2017). Several research groups have found no significant impact of dienogest on oocyte quality or fertilization rates in women with endometriosis undergoing IVF (Kim et al., 2017, Barra et al., 2020). Barra and colleagues compared IVF outcomes in patients with endometriosis with and without pre-treatment with dienogest for 3 months. They found no differences in the number of MII oocytes or embryo quality between groups, although in women with large endometriomas, dienogest treatment significantly increased the number of oocytes retrieved, two-pronuclear embryos and blastocysts compared to controls (Barra et al., 2020). More recently a negative effect of dienogest on reproductive outcomes has been suggested. Women with endometriosis taking dienogest prior to IVF were found to have a lower number of mature oocytes retrieved, lower fertilisation rates and lower livebirth rate (Tamura et al. 2019, Sakamoto et al., 2021). Overall, the evidence on the impact of dienogest on oocyte quality in women with endometriosis is mixed and further research is needed.

Antioxidants have been proposed as a therapeutic approach to improve oocyte quality in patients with endometriosis due to the association between increased oxidative stress and poor oocyte quality. One study found that the administration of vitamins C and E to patients for 6 months significantly decreased plasma oxidative stress markers, with a trend towards increased pregnancy rates when compared to women receiving placebo (Mier-Cabrera et al., 2008). Porpora et al. reported that N-acetyl cysteine (NAC) supplementation decreases endometrioma size compared to no treatment, with no difference in pregnancy rates (Porpora et al., 2013). These preliminary findings with antioxidant supplementation need further evaluation.

Pentoxifylline has anti-angiogenic effects and has been postulated to lead to endometriosis lesion regression (Pellicer et al., 2021). Some studies have suggested that pentoxifylline may improve oocyte quality, fertilisation rates and embryo development in women with endometriosis (Barri et al., 2001 and Oliviera et al., 2009) whereas others have found no beneficial effect on oocyte and embryo quality (Alborzi et al., 2007, Somigliana et al., 2019). The effects of pentoxifylline have been evaluated in a recent Cochrane systematic review based on three randomised controlled trials in 285 patients, which showed that overall the evidence for the effect of pentoxifylline versus placebo on clinical pregnancy rates is uncertain and there are no trials that have reported on the effects of pentoxifylline on live birth rate (Grammatis, et al., 2021).

There is limited research on the impact of metformin on oocyte quality in women with endometriosis. Metformin is an anti-inflammatory agent with a modulatory effect on sex-steroid production. Foda and Aal reported that pregnancy rates were significantly higher in patients with Stages I–II endometriosis treated with metformin compared to no treatment (25.71% vs 11.76%) (Foda and Aal, 2012). Some studies have suggested a positive impact of metformin on oocyte quality, fertilisation rate, clinical pregnancy and livebirth rate (Palomba et al., 2008, Kuang et al., 2017), in contrast to others which show no difference (Badawy et al., 2011). Overall, the evidence on the impact of metformin on oocyte quality in women with endometriosis is mixed and further studies are needed to fully evaluate its effect.

A few studies have investigated the role of surgical treatment in women with endometriosis undergoing IVF, though there are no randomised controlled trials. A systematic review and meta-analysis comparing reproductive outcomes in patients who underwent surgery for deep infiltrative endometriosis (DIE) before IVF versus patients who underwent IVF without previous surgery for DIE showed that there may be a beneficial role for surgery prior to IVF treatment, though there is some concern over the accuracy of their analysis and the significant loss to follow up (Casals et al., 2021). One research group has compared surgical treatment for minimal and mild endometriosis with diagnostic laparoscopy alone in 661 women prior to undergoing IVF treatment (Opoien et al., 2011). Notably, duration of infertility and time interval between surgery and IVF treatment were substantially different between the groups, which may in itself entirely account for the minor difference in livebirth rates (27.7% vs 20.6%) (Opoien et al., 2011). Nevertheless, women with ASRM stage I and II endometriosis who underwent surgical removal of all visible endometriosis lesions had significantly improved implantation rates, pregnancy rates and livebirth rates and were noted to have

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a shorter time to pregnancy and higher cumulative pregnancy rate (Opoien et al., 2011). Several studies have evaluated the impact of surgery for endometriomas including a systematic review and meta-analysis by Alborzi and colleagues, reporting no significant difference in pregnancy rate when compared to other treatments such as surgery combined with IVF, IVF alone or aspiration with or without sclerotherapy followed by IVF (Alborzi et al., 2019, Demirdag et al., 2021, Hernandez et al., 2023).

Conclusions and Future research

Endometriosis is a heterogeneous disease associated with infertility. The presence of endometriosis may reduce oocyte quality and embryo quality. However, this does not appear to translate to a clear clinical impact on IVF outcome. Results from meta-analyses addressing IVF outcomes in affected women suggest that the reduction in the number of mature oocytes retrieved is associated with the presence of endometriosis while a reduction in fertilisation rates is more likely to be associated with minimal/mild rather than with moderate/severe disease (Barnhart et al., 2002, Harb et al., 2013, Barbosa et al., 2014, Hamdan et al., 2015, Yang et al., 2015, Qu et al., 2022). Overall, there does not appear to be a negative impact of endometriosis on live birth rate following IVF, despite lower oocyte yield and altered oocyte and embryo quality.

However further research is needed, particularly regarding the effect of different stages of the disease, its location and the impact of previous medical and surgical treatment. Surgery in women with endometriosis has not been shown to improve reproductive outcomes following IVF and may further reduce ovarian reserve. Data on the impact of medical treatments for endometriosis on IVF remains limited. There is a need for well-designed randomised controlled trials to further evaluate the role of surgical and medical treatment options in women with endometriosis undergoing IVF and the impact of the severity of endometriosis and its location.

Development of an updated consensus on oocyte and embryo quality assessment parameters for use in future research studies is fundamental. A greater understanding of the effect of endometriosis on ovarian function will allow better timing and tailoring of medical and surgical treatments. As the field of fertility preservation grows, a greater understanding of the impact of the disease on oocyte quality is fundamental to appropriately counsel suitable patients affected by endometriosis for fertility preservation.

References

1. Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, Rich-Edwards JW, Barbieri RL, Missmer SA. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod. 2016 Jul;31(7):1475-82. doi: 10.1093/humrep/dew085.
2. Zondervan K, Becker C, Missmer S. Endometriosis. N Engl J Med. 2020;382:1244–56
3. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. Fertil Steril. 2002;77(6):1148–55.
4. Harb H, Gallos I, Chu J, Harb M, Coomarasamy A. The effect of endometriosis on in vitro fertilisation outcome: a systematic review and meta-analysis. Bjog Int J Obstetrics Gynaecol. 2013;120(11):1308–20.
5. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. Hum Reprod Update. 2015;21(6):809–25.
6. Yang C, et al. Impact of ovarian endometrioma on ovarian responsiveness and IVF: a systematic review and meta-analysis. Reprod Biomed Online. 2015
7. Barbosa MA, et al. Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2014
8. Qu H, et al. The effect of endometriosis on IVF/ICSI and perinatal outcome: A systematic review and meta-analysis. J Gynecol Obstet Hum Reprod. 2022
9. Senapati S, Sammel MD, Morse C, Barnhart KT. Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database. Fertil Steril. 2016 Jul;106(1):164-171.e1.

10. Murta M, Machado RC, Zegers-Hochschild F, Checa MA, Sampaio M, Geber S. Endometriosis does not affect live birth rates of patients submitted to assisted reproduction techniques: analysis of the Latin American Network Registry database from 1995 to 2011. J Assist Reprod Genet. 2018 Aug;35(8):1395-1399.
11. Kamath M, Subramanian V, Antonisamy B, Sunkara S. Endometriosis and oocyte quality: An analysis of 13,614 donor oocyte recipient and autologous IVF cycles. Hum Reproduction Open. 2022;2022(3):hoac025.
12. Alpha Scientists in Reproductive Medicine; ESHRE Special Interest Group Embryology. Istanbul consensus workshop on embryo assessment: Proceedings of an expert meeting. Reprod Biomed Online. 2011, 22, 632–646.
13. Van Blerkom J, Henry G. Oocyte dysmorphism and aneuploidy in meiotically mature human oocytes after ovarian stimulation. Hum Reprod. 1992 Mar;7(3):379-90. doi: 10.1093/oxfordjournals.humrep.a137655.
14. Gianaroli L, Magli MC, Cavallini G, Crippa A, Capoti A, Resta S, et al.. Predicting aneuploidy in human oocytes: key factors which affect the meiotic process. *Hum Reprod.* (2010) 25:2374–86. 10.1093/humrep/deq123
15. Setti AS, Figueira RC, Braga DP, Colturato SS, Iaconelli A Jr, Borges E Jr. Relationship between oocyte abnormal morphology and intracytoplasmic sperm injection outcomes: a meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2011 Dec;159(2):364-70.
16. Sanchez A, Vanni VS, Bartiromo L, Papaleo E, Zilberberg E, Candiani M, Orvieto R, Viganò P. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res. 2017;10(1):43.
17. ESHRE Endometriosis Guideline Development Group. 2022 European Society for Human Reproduction and Embryology Guideline: Endometriosis.
18. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. Fertil Steril. 2012 Sep;98(3):591-8.
19. Goud P, Goud AP, Joshi N, Puscheck E, Diamond M, Abu-Soud H. Dynamics of nitric oxide, altered follicular microenvironment, and oocyte quality in women with endometriosis. Fertil Steril. 2014 Jul;102(1):151-159.e5. doi: 10.1016/j.fertnstert.2014.03.053.
20. Kasapoglu I, Kuspinar G, Saribal S, Turk P, Avcı B, Uncu G. Detrimental effects of endometriosis on oocyte morphology in intracytoplasmic sperm injection cycles: a retrospective cohort study. Gynecol Endocrinol. 2017;34(3):1–6.
21. Simón C, Gutiérrez A, Vidal A, Santos MJ de los, Tarín JJ, Remohí J, Pellicer A. Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Hum Reprod. 1994;9(4):725–9.
22. Sung L, Mukherjee T, Takeshige T, Bustillo M, Copperman AB. Endometriosis is not detrimental to embryo implantation in oocyte recipients. J Assist Reprod Genet. 1997 Mar;14(3):152-6.
23. Díaz I, Navarro J, Blasco L, Simón C, Pellicer A, Remohí J. Impact of stage III-IV endometriosis on recipients of sibling oocytes: matched case-control study. Fertil Steril. 2000 Jul;74(1):31-4. doi: 10.1016/s0015-0282(00)00570-7.
24. Robin C, Uk A, Decanter C, Behal H, Collinet P, Rubod C, Barbotin AL, Robin G. Impact of endometriosis on oocyte morphology in IVF-ICSI: retrospective study of a cohort of more than 6000 mature oocytes. Reprod Biol Endocrin. 2021;19(1):160.
25. Metzemaekers J, Lust E, Rhemrev J, Geloven NV, Twijnstra A, Westerlaken LVD, Jansen F. Prognosis in fertilisation rate and outcome in IVF cycles in patients with and without endometriosis: a population-based comparative cohort study with controls. Facts Views Vis Obgyn. 2021;13(1):27–34.
26. Filippi F, Benaglia L, Paffoni A, Restelli L, Vercellini P, Somigliana E, Fedele L. Ovarian endometriomas and oocyte quality: insights from in vitro fertilization cycles. Fertil Steril. 2014 Apr;101(4):988-93.e1.
27. Yang C, Geng Y, Li Y, Chen C, Gao Y. Impact of ovarian endometrioma on ovarian responsiveness and IVF: a systematic review and meta-analysis. Reprod Biomed Online. 2015;31(1):9–19.
28. Demirel C, Bastu E, Aydogdu S, Donmez E, Benli H, Tuysuz G, Keskin G, Buyru F. The Presence of Endometrioma Does Not Impair Time-Lapse Morphokinetic Parameters and Quality of Embryos: A Study On Sibling Oocytes. Reprod Sci. 2016 Aug;23(8):1053-7.
29. Dongye H, et al. The Impact of Endometriosis on Embryo Quality in in-vitro Fertilization/Intracytoplasmic Sperm Injection: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021
30. Nakagawa K, Hisano M, Sugiyama R, Yamaguchi K. Measurement of oxidative stress in the follicular fluid of infertility patients with an endometrioma. Arch Gynecol Obstet. 2016;293:197–202

31. Matsuzaki S, Schubert B. Oxidative stress status in normal ovarian cortex surrounding ovarian endometriosis. Fertil Steril 2010;93: 2431–2432.
32. Kitajima, M.; Dolmans, M.-M.; Donnez, O.; Masuzaki, H.; Soares, M.; Donnez, J. Enhanced Follicular Recruitment and Atresia in Cortex Derived from Ovaries with Endometriomas. Fertil. Steril. 2014, 101, 1031–1037
33. Mansour, G.; Sharma, R.K.; Agarwal, A.; Falcone, T. Endometriosis-Induced Alterations in Mouse Metaphase II Oocyte Microtubules and Chromosomal Alignment: A Possible Cause of Infertility. Fertil. Steril. 2010, 94, 1894–1899
34. Prieto L, Quesada JF, Cambero O, Pacheco A, Pellicer A, Codoceo R, Garcia-Velasco JA. Analysis of follicular fluid and serum markers of oxidative stress in women with infertility related to endometriosis. Fertil Steril. 2012 Jul;98(1):126-30.
35. Regiani T, Cordeiro FB, da Costa Ldo V, Salgueiro J, Cardozo K, Carvalho VM, Perkel KJ, Zylbersztejn DS, Cedenho AP, Lo Turco EG. Follicular fluid alterations in endometriosis: label-free proteomics by MS(E) as a functional tool for endometriosis. Syst Biol Reprod Med. 2015;61(5):263-76.
36. Sanchez AM, Papaleo E, Corti L, Santambrogio P, Levi S, Viganò P, Candiani M, Panina-Bordignon P. Iron availability is increased in individual human ovarian follicles in close proximity to an endometrioma compared with distal ones. Hum Reprod. 2014;29(3):577–83.
37. Ferrero H, Corachán A, Aguilar A, Quiñonero A, Carbajo-García MC, Alamá P, Tejera A, Taboas E, Muñoz E, Pellicer A, Domínguez F. Single-cell RNA sequencing of oocytes from ovarian endometriosis patients reveals a differential transcriptomic profile associated with lower quality. Hum Reprod. 2019 Jul 8;34(7):1302-1312.
38. Avedano C, Franchi A, Duran H, Oehninger S. DNA fragmentation of normal spermatozoa negatively impacts embryo quality and intracytoplasmatic sperm injection outcome. Fertil Steril. 2010;94:549–57.
39. Anifandis G, Bounartzi T, Messini CI, Dafopoulos K, Markandona R, Sotiriou S, et al. Sperm DNA fragmentation measured by Halosperm does not impact on embryo quality and ongoing pregnancy rates in IVF/ICSI treatments. Andrologia. 2015;47:295–302.
40. Ashrafi M, Fakheri T, Kiani K, Sadeghi M, Akhoond MR. Impact of the endometrioma on ovarian response and pregnancy rate in in vitro fertilization cycles. *Int J Fertil Steril.* 2014;8(1):29–34.
41. Paffoni A, Bolis V, Ferrari S, Benaglia L, Vercellini P, Somigliana E. The Gametotoxic Effects of the Endometrioma Content: Insights From a Parthenogenetic Human Model. Reprod Sci. 2019 May;26(5):573-579.
42. Pellicer A, Navarro J, Bosch E, Garrido N, Garcia-Velasco JA, Remohi J, et al. Endometrial quality in infertile women with endometriosis. Ann N Y Acad Sci. 2001;943:122–30.
43. Brizek, C.L.; Schlaff, S.; Pellegrini, V.A.; Frank, J.B.; Worrilow, K.C. Increased Incidence of Aberrant Morphological Phenotypes in Human Embryogenesis–an Association with Endometriosis. J. Assist. Reprod. Genet. 1995, 12, 106–112.
44. Alshehre SM, Narice BF, Fenwick MA, Metwally M. The impact of endometrioma on in vitro fertilisation/intra-cytoplasmic injection IVF/ICSI reproductive outcomes: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021 Jan;303(1):3-16. doi: 10.1007/s00404-020-05796-9.
45. Sanchez AM, Pagliardini L, Cermisoni GC, Privitera L, Makieva S, Alteri A, Corti L, Rabellotti E, Candiani M, Viganò P. Does Endometriosis Influence the Embryo Quality and/or Development? Insights from a Large Retrospective Matched Cohort Study. Diagnostics. 2020;10(2):83.
46. Juneau C, Kraus E, Werner M, Franasiak J, Morin S, Patounakis G, Molinaro T, Ziegler D de, Scott RT. Patients with endometriosis have aneuploidy rates equivalent to their age-matched peers in the in vitro fertilization population. Fertil Steril. 2017;108(2):284–8.
47. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev. 2007 Jul 18;2007(3):CD000155.
48. Kim SJ, Choo CW, Kim SK, Lee JR, Jee BC, Suh CS, Lee WD, Kim SH. The effects of letrozole on women with endometriosis undergoing ovarian stimulation for in vitro fertilization. Gynecol Endocrinol 2020;36:257–260.
49. Cantor A, Tannus S, Son WY, Tan SL, Dahan MH. A comparison of two months pretreatment with GnRH agonists with or without an aromatase inhibitor in women with ultrasound-diagnosed ovarian endometriomas undergoing IVF. Reprod Biomed Online 2019;38: 520–527.

50. Georgiou E, Melo P, Baker P, Sallam H, Arici A, Garcia-Velasco J, Abou-Setta A, Becker C, Granne I. Long-term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis. Cochrane Db Syst Rev. 2019;2019(11).
51. Muller V, Kogan I, Yarmolinskaya M, Niauri D, Gzgzyan A, Aylamazyan E. Dienogest treatment after ovarian endometrioma removal in infertile women prior to IVF. Gynecol Endocrinol. 2017;33(sup1):18-21.
52. Kim JH, Kim JW, Lee J, Yang M, Kim M, Kim SK. Dienogest does not negatively affect oocyte and embryo quality: a retrospective study of women with endometriosis. Gynecological Endocrinology. 2017;33(5), 356-359.
53. Tamura H, Nakayama T, Kanno M, Kaneko Y, Minase G, Terauchi F. Impact of dienogest on fertility preservation in patients with endometriosis. Reproductive Sciences. 2016;23(3), 371-376
54. Sakamoto Y, Kishi Y, Takahashi K, Yoshioka S, Araki R, Fujii T, Irahara M. Dienogest may reduce the number of mature oocytes retrieved in women with endometriosis during in vitro fertilization treatment. Fertility and Sterility. 2021;115(1), 121-127.
55. Mier-Cabrera J, Genera-García M, De la Jara-Díaz J, Perichart-Perera O, Vadillo-Ortega F, Hernández-Guerrero C. Effect of vitamins C and E supplementation on peripheral oxidative stress markers and pregnancy rate in women with endometriosis. Int J Gynaecol Obstet 2008;100:252–256
56. Porpora MG, Brunelli R, Costa G, Imperiale L, Krasnowska EK, Lundeberg T, Nofroni I, Piccioni MG, Pittaluga E, Ticino A et al. A promise in the treatment of endometriosis: an observational cohort study on ovarian endometrioma reduction by N-acetylcysteine. Evid Based Complement Alternat Med 2013;2013:1–7.
57. Pellicer N, Galliano D, Herraiz S, Bagger YZ, Arce Jc, Pellicer A. Use of dopamine agonists to target angiogenesis in women with endometriosis. Hum Reprod 2021;36:850–858.
58. Barri P, Coroleu B, Tur R, Barri-Soldevila P, Veiga A. Effects of pentoxifylline on in vitro fertilization and embryo development in patients with endometriosis. Journal of Assisted Reproduction and Genetics, 2001;18(6), 326-329.
59. Oliveira J, Baruffi R, Mauri A, Petersen C, Borges M, Franco Jr J. Pentoxifylline enhances the effects of recombinant follicle-stimulating hormone in women with endometriosis undergoing controlled ovarian stimulation and intrauterine insemination: a prospective, randomized, double-blinded, placebo-controlled trial. Fertility and Sterility. 2009;91(6), 2450-2455.
60. Alborzi S, Ghotbi S, Parsanezhad ME, Dehbashi S, Alborzi S, Alborzi M. Pentoxifylline therapy after laparoscopic surgery for different stages of endometriosis: a prospective, double-blind, randomized, placebo-controlled study. J Minim Invasive Gynecol. 2007 Jan-Feb;14(1):54-8. doi: 10.1016/j.jmig.2006.06.024.
61. Hernández A, Sanz A, Spagnolo E, Lopez A, Jorge PM, Iniesta S, Rodríguez E, Prada SF, Ramiro-Cortijo D. Impact of Ovarian Endometrioma and Surgery on Reproductive Outcomes: A Single-Center Spanish Cohort Study. Biomed. 2023;11(3):844.
62. Demirdag E, Guler I, Selvi I, Akdulum MFC, Canan S, Erdem A, Erdem M. Analysis of 2438 cycles for the impact of endometrioma and its surgery on the IVF outcomes. Eur J Obstet Gyn R B. 2021;263:233–8.
63. Somigliana E, Scafuro M, Benaglia L, Ragni G, Viganò P. Pentoxifylline in women with endometriosis undergoing in vitro fertilization: a randomized controlled trial. Human Reproduction, 2019;34(7), 1254-1260.
64. Grammatis AL, Georgiou EX, Becker CM. Pentoxifylline for the treatment of endometriosis-associated pain and infertility. Cochrane Database Syst Rev. 2021 Aug 25;8(8):CD007677. doi: 10.1002/14651858.CD007677.
65. Foda, A and I Aal. Metformin as a new therapy for endometriosis, its effects on both clinical picture and cytokines profile. Middle East Fertility Society Journal 2012;17(4): 262-267.
66. Palomba S, Falbo A, Russo T, Battaglia F, Tolino, A. Metformin administration and pregnancy rate in women with polycystic ovary syndrome and known infertility. Obstetrics & Gynecology, 2008;111(4), 959-968.
67. Kuang Y, Chen Q, Hong Q, Lyu Q, Ai A, Fu Y, Li Y. Metformin therapy for the management of infertility in women with polycystic ovary syndrome. Scientific Reports, 2017; 7(1), 1-7.
68. Badawy A, Elnashar, A, El-Ashry M. One-day versus multiple-day administration of metformin for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a randomized controlled trial. Gynecological Endocrinology. 2011;27(10), 805-810.

69. Casals G, Carrera M, Domínguez JA, Abrão MS, Carmona F. Impact of Surgery for Deep Infiltrative Endometriosis before In Vitro Fertilization: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021 Jul;28(7):1303-1312.e5.
70. Opøien HK, Fedorcsak P, Byholm T, Tanbo T. Complete surgical removal of minimal and mild endometriosis improves outcome of subsequent IVF/ICSI treatment. Reprod Biomed Online. 2011 Sep;23(3):389-95. doi: 10.1016/j.rbmo.2011.06.002.
71. Alborzi S, Zahiri Sorouri Z, Askari E, Poordast T, Chamanara K. The success of various endometrioma treatments in infertility: A systematic review and meta-analysis of prospective studies. Reprod Med Biol. 2019 Jun 19;18(4):312-322.