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Infertility in Endometriosis: Understanding Its origins, diagnostic challenges and treatment complexities

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Abstract

Endometriosis, a complex chronic inflammatory condition, presents significant challenges in understanding its origins, diagnosing its manifestations, and managing its impact on fertility. This comprehensive review explores the intricate relationship between endometriosis and infertility, addressing theories on its pathogenesis, mechanisms affecting fertility, diagnostic modalities, and treatment complexities. Pathogenesis theories, including Sampson's theory and the stem cell theory, shed light on the genetic predisposition and mechanisms underlying endometriosis development. Endometriosis impacts fertility through various mechanisms, including anatomical distortion, steroid imbalance, and disrupted immunological environments. Diagnosis remains challenging, with laparoscopy as the gold standard and imaging modalities like transvaginal sonography and MRI serving as adjuncts. Treatment strategies involve a personalized approach based on disease classification, patient characteristics, and preferences, with options ranging from surgery to in-vitro fertilization (IVF). The choice between surgery and IVF remains debatable, with ongoing trials seeking to provide clarity. IVF protocols and transfer types pose additional complexities, with emerging adjuvants offering potential benefits. Concurrent adenomyosis further complicates IVF outcomes, emphasizing the need for specialized management strategies. Ongoing research initiatives hold promise for refining treatment pathways and improving clinical outcomes in this challenging clinical scenario.

Keywords: Endometriosis; Infertility; *In-vitro* fertilization; IVF protocol; Pre-IVF adjuvants

1. Introduction

The traditional definition of endometriosis as the presence of endometrial tissue outside the uterine cavity fails to capture the intricate nature of the condition and its significant impact. As such, a revised definition characterizes it as a complex clinical syndrome marked by estrogen-dependent chronic inflammation of pelvic tissues, accompanied by recurrent and persistent pelvic pain (chronic pelvic pain) and fertility issues during the reproductive years. Despite this clarification, the precise mechanisms underlying its manifestations remain elusive, particularly in terms of fertility impairment [1].

Endometriosis affects a substantial portion of women of reproductive age, i.e., around 10%, and about half of those seeking fertility services [2]. However, the most significant hurdle posed by this condition is the challenge of early diagnosis. The longer endometriosis remains undetected and untreated within the body, the more detrimental its effects on fertility potential. This issue is compounded by the natural decline in ovarian reserve as women age. The delay in diagnosing endometriosis, which can span anywhere from 4 to 11 years [3], represents a considerable portion of a woman's reproductive lifespan. During this time, individuals often suffer silently due to the limitations of current medical practices.

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This review delves into the narrative surrounding endometriosis and its intricate relationship with infertility, beginning with theories regarding its origins, continues with exploring how endometriosis impacts women's reproductive capabilities, the various methods of diagnosis available, and finally discussing the strategies implemented to address and fulfil the desire for motherhood among affected women.

1.1. Pathogenesis

- *Sampson's theory of Retrograde Menstruation* [4]: According to this theory, viable endometrial tissue flows backward into the pelvic cavity during menstruation. Once there, it adheres to tissues, proliferates, and responds to cyclical hormonal changes, mimicking the menstrual stages outside the uterine cavity. While retrograde menstruation is common, occurring in about 90% of women, the reasons why only 10% develop endometriosis remain unclear.
- *Coelomic metaplasia and Mullerianosis* [5]: Embryological remnants may undergo metaplasia, giving rise to endometrial-like tissue. This theory could explain rare cases of endometriosis in individuals who do not menstruate, such as those with Mayer-Rokitansky-Kuster-Hauser syndrome, as well as instances where endometriosis occurs in distant areas like the diaphragm and pleura.
- *Hematogenous and lymphatic spread* [6]: Endometrial tissue may spread to distant sites via the bloodstream and lymphatic vessels.
- *Stem cell theory* [7]: This theory partially supports Sampson's theory by addressing why only a fraction of women with retrograde menstruation develop endometriosis. It suggests that bone marrow stem cells contribute to the pool of endometrial progenitor cells. Individuals with endometriosis may have more pluripotent cells in their endometrial tissue, which, when shed during retrograde menstruation, can give rise to additional endometrial-like tissue outside the uterine cavity [8].
- *Genetics*: While multiple genes likely play a role in endometriosis, mothers can pass the condition on to their daughters, and its severity tends to increase across subsequent generations [9].

1.2. Impact of endometriosis on fertility

- *Painful Intercourse*: Endometriosis often manifests as chronic pelvic pain, significantly impacting a woman's sexual life. This can result in reduced desire and frequency of intercourse, subsequently lowering the chances of natural conception.
- *Anatomical Distortion*: Inflammation and fibrosis associated with endometriosis can lead to significant impairments in reproductive mechanisms. This includes disruptions to processes like oocyte pickup by the fallopian tube, its transport to the ampulla, and sperm movement, ultimately hindering fertilization due to disturbances in tubal motility [10].
- *Effect on Egg Number and Quality*: While there is debate surrounding the exact impact, many studies suggest that endometriosis can diminish ovarian reserve. This is primarily attributed to the presence of endometriomas, which can damage ovarian tissue through compression and the release of inflammatory substances. Assessing egg quality is complex, with various studies using different endpoints, such as embryo morphology [11], time-lapse grading [12] or the presence of clinical pregnancy [13]. Without a standardized definition, it's challenging to draw conclusive findings regarding the effect of endometriosis on egg quality.
- *Hormone Imbalance*: Endometriosis creates an environment characterized by estrogen dominance and progesterone resistance. This hormonal imbalance detrimentally affects reproductive tissues, particularly during the crucial luteal phase. In this phase, progesterone plays a vital role in facilitating communication between the egg and endometrium, setting the stage for embryo implantation upon fertilization. Reduced progesterone secretion from granulosa cells can impair oocyte maturation [14] and contribute to anovulation [15]. Luteinized unruptured follicle syndrome, observed more frequently in endometriosis cases, occurs when follicles fail to release eggs despite luteinization [16]. Additionally, the process of decidualization, essential for implantation during the luteal phase, may be compromised in endometriosis, leading to implantation failure and early pregnancy loss. Ultimately, the steroid imbalance in endometriosis reduces endometrial receptivity [17] diminishing the ability of the endometrium to support embryo implantation and growth, thereby contributing to infertility.
- *Genomic Insights*: Studies examining gene expression patterns have revealed that upregulation of certain homeobox genes plays a crucial role in the decidualization process, facilitating successful implantation. However, transcriptomic analyses of endometrial tissues from individuals with endometriosis have shown dysregulation in the levels of HOXA10 and HOXA11, both key homeobox genes involved in this process [18]. This impairment in gene expression contributes to reduced endometrial receptivity and subsequent implantation failure in patients with endometriosis.

- *Disrupted Immunological Environment*: Successful implantation hinges on maintaining a delicate balance between pro-inflammatory and anti-inflammatory factors, including various cytokines and growth factors. However, in the context of endometriosis, chronic inflammation prevails, characterized by an imbalance favouring pro-inflammatory mechanisms [19]. Treg cells, a specialized subset of T-cells responsible for modulating immune responses by secreting anti-inflammatory cytokines, play a crucial role in facilitating pregnancy establishment. In individuals with endometriosis, there is a notable decrease in the Treg cell population, which correlates strongly with implantation failure and early pregnancy loss [20].
- *Concurrent Adenomyosis and Endometriosis*: While numerous studies indicate a high prevalence of adenomyosis among individuals with endometriosis (79% in MRI-diagnosed endometriosis cases [21]), estimating the exact prevalence is challenging due to diagnostic complexities associated with both conditions. Many studies have not utilized the Morphological Uterus Sonographic assessment criteria (MUSA) for adenomyosis diagnosis [22] highlighting the need for further investigation in this area. Adenomyosis itself can contribute to infertility through various mechanisms, including increased uterine peristalsis and impaired endometrial receptivity caused by an inflammatory microenvironment. Among individuals undergoing in-vitro fertilization (IVF), those with adenomyosis demonstrate a notable decrease in pregnancy rates, as reported in studies [23].

1.3. Diagnosis

Diagnosing endometriosis poses a significant challenge, primarily due to the lack of non-invasive diagnostic methods. Endometriosis typically presents in three main forms: peritoneal (superficial), ovarian (endometriomas), and deep endometriosis (DE) [24]. However, existing diagnostic tools may not capture all these types effectively.

- *Laparoscopy*: While laparoscopy with histopathological examination of endometriotic deposits remains the gold standard for diagnosis, the decision to undergo surgery is often delayed, particularly in younger women. Given that approximately half of infertile women have endometriosis, suspicion of the condition warrants consideration, especially in the presence of symptoms such as cyclic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria, and non-cyclic chronic pelvic pain [25].
- *Transvaginal Sonography (TVUS*): Among non-invasive modalities, TVUS is typically the initial recommended investigation [26]. While TVUS can detect ovarian endometriomas, it is less effective for detecting peritoneal endometriosis. Deep endometriosis, involving structures like the uterosacral ligaments, bowel, rectovaginal septum, bladder, pelvic ureter, parametrium, and pelvic wall, can be identified using TVUS but requires specialized training.
- *MRI* serves as a second-line imaging modality for detecting both endometriomas and deep endometriosis. Although MRI offers higher diagnostic potential than TVUS [27], factors such as accessibility and cost often position it as a secondary choice in clinical practice
- *Biomarkers*: Numerous blood biomarkers have been investigated for their potential to serve as non-invasive tests for diagnosing endometriosis. These biomarkers encompass a range of factors including growth factors, apoptosis markers, cell adhesion molecules, hormones, immune and inflammation markers, microRNAs, tumour markers, and oxidative stress markers. However, according to Cochrane evidence, none of these biomarkers demonstrate sufficient accuracy for clinical use [28]. MicroRNAs, a type of non-coding RNA involved in post-transcriptional mRNA modification [29] have recently gained significant attention. Among them, microRNA200 has been extensively studied due to its association with early-stage endometriosis. However, the role of microRNAs in diagnosing endometriosis remains controversial and requires further investigation.

2. Management of endometriosis in infertility

- *Understanding the Classification System*: Effective management of endometriosis begins with understanding its classification system. The revised ASRM (American Society of Reproductive Medicine) classification, based on surgical staging, assesses the severity of endometriotic deposits in the peritoneum, ovary, tube, and cul-de-sac. There are four stages in this system and it's essential to note that this staging system focuses on the severity of surgical disease rather than clinical symptoms like pain and infertility.
- The Endometriosis Fertility Index (EFI), developed by Adamson and Pasta in 2009, provides a likelihood of achieving a non-assisted reproductive technology (ART) pregnancy (natural conception or after intrauterine insemination) within three years post-surgery [30]. Individuals with an EFI score of less than 4 are advised to consider immediate IVF, as their chances of a non-ART pregnancy are minimal.
- *Role of medical therapy*: Medical management does not play a role in addressing infertility associated with endometriosis, as it predominantly involves suppressing the hypothalamic-pituitary-ovarian axis, potentially delaying conception [26]. It may be considered solely if the woman opts to postpone conception and seeks relief from pain [26]. The Cochrane systematic review, which advocates for post-surgical GnRH agonist treatment

based on a slight increase in pregnancy rates (supported by weak evidence), did not prioritize pregnancy rate as a primary objective [31]. Additionally, the review did not conduct sensitivity analyses on the included data. Most studies assessing pregnancy outcomes have administered GnRH agonists for a duration of 3 months, with follow-up periods ranging between 1 to 2 years. However, the long-term efficacy of these drugs remains uncertain. Moreover, the review does not address infertility interventions such as IUI or IVF in the included studies.

2.1. Role of surgery and/or IVF

2.1.1. Favour surgery

- Stages I/II: Most cases of stages I/II endometriosis are not detectable through imaging and require laparoscopy for diagnosis. Studies suggest that patients with these stages who undergo surgery have a higher likelihood of spontaneous conception [32,33]. However, the number needed to treat rASRM stage I/II cases is 12, implying that 12 operative laparoscopies are necessary to yield one additional pregnancy among these patients. Given that approximately 30% of cases taken for surgery are diagnosed as rASRM stage I/II, this translates to a requirement of 40 laparoscopies to achieve one additional pregnancy [34]. This approach may prove impractical in resource-constrained settings. Consequently, many centres adopt a policy of treating all such cases as unexplained infertility, as imaging fails to provide evidence of endometriosis, managing them accordingly.

Moreover, within stage I/II cases, it is essential to distinguish between superficial and deep disease, as individuals with superficial disease may exhibit a more favourable response to surgical correction of anatomy. With advancements in ultrasound technology, detecting deep endometriosis before surgery has become feasible. Consequently, these cases may now be managed differently, potentially avoiding diagnostic laparoscopy or categorizing them as unexplained infertility.

Those with rASRM stage I/II disease, have a high EFI score and are therefore considered to have a good prognosis. They may be offered intrauterine insemination (IUI) with ovarian stimulation using clomiphene citrate [35]. For those with lower EFI scores, in-vitro fertilization (IVF) is often recommended. In summary, most cases of stage I/II disease exhibit a high EFI, indicating a favourable prognosis with a greater likelihood of achieving a non-ART pregnancy.

Stages III/IV endometriosis typically involves deep endometriosis and/or ovarian endometriomas, presenting a more complex management scenario. Treatment options include surgery followed by attempts at natural conception or IUI cycles, immediate progression to IVF without prior surgery, or surgery followed by IVF. A prospective cohort study focusing on individuals with advanced endometriosis and good prognosis (EFI>3) after conservative surgery indicated that post-surgery non-IVF treatments may yield similar pregnancy rates as IVF. These patients underwent conservative surgery involving complete resection of endometriotic lesions and reconstruction of reproductive anatomy. They were divided into two groups: one group initiated IVF treatment, while the other did not. Both cohorts were monitored for 36 months, revealing no significant difference in clinical pregnancy rates and live birth rates between the two groups [36]. The most number of pregnancies were within 6 months post-surgery and therefore utmost one-year post-surgery may be provided for natural conception for good prognosis patients [36].

The SVIDOE trial (Surgery Versus IVF for Deep and Ovarian Endometriosis) protocol has been published, intending to further explore the option of surgery vs IVF in advanced endometriosis. Patients diagnosed with these conditions via transvaginal ultrasound (TVUS) will be randomized into either surgery followed by one year of follow-up or three cycles of standard IVF. This trial aims to assess the likelihood of spontaneous pregnancies post-surgery and compare the time to pregnancy between the surgery-only and IVF-only approaches [37]. The results of this trial will provide valuable insights into the optimal management strategy post-surgery and the potential timeframe for attempting natural conception.

2.1.2. Favour IVF:

Currently, in cases of advanced endometriosis scheduled for in vitro fertilization (IVF), the European Society of Human Reproduction and Embryology (ESHRE) typically does not recommend surgery before IVF, except in special circumstances such as when a large endometrioma might impede access to follicles during oocyte retrieval [26]. Surgical intervention is not advised for endometriomas smaller than 3 cm in size, as it does not improve pregnancy rates but can significantly diminish ovarian reserve, particularly in less experienced hands [38]. Consequently, surgery for endometriomas is not recommended solely to enhance fertility [26].

For patients with deep endometriosis, a recent systematic review and meta-analysis indicated that undergoing surgery before in vitro fertilization (IVF) can enhance pregnancy rates [39]. However, many of the reported studies were retrospective, leading to potential selection bias. Additionally, comprehensive safety data should be reported to provide a thorough assessment of the risks and benefits associated with surgery. Moreover, it's important to note that surgical outcomes may vary depending on the expertise of the surgical team, and findings from studies conducted at specialized centres may not be universally applicable.

Due to the lack of robust evidence and the limited availability of trained surgeons capable of managing the potential complications associated with these surgeries, many patients opt to proceed directly to IVF without undergoing surgery. Advocates of surgery emphasize the importance of surgical expertise to minimize the impact on ovarian reserve and maximize the chances of conception and pain relief. Ultimately, the decision to pursue surgery or IVF depends on various factors, including the severity of endometriosis, age, ovarian reserve, presence of male factor infertility, previous surgeries, and patient preferences based on the severity of pain and desire to expedite conception [40]. Moreover, in cases where disease progression or the risk of ovarian malignancy is a concern, surgery may still be considered following IVF.

2.2. Challenges in IVF for Endometriosis (Figure 1)

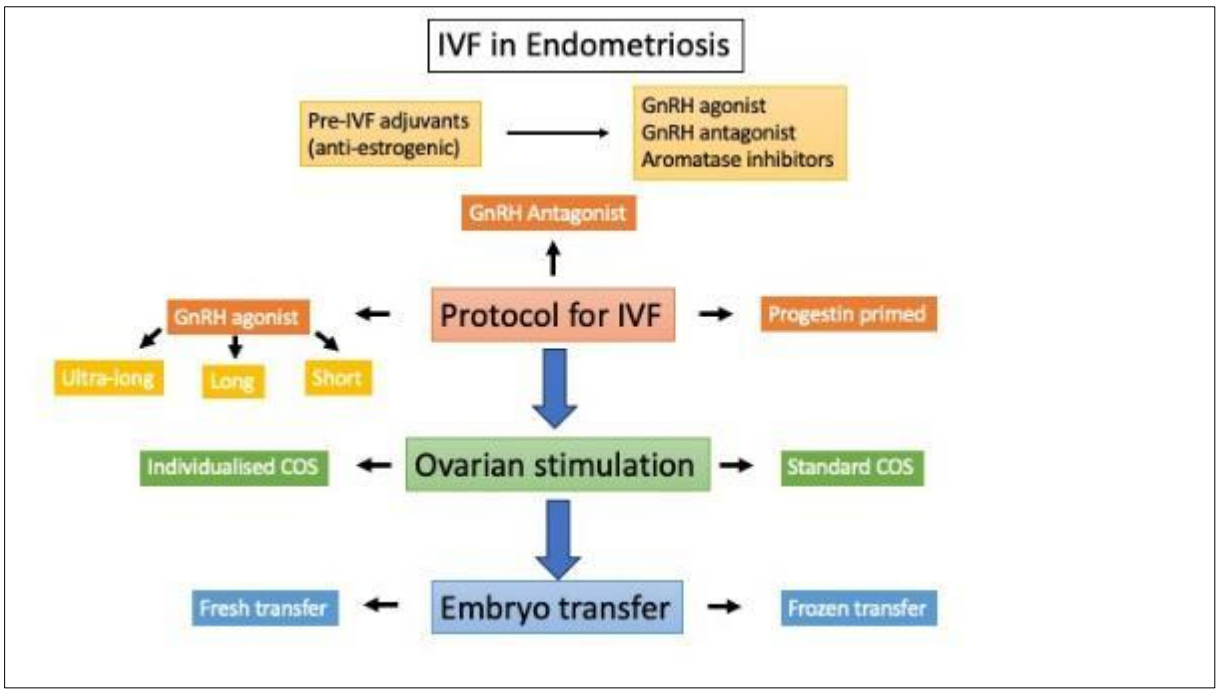

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Figure 1 Challenges in IVF for Endometriosis

2.2.1. Selection of IVF Protocol

A systematic review and meta-analysis of randomized controlled trials (RCTs) suggest that the ultra-long protocol is superior to other down-regulation protocols, such as long agonist and short agonist protocols, in terms of pregnancy rates among patients with stage III/IV endometriosis. However, caution is warranted as non-RCTs did not consistently show similar results [41].

In a recent RCT comparing clinical pregnancy rates between the standard long protocol and the ultra-long protocol (involving GnRH agonist for 3 months) for IVF post-surgery, the determined sample size was not reached due to patient reluctance towards the longer treatment duration of the ultra-long protocol. Consequently, only 42 subjects were randomized (21 in each arm), and no significant difference in clinical pregnancy rates was observed between both groups. However, the ultra-long protocol required higher dosages of gonadotropins and longer stimulation durations [42].

Another RCT comparing GnRH agonist with antagonist protocol divided patients into three groups based on their endometriosis status and surgical history. Among those with stage I/II endometriosis, no difference in pregnancy rates

was found between the GnRH agonist (long) protocol and the GnRH antagonist protocol. However, for patients who underwent endometrioma surgery, there was a significant decline in oocytes retrieved in the GnRH antagonist group, with a 10% reduction in clinical pregnancy rates compared to the GnRH agonist group. The study also indicated reduced oocyte yield in the GnRH antagonist group for patients with endometrioma but without prior surgery which further emphasizes better outcomes with GnRH agonist protocol for advanced endometriosis [43].

In a retrospective study comparing three protocols—long GnRH-agonist, ultra-long, and GnRH antagonist—among endometriosis cases with diminished ovarian reserve who had undergone endometrioma surgery, no significant differences were found in oocyte yield or live birth rate among the groups. However, the clinical pregnancy rate was significantly higher in the ultra-long group. The GnRH antagonist group had the lowest treatment cost due to the shortest duration and lowest dose of gonadotropins [44]. Notably, this study only evaluated outcomes after fresh embryo transfer and thus did not address cumulative pregnancy rates, which could have provided additional insights.

In another RCT comparing progesterone-primed ovarian stimulation (PPOS) using medroxyprogesterone acetate against the ultra-long protocol for endometriosis, significant differences were observed in the required gonadotropin for stimulation, while no difference was found in the number of mature oocytes retrieved and pregnancy rates [45]. Similarly, a prospective cohort study for cost-effectiveness analysis comparing PPOS versus antagonist protocol in women with endometriosis undergoing fertility preservation showed no difference in oocyte yield but significantly reduced cost in the PPOS group [46]. Age, prior ovarian surgery, and anti-Müllerian hormone (AMH) levels were identified as the main determinants for the number of eggs retrieved.

While several studies have reported better results with the ultra-long protocol, its higher cost and prolonged treatment duration may make the long protocol a more feasible option, especially for patients with prior endometrioma surgery and reduced ovarian reserve. The PPOS protocol has shown similar outcomes to the ultra-long protocol at a lower cost, providing another potential option. Ultimately, the selection of the best IVF protocol for endometriosis should be tailored to individual patient characteristics and preferences.

2.2.2. Individualized vs standard ovarian stimulation

Individualizing the dosage of gonadotropins according to anti-mullerian hormone levels is a potential approach[47]. However, there is insufficient research to support customizing the dosage of gonadotropins based on factors such as the stage of disease, presence of adenomyosis, or other variables influencing pregnancy outcomes. Additionally, there is a lack of studies examining the adjunctive use of recombinant LH. Nevertheless, in studies employing the ultra-long GnRH agonist protocol, the early administration of LH during stimulation has been recommended due to profound pituitary suppression.

2.2.3. Fresh vs Frozen embryo transfer

A systematic review and meta-analysis of retrospective cohort studies revealed higher live birth rates following frozen embryo transfer compared to fresh embryo transfer, albeit with significantly increased miscarriage rates in the fresh transfer group [48]. However, the inclusion of only retrospective studies introduces a high risk of selection bias, as patients with more high-grade embryos are more likely to undergo frozen transfer than those with fewer or lower-grade embryos. Another systematic review highlights a higher risk of placenta accreta spectrum disorder in endometriosis patients, particularly those undergoing frozen embryo transfer [49]. Furthermore, a large nationwide cohort study reaffirms the elevated risk of pre-eclampsia associated with artificial cycle frozen embryo transfer [50]. Given the lack of sufficient evidence, opting for frozen embryo transfer in endometriosis patients may not be advisable.

2.2.4. Mechanisms underlying the decreased IVF success-

Studies indicate that IVF in endometriosis often results in low oocyte yield and reduced fertilization rates, consequently leading to lower pregnancy rates [51]. Possible reasons for this include diminished ovarian reserve, impaired folliculogenesis, and reduced endometrial receptivity due to the inflammatory microenvironment in the ovaries and endometrial tissues. However, a recent study challenged the long-standing speculation that endometriosis affects folliculogenesis, ultimately impacting the number and quality of embryos and cumulative pregnancy rates. This study suggested that prior endometrioma surgery was the primary confounder leading to lower oocyte yield in endometriosis patients, indicating that endometriosis itself does not significantly affect folliculogenesis, embryo competence, or endometrial receptivity [52] Additionally, reduced oocyte yield may also result from operator-dependent decisions to avoid complete oocyte pick-up to prevent puncturing endometriomas and reduce the risk of infection. Criticism has been directed at meta-analyses synthesized from observational studies due to inherent biases, with recommendations for synthesizing information using matched cohorts to adjust for relevant confounders [52]. Furthermore, a large

retrospective study comparing donor versus autologous cycles in endometriosis patients revealed no difference in live birth rates between those receiving donor eggs and those using their own eggs [53]. This finding suggests that replacing eggs of endometriotic patients with donor eggs does not improve outcomes, further supporting the notion that poor egg quality may not be the primary cause of lower pregnancy rates in endometriosis patients.

2.2.5. Pre-IVF Adjuvants

To address the challenges posed by poorer IVF outcomes in endometriosis patients, various strategies have been explored, including surgery and medical therapies targeting ovarian estrogen production. These approaches aim to reduce the disease burden by minimizing endometriotic deposits. Similar to the role of surgery, the effectiveness of pre-IVF medications is subject to debate. Progestins, combined oral contraceptives, GnRH agonists, and GnRH antagonists are among the drugs used, either alone or in combination. According to ESHRE, none of these medical therapies have shown robust evidence of improving IVF outcomes [54].

A Cochrane review focusing on long-term GnRH therapy before standard IVF, encompassing eight randomized controlled trials (RCTs), yielded uncertain evidence regarding live birth rates, with some indication of a reduced rate after GnRH agonist use. However, the quality of evidence was deemed low, primarily due to the limited number of studies reporting live birth rates [55]. Most studies included in the review involved prior surgery before initiating GnRH agonist treatment, with the majority reporting clinical pregnancy rates. However, these studies were underpowered, underscoring the need for further trials and network meta-analyses with matched subjects to address potential confounders such as prior endometrioma surgery and adenomyosis.

An RCT comparing dienogest pretreatment with standard long IVF protocol versus ultra-long protocol demonstrated no significant difference in the number of retrieved oocytes or pregnancy rates. However, the dienogest arm showed significantly lower treatment costs and better quality of life indices [56]. This trial was based on the assumption that the potentially beneficial effects of the ultra-long protocol could be achieved with a cost-effective approach using dienogest.

Another RCT evaluating letrozole in combination with gonadotropin stimulation within a long protocol setting showed reduced gonadotropin requirements and comparable pregnancy rates to standard IVF [57]. The capacity of Letrozole to enhance endogenous gonadotropin secretion might offer advantages in cases of poor responders with endometriosis. Additionally, its hypoestrogenic properties could potentially alleviate the disease burden and inflammatory environments.

The ongoing multicentric double-blinded RCT known as the PREGNANT trial aims to assess the efficacy of oral GnRH antagonist Elagolix as pre-treatment for IVF in endometriosis patients. The hypothesis is that Elagolix may outperform GnRH agonists in terms of pregnancy outcomes while offering fewer side effects and shorter treatment duration [58]. Results from this trial are eagerly awaited.

2.2.6. Endometriosis with adenomyosis undergoing IVF-

Endometriosis cases complicated by adenomyosis add another layer of complexity to IVF outcomes. In a retrospective analysis, the live birth rates following IVF with an ultra-long protocol and fresh embryo transfer were 11% for those with endometriosis and adenomyosis, 12% for adenomyosis alone, 27% for endometriosis alone, and 27% for non-endometriosis cases (serving as controls with tubal infertility) [59]. The similar live birth rates observed between endometriosis cases (without prior surgery) and tubal infertility cases suggest that endometriosis itself may not significantly impact IVF outcomes. However, adenomyosis has been shown to have a substantial effect on IVF outcomes [60], underscoring the need for studies focusing on optimal strategies for improved results in such cases. A cohort study comparing adenomyosis patients undergoing IVF with a long GnRH agonist protocol versus an ultra-long protocol found that despite lower oocyte and embryo yield, the ultra-long protocol yielded a higher clinical pregnancy rate in fresh cycles [61]. Another retrospective study suggested that in adenomyosis cases, IVF with an antagonist protocol followed by frozen embryo transfer after pretreatment with GnRH agonist resulted in the best pregnancy rate compared to fresh embryo transfer using both agonist and antagonist protocols [62] although the difference was not statistically significant. Given these conflicting findings, further research, particularly focusing on individuals with concurrent endometriosis and adenomyosis, is warranted.

3. Conclusion

Endometriosis, an estrogen-dependent chronic inflammatory condition, significantly affects fertility, compounded by diagnostic complexities and declining ovarian reserve. Its pathogenesis, primarily attributed to Sampson's theory, is

further supported by the stem cell theory, indicating a genetic predisposition to the development of endometriosis. Mechanistically, it impacts ovarian function, sex hormones, and endometrial receptivity, leading to reduced egg count, quality, fertilization, and impaired implantation processes. While advanced ultrasonography and biochemical markers like microRNAs aid in diagnosis, they have limitations. Treatment involves classifying the disease and tailoring interventions based on individual factors such as age, symptoms, disease severity, ovarian reserve, other causes of infertility, prior surgeries and patient preferences. The choice between surgery and in-vitro fertilization (IVF) remains contentious, with ongoing trials like SVIDOE offering potential insights. Decision-making regarding IVF protocols and transfer types is complex, with the ultra-long protocol showing promise in fresh transfer cycles despite drawbacks like cost and prolonged treatment duration. Frozen embryo transfer may offer slightly higher success rates but is associated with adverse outcomes like placenta accrete spectrum disorders and pre-eclampsia, necessitating individual risk-benefit analysis. Pre-IVF adjuvants like progestins, combined oral contraceptives, and GnRH agonists/antagonists have been of limited benefit. Emerging options like Dienogest, Letrozole, and Elagolix offer newer avenues with potentially fewer side effects. Additionally, the impact of concurrent adenomyosis on IVF outcomes underscores the need for specialized management strategies. Ongoing research initiatives, including randomized controlled trials, hold promise for refining treatment pathways and improving clinical outcomes.

Compliance with ethical standards

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The authors declare no conflict of interest for this article.

References

[1] Taylor HS, Kotlyar AM, Flores VA: Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. The Lancet. 2021, 397:839–52. 10.1016/S0140-6736(21)00389-5

[2] Counseller VS, Crenshaw JL: A clinical and surgical review of endometriosis. American Journal of Obstetrics and Gynecology. 1951, 62:930–42. 10.1016/0002-9378(51)90180-9

[3] Agarwal SK, Chapron C, Giudice LC, et al.: Clinical diagnosis of endometriosis: a call to action. American Journal of Obstetrics and Gynecology. 2019, 220:354.e1-354.e12. 10.1016/j.ajog.2018.12.039

[4] Sampson JA: Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. American Journal of Obstetrics and Gynecology. 1927, 14:422–69. 10.1016/S0002-9378(15)30003-X

[5] Müllerianosis. Histology and Histopathology. 2007, 1161–6. 10.14670/HH-22.1161

[6] Vinatier D, Orazi G, Cosson M, Dufour P: Theories of endometriosis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2001, 96:21–34. 10.1016/S0301-2115(00)00405-X

[7] Mints M, Jansson M, Sadeghi B, Westgren M, Uzunel M, Hassan M, Palmblad J: Endometrial endothelial cells are derived from donor stem cells in a bone marrow transplant recipient. Human Reproduction. 2007, 23:139–43. 10.1093/humrep/dem342

[8] Leyendecker G: Endometriosis results from the dislocation of basal endometrium. Human Reproduction. 2002, 17:2725–36. 10.1093/humrep/17.10.2725

[9] Dalsgaard T, Hjordt Hansen MV, Hartwell D, Lidegaard O: Reproductive prognosis in daughters of women with and without endometriosis. Human Reproduction. 2013, 28:2284–8. 10.1093/humrep/det231

[10] Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H: Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. Human Reproduction. 1996, 11:1542–51. 10.1093/oxfordjournals.humrep.a019435

[11] Dongye H, Ji X, Ma X, Song J, Yan L: The Impact of Endometriosis on Embryo Quality in in-vitro Fertilization/Intracytoplasmic Sperm Injection: A Systematic Review and Meta-Analysis. Front Med. 2021, 8:669342. 10.3389/fmed.2021.669342

[12] Freis A, Dietrich JE, Binder M, Holschbach V, Strowitzki T, Germeyer A: Relative Morphokinetics Assessed by Time-Lapse Imaging Are Altered in Embryos From Patients With Endometriosis. Reprod Sci. 2018, 25:1279–85. 10.1177/1933719117741373

[13] Simón C, Gutiérrez A, Vidal A, De Los Santos MJ, Tarín JJ, Remohí J, Pellicer A: Outcome of patients with endometriosis in assisted reproduction: results from in-vitro fertilization and oocyte donation. Human Reproduction. 1994, 9:725–9. 10.1093/oxfordjournals.humrep.a138578

[14] Skrzypczak J: Morphology and steroidogenesis of cultured granulosa cells from endometrioidally changed ovaries. Exp Clin Endocrinol Diabetes. 2009, 103:228–32. 10.1055/s-0029-1211355

[15] Cahill DJ: Pituitary-ovarian dysfunction and endometriosis. Human Reproduction Update. 2000, 6:56–66. 10.1093/humupd/6.1.56

[16] Dmowski WP, Rao R, Scommegna A: The Luteinized Unruptured Follicle Syndrome and Endometriosis. Fertility and Sterility. 1980, 33:30–4. 10.1016/S0015-0282(16)44473-0

[17] Al-Sabbagh M, Lam EW-F, Brosens JJ: Mechanisms of endometrial progesterone resistance. Molecular and Cellular Endocrinology. 2012, 358:208–15. 10.1016/j.mce.2011.10.035

[18] Zanatta A, Rocha AM, Carvalho FM, et al.: The role of the Hoxa10/HOXA10 gene in the etiology of endometriosis and its related infertility: a review. J Assist Reprod Genet. 2010, 27:701–10. 10.1007/s10815-010-9471-y

[19] Berbic M, Schulke L, Markham R, Tokushige N, Russell P, Fraser IS: Macrophage expression in endometrium of women with and without endometriosis. Human Reproduction. 2009, 24:325–32. 10.1093/humrep/den393

[20] Hey-Cunningham AJ, Riaz A, Fromm PD, Kupresanin F, Markham R, McGuire HM: Circulating and Endometrial Regulatory T Cell and Related Populations in Endometriosis and Infertility: Endometriosis Is Associated with Blunting of Endometrial Cyclical Effects and Reduced Proportions in Moderate-Severe Disease. Reprod Sci. 2022, 29:229–42. 10.1007/s43032-021-00658-4

[21] Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G: Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging. Human Reproduction. 2005, 20:2309–16. 10.1093/humrep/dei021

[22] Van Den Bosch T, De Bruijn AM, De Leeuw RA, et al.: Sonographic classification and reporting system for diagnosing adenomyosis. Ultrasound in Obstet & Gyne. 2019, 53:576–82. 10.1002/uog.19096

[23] Liang T, Zhang W, Pan N, Han B, Li R, Ma C: Reproductive Outcomes of In Vitro Fertilization and Fresh Embryo Transfer in Infertile Women With Adenomyosis: A Retrospective Cohort Study. Front Endocrinol. 2022, 13:865358. 10.3389/fendo.2022.865358

[24] Nisolle M, Donnez J: Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertility and Sterility. 1997, 68:585–96. 10.1016/S0015-0282(97)00191-X

[25] Rolla E: Endometriosis: advances and controversies in classification, pathogenesis, diagnosis, and treatment. F1000Res. 2019, 8:529. 10.12688/f1000research.14817.1

[26] Becker CM, Bokor A, Heikinheimo O, et al.: ESHRE guideline: endometriosis. Human Reproduction Open. 2022, 2022:hoac009. 10.1093/hropen/hoac009

[27] Gerges B, Li W, Leonardi M, Mol BW, Condous G: Meta-analysis and systematic review to determine the optimal imaging modality for the detection of uterosacral ligaments/torus uterinus, rectovaginal septum and vaginal deep endometriosis. Human Reproduction Open. 2021, 2021:hoab041. 10.1093/hropen/hoab041

[28] Nisenblat V, Bossuyt PM, Shaikh R, et al.: Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews. 2016, 2016:. 10.1002/14651858.CD012179

[29] Bartel DP: MicroRNAs. Cell. 2004, 116:281–97. 10.1016/S0092-8674(04)00045-5

[30] Adamson GD, Pasta DJ: Endometriosis fertility index: the new, validated endometriosis staging system. Fertility and Sterility. 2010, 94:1609–15. 10.1016/j.fertnstert.2009.09.035

[31] Chen I, Veth VB, Choudhry AJ, et al.: Pre- and postsurgical medical therapy for endometriosis surgery. Cochrane Database of Systematic Reviews. 2020, 2020:. 10.1002/14651858.CD003678.pub3

[32] Hodgson RM, Lee HL, Wang R, Mol BW, Johnson N: Interventions for endometriosis-related infertility: a systematic review and network meta-analysis. Fertility and Sterility. 2020, 113:374-382.e2. 10.1016/j.fertnstert.2019.09.031

[33] Jin X, Ruiz Beguerie J: Laparoscopic surgery for subfertility related to endometriosis: A meta-analysis. Taiwanese Journal of Obstetrics and Gynecology. 2014, 53:303–8. 10.1016/j.tjog.2013.02.004

[34] American Society of Reproductive Medicine: Endometriosis and Infertility: A committee opinion (2012). Accessed: https://www.asrm.org/practice-guidance/practice-committee-documents/endometriosis-and-infertility-a-committee-opinion-2012/.

[35] Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T: No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertility and Sterility. 2006, 86:566–71. 10.1016/j.fertnstert.2006.01.044

[36] Demir E, Soyman Z, Kelekci S: Outcomes between non-IVF and IVF treatment after laparoscopic conservative surgery of advanced endometriosis with Endometriosis Fertility Index score >3. Medicine. 2022, 101:e30602. 10.1097/MD.0000000000030602

[37] Ottolina J, Vignali M, Papaleo E, et al.: Surgery versus IVF for the treatment of infertility associated to ovarian and deep endometriosis (SVIDOE: Surgery Versus IVF for Deep and Ovarian Endometriosis). Clinical protocol for a multicenter randomized controlled trial. PLoS ONE. 2022, 17:e0271173. 10.1371/journal.pone.0271173

[38] Muzii L, Miller CE: The Singer, Not the Song. Journal of Minimally Invasive Gynecology. 2011, 18:666–7. 10.1016/j.jmig.2011.06.016

[39] 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. Journal of Minimally Invasive Gynecology. 2021, 28:1303-1312.e5. 10.1016/j.jmig.2021.02.007

[40] Lessey BA, Gordts S, Donnez O, Somigliana E, Chapron C, Garcia-Velasco JA, Donnez J: Ovarian endometriosis and infertility: in vitro fertilization (IVF) or surgery as the first approach? Fertility and Sterility. 2018, 110:1218–26. 10.1016/j.fertnstert.2018.10.003

[41] Cao X, Chang H, Xu J, et al.: The effectiveness of different down-regulating protocols on in vitro fertilization-embryo transfer in endometriosis: a meta-analysis. Reprod Biol Endocrinol. 2020, 18:16. 10.1186/s12958-020-00571-6

[42] Tomassetti C, Beukeleirs T, Conforti A, Debrock S, Peeraer K, Meuleman C, D'Hooghe T: The ultra-long study: a randomized controlled trial evaluating long-term GnRH downregulation prior to ART in women with endometriosis. Human Reproduction. 2021, 36:2676–86. 10.1093/humrep/deab163

[43] Pabuccu R, Onalan G, Kaya C: GnRH agonist and antagonist protocols for stage I–II endometriosis and endometrioma in in vitro fertilization/intracytoplasmic sperm injection cycles. Fertility and Sterility. 2007, 88:832–9. 10.1016/j.fertnstert.2006.12.046

[44] Zhao F, Lan Y, Chen T, et al.: Live birth rate comparison of three controlled ovarian stimulation protocols for in vitro fertilization-embryo transfer in patients with diminished ovarian reserve after endometrioma cystectomy: a retrospective study. J Ovarian Res. 2020, 13:23. 10.1186/s13048-020-00622-x

[45] Guo H, Du T, Gao H, Xi Q, Wu L, Lyu Q, Zhu Q: The comparison of two different protocols ultra-long versus medroxyprogesterone acetate in women with ovarian endometriosis: a prospective randomized controlled trial. Reprod Health. 2022, 19:198. 10.1186/s12978-022-01500-z

[46] Mathieu d'Argent E, Ferrier C, Zacharopoulou C, et al.: Outcomes of fertility preservation in women with endometriosis: comparison of progestin-primed ovarian stimulation versus antagonist protocols. J Ovarian Res. 2020, 13:18. 10.1186/s13048-020-00620-z

[47] Hosseini E: Controlled Ovarian Stimulation in Endometriosis Patients Can Be Individualized by Anti-Mullerian Hormone Levels. Acta Endo (Buc). 2017, 13:195–202. 10.4183/aeb.2017.195

[48] Chang Y, Shen M, Wang S, Li X, Duan H: Association of embryo transfer type with infertility in endometriosis: a systematic review and meta-analysis. J Assist Reprod Genet. 2022, 39:1033–43. 10.1007/s10815-022-02460-w

[49] Matsuzaki S, Ueda Y, Nagase Y, et al.: Placenta Accreta Spectrum Disorder Complicated with Endometriosis: Systematic Review and Meta-Analysis. Biomedicines. 2022, 10:390. 10.3390/biomedicines10020390

[50] Epelboin S, Labrosse J, De Mouzon J, et al.: Higher risk of pre-eclampsia and other vascular disorders with artificial cycle for frozen-thawed embryo transfer compared to ovulatory cycle or to fresh embryo transfer following in vitro fertilization. Front Endocrinol. 2023, 14:1182148. 10.3389/fendo.2023.1182148

[51] Horton J, Sterrenburg M, Lane S, Maheshwari A, Li TC, Cheong Y: Reproductive, obstetric, and perinatal outcomes of women with adenomyosis and endometriosis: a systematic review and meta-analysis. Human Reproduction Update. 2019, 25:593–633. 10.1093/humupd/dmz012

[52] Somigliana E, Li Piani L, Paffoni A, et al.: Endometriosis and IVF treatment outcomes: unpacking the process. Reprod Biol Endocrinol. 2023, 21:107. 10.1186/s12958-023-01157-8

[53] Kamath MS, Subramanian V, Antonisamy B, Sunkara SK: Endometriosis and oocyte quality: an analysis of 13 614 donor oocyte recipient and autologous IVF cycles. Human Reproduction Open. 2022, 2022:hoac025. 10.1093/hropen/hoac025

[54] De Ziegler D, Gayet V, Aubriot FX, et al.: Use of oral contraceptives in women with endometriosis before assisted reproduction treatment improves outcomes. Fertility and Sterility. 2010, 94:2796–9. 10.1016/j.fertnstert.2010.05.056

[55] Georgiou EX, Melo P, Baker PE, et al.: Long-term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis. Cochrane Database of Systematic Reviews. 2019, 2019:. 10.1002/14651858.CD013240.pub2

[56] Khalifa E, Mohammad H, Abdullah A, Abdel-Rasheed M, Khairy M, Hosni M: Role of suppression of endometriosis with progestins before IVF-ET: a non-inferiority randomized controlled trial. BMC Pregnancy Childbirth. 2021, 21:264. 10.1186/s12884-021-03736-2

[57] Ebrahimi M, Akbari Asbagh F, Davari Tanha F, Pakniat H, Feizabad E, Rasouli Y: Co-treatment of gonadotropin and letrozole in infertile women with endometriosis: A double-blind randomized clinical trial. Int J Reprod Biomed. 2022, 20:483–90. 10.18502/ijrm.v20i6.11444

[58] Taylor H, Li HJ, Carson S, et al.: Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): study protocol for a prospective, double-blind, placebo-controlled trial. BMJ Open. 2022, 12:e052043. 10.1136/bmjopen-2021-052043

[59] Sharma S, Bathwal S, Agarwal N, Chattopadhyay R, Saha I, Chakravarty B: Does presence of adenomyosis affect reproductive outcome in IVF cycles? A retrospective analysis of 973 patients. Reproductive BioMedicine Online. 2019, 38:13–21. 10.1016/j.rbmo.2018.09.014

[60] Younes G, Tulandi T: Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertility and Sterility. 2017, 108:483-490.e3. 10.1016/j.fertnstert.2017.06.025

[61] Hou X, Xing J, Shan H, et al.: The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reproductive BioMedicine Online. 2020, 41:845–53. 10.1016/j.rbmo.2020.07.027

[62] Park CW, Choi MH, Yang KM, Song IO: Pregnancy rate in women with adenomyosis undergoing fresh or frozen embryo transfer cycles following gonadotropin-releasing hormone agonist treatment. Clin Exp Reprod Med. 2016, 43:169. 10.5653/cerm.2016.43.3.169