ENDOMETRIOSIS SYMPOSIUM

1. Obstetrician-gynecologist. Niu Vida Specialized Assisted Reproduction Center. Vice President of the Peruvian Fertility Society. ORCID: 0009-0001-7118-4818
2. Obstetrician-gynecologist. Niu Vida Specialized Assisted Reproduction Center. Orcid. 0009-0003-5122-344X
3. Obstetrician-gynecologist. Delgado Clinic. Orcid. 0009-0005-1552-8662
4. Biologist. Niu Vida Specialized Center for Assisted Reproduction. Orcid. 0009-0002-4742-4620
5. Obstetrician-gynecologist. Montesur Clinic. Lima, Peru. Orcid. 0000-0003-3236-4741

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Correspondence author::
Dr. Carlos Alfredo Vergara Herrera
✉ carlos.vergara.herrera@niuvida.com

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Endometriosis: why assisted reproduction?

Endometriosis ¿por qué reproducción asistida?

Drs. Carlos Alfredo Vergara Herrera[1], Carlos Alberto Vergara Ascenzo[2], Alberto German Ascenzo Battistini[3], Blgo. Carlos Duarte[4], Dr. Alberto Ascenzo Palacio[5]

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ABSTRACT

Endometriosis is a chronic, estrogen-dependent gynecological disease that affects approximately 10% of women of reproductive age and is associated with infertility in up to 50% of cases[1]. The link between endometriosis and infertility is explained by anatomical distortion, peritoneal inflammation, decreased ovarian reserve, and impaired endometrial receptivity[2]. Traditionally, laparoscopic surgery has been used as a first-line approach to restore pelvic anatomy; however, its benefits in terms of live birth rates are limited and it carries the risk of reducing ovarian reserve.[3] In contrast, in vitro fertilization (IVF) has demonstrated higher cumulative pregnancy rates in a shorter time, bypassing the anatomical and pathophysiological barriers of the disease[4]. International societies such as ESHRE currently discourage routine surgery before IVF and recommend prioritizing assisted reproduction, reserving surgical intervention for selected cases: severe pelvic pain, large endometriomas (>4 cm) preventing access to follicles during oocyte retrieval[5], or those suspicious for malignancy, given the 1–1.5% increased risk of ovarian cancer in these patients[6, 7, 8]. Surgery is also indicated in cases of hydrosalpinx or organ involvement.[5]. This review summarizes the most recent evidence and argues why assisted reproduction should be considered the central strategy in managing endometriosis-associated infertility.

Keywords: Endometriosis; infertility; assisted reproduction; in vitro fertilization; surgery.

RESUMEN

La endometriosis es una enfermedad ginecológica crónica, estrógeno-dependiente, que afecta aproximadamente al 10% de las mujeres en edad reproductiva y se asocia a infertilidad en hasta el 50% de los casos.[1] El vínculo entre endometriosis e infertilidad se explica por la distorsión anatómica, la inflamación peritoneal, la disminución de la reserva ovárica y la alteración de la receptividad endometrial[2]. Tradicionalmente, la cirugía laparoscópica se empleó como primera línea para restaurar la anatomía pélvica, pero sus beneficios en términos de nacidos vivos son limitados y se asocia a riesgos de reducción de la reserva ovárica[3]. En contraste, la fertilización in vitro (FIV) ha demostrado mayores tasas acumuladas de embarazo en menor tiempo, evitando las barreras anatómicas y fisiopatológicas de la enfermedad[4]. Actualmente, sociedades internacionales como ESHRE desaconsejan la cirugía rutinaria antes de FIV y recomiendan priorizar la reproducción asistida, reservando la intervención quirúrgica para casos seleccionados: dolor pélvico severo, endometriomas grandes mayores de 4 cm que no permiten el acceso a los folículos para la aspiración folicular[5] o sospechosos de patología oncogénica, ya que estas pacientes tienen una prevalencia de 1 a 1.5 % de mayor incidencia de cáncer de ovario[6, 7, 8]. Asimismo, se indica la cirugía en casos de hidrosálpinx o compromiso de órganos[5]. Este trabajo revisa la evidencia reciente y argumenta por qué la reproducción asistida debe considerarse la estrategia central en la infertilidad asociada a endometriosis.

Palabras clave: Endometriosis; infertilidad; reproducción asistida; fertilización in vitro; cirugía.

Introducción

Endometriosis is a chronic, estrogen-dependent gynecological disease characterized by the presence of endometrial tissue outside the uterine cavity. It is estimated to affect approximately 10% of women of reproductive age and 30-50% of women with infertility[1, 9]. The disease manifests itself with chronic pelvic pain, dysmenorrhea, dyschezia, dyspareunia, and subfertility, generating a strong physical, emotional, social, and occupational impact.

The link between endometriosis and infertility is complex and multifactorial. The disease can cause pelvic anatomical distortion, adhesions, chronic inflammation of the peritoneal fluid, alterations in oocyte and embryo quality, and even a reduction in endometrial receptivity[2]. These mechanisms hinder natural or spontaneous conception, making endometriosis one of the main diagnoses in infertility consultations.

Surgery modestly increased the rate of spontaneous pregnancy compared to no intervention[3]. However, in moderate or severe cases, reproductive outcomes after surgery are much more uncertain and are accompanied by surgical risks and, above all, a reduction in ovarian reserve, especially when endometriomas are removed[10]. With the development of in vitro fertilization (IVF), the management paradigm has changed substantially. IVF allows many of the barriers imposed by endometriosis to be circumvented by directly aspirating the oocytes, performing fertilization in the laboratory, and transferring the embryos to the uterus, with success rates that far exceed those of expectant management or repeat surgery[11, 12].

Endometriosis represents a major challenge in reproductive medicine, significantly affecting fertility. Various ovarian stimulation protocols have been used in in vitro fertilization (IVF) treatments, including long protocols with GnRH agonists, short protocols with GnRH antagonists, and more recently, protocols using progestogens (PPOS). Current evidence indicates that none of these protocols is superior to the others, with comparable results in terms of number of oocytes obtained, fertilization rates, embryo development, and pregnancy[13]. However, the PPOS protocol has proven to be a safe and effective alternative in women over 35 years of age, as it is associated with a higher proportion of euploid embryos and a lower rate of chromosomal mosaicism, according to a retrospective cohort study by Wan et al.[14]. Therefore, the choice of protocol should be based on individual factors, prioritizing safety, accessibility, and the opportunity for early intervention.

Likewise, in a study of patients with endometriosis, 27,204 oocytes were analyzed to determine whether this disease could negatively affect them, and it was concluded that it did not affect morphology, fertilization, blastocyst formation, or pregnancy rates, strengthening assisted fertilization due to its efficiency in achieving pregnancy in infertile patients with endometriosis[15].

Currently, routine surgery is not recommended before assisted reproduction treatment, except in cases of severe pain, large endometriomas, or suspicion of malignant neoplasia, hydrosalpinx, or organ compromise[5]. Thus, early initiation of assisted reproduction treatments, with an emphasis on IVF, is prioritized to maximize the probability of live birth in the shortest possible time.

Endometriosis is a gynecological disease with an estimated heritable genetic burden of 10 to 12% and a twofold risk in women with affected first-degree relatives. Conventional treatments, based mainly on hormone therapies and surgery, have significant limitations, especially in women who wish to preserve their fertility.

Methodology

To prepare this paper, a narrative review was conducted with a critical approach to the current and relevant scientific literature on endometriosis and infertility. The search was conducted between June and August 2025 in the PubMed/MEDLINE, Scopus, Dialnet, NIH, and Cochrane Library databases, using combinations of keywords in English and Spanish: endometriosis, infertility, assisted reproduction, IVF, surgery, management, live birth.

The following inclusion criteria were established:

1. Clinical guidelines and international consensus statements from high-impact scientific societies (ESHRE, ASRM, NICE, WES, British Fertility Society).

2. Controlled clinical trials, systematic reviews, and meta-analyses published in the last 10 years, with an emphasis on recent articles (< 5 years).

3. Studies published in indexed journals of an experimental and/or observational nature.

Priority was given to evidence reporting clinical pregnancy and live birth rates, as well as the impact of surgery on ovarian reserve and IVF outcomes. Duplicate articles, studies with sma-

ll samples, and non-indexed publications were excluded. With this approach, the present study seeks to integrate the highest quality clinical evidence with current international recommendations, offering an analysis geared toward the practice of gynecologists specializing in infertility.

Pathophysiology of infertility in endometriosis

The pathophysiology of endometriosis is complex and multifactorial, involving multiple genetic factors such as point mutations and mRNA misordering, possibly generated by these chromosomal mutations. Likewise, there are epigenetic factors that could increase this harmful process of invasion and implantation of these endometrial foci outside the endometrial cavity, causing persistent estrogen overload and resistance to progesterone, which alter the defense system with immune dysfunction, failing to monitor and eliminate ectopic endometrial cells, allowing the survival, adhesion, and proliferation of these aberrant implants in a chronic inflammatory peritoneal environment, increasing cytokines (IL-6, TNF-α), chemokines, and growth factors, causing pain and infertility.

Likewise, we have altered immune cells such as macrophages that promote lymphocytes (T and B) with NK dysfunction, which facilitates this abnormal implantation[16]. A relationship is also being found between the microbiota and the strobolome and derived metabolites such as quinic acid, facilitating the growth of endometriotic lesions, possibly through modulations of the immune system in the pathophysiology of endometriosis in preclinical studies[17].

Likewise, subfertility in endometriosis results from a combination of mechanisms, ranging from anatomical distortion due to adhesions that limit oocyte capture and tubal transport, the inflammatory peritoneal microenvironment, rich in cytokines and reactive oxygen species that impair sperm function and early embryonic development, as well as immunological alterations and a less receptive endometrium due to changes in implantation molecules such as integrins and HOXA10[2, 1, 9, 18]. At the same time, ovarian endometriomas add a component of reserve deterioration: oxidative stress and the iron load of the cystic content are associated with follicular loss and decreased AMH, with a poorer response to stimulation[19,20]. This pathophysiology explains why "bypassing" the pelvic and peritoneal environment through IVF is biologically plausible: transvaginal oocyte retrieval, in vitro fertilization, and direct transfer to the uterus avoid passage through the fallopian tubes and peritoneal cavity, where the barriers characteristic of the disease are concentrated[2].

Role of assisted reproduction in infertility due to endometriosis

In vitro fertilization (IVF) is currently the most effective therapeutic strategy for treating infertility associated with endometriosis. Unlike spontaneous conception or repeated attempts at surgery, IVF directly overcomes the main pathophysiological barriers: it avoids anatomical distortion and peritoneal inflammation, reduces the impact of tubal damage and the hostile microenvironment, and circumvents the potential decrease in endometrial receptivity through controlled embryo transfer[4, 12].

So how does this translate into the clinical decision between surgery and IVF? In minimal or mild endometriosis (rASRM I-II), the Cochrane review showed that treating superficial lesions increases the rate of viable intrauterine pregnancy compared to diagnostic laparoscopy alone (OR 1.9; moderate-quality evidence)[3]. However, this relative benefit does not guarantee an advantage in live births nor does it justify, on its own, delaying referral to assisted reproduction/IVF centers when reproductive time is critical (age ≥35 years, prolonged infertility, or low endometriosis fertility index (EFI) and other female or male reproductive factors), a position that is explicitly stated in the guidelines[18].

In moderate to severe stages (III–IV) and in the presence of endometriomas, the balance shifts for two reasons. First, ovarian surgery can decrease ovarian reserve: meta-analyses document significant decreases in AMH after endometrioma cystectomy, especially in bilateral or reoperated cases[19,20]. Second, removing the endometrioma before IVF does not improve IVF outcomes (neither the clinical pregnancy rate nor the live birth rate) compared to not operating, according to the systematic review and meta-analysis by[21]; on the contrary, it may reduce the number of oocytes retrieved. In fact, the ES-

HRE 2022 guideline recommends not routinely performing surgery before ART to improve live births[18].

The case of deep endometriosis (DIE) warrants further analysis. A meta-analysis focusing on DIE surgery before IVF suggested an improvement in pregnancy and live birth rates in those who underwent surgery. However, it lacked randomized controlled trials (RCTs) and showed a high risk of bias, so its conclusions require confirmation[10]. The most recent evidence, with broad inclusion of subtypes, indicates that operating before IVF/ICSI does not increase live births or ongoing pregnancies compared to going directly to IVF/ICSI[22]. In summary, the overall weight of evidence and guidelines favors prioritizing IVF in most infertile patients with moderate to severe endometriosis, reserving surgery for specific clinical indications (severe pain, suspected malignancy, inability to access follicles during ovarian puncture, hydrosalpinx, organ involvement) and avoiding reoperations that further compromise ovarian reserve[18].

In cases of deep endometriosis (DIE), surgical treatments carry a higher risk of complications and a longer recovery time, as well as the risk of recurrence, and do not guarantee pregnancy. In comparison, assisted reproduction methods avoid surgical complications and offer the possibility of achieving pregnancy in a shorter time. The problem with assisted fertilization is that it may require several attempts and does not resolve or alleviate pelvic symptoms, in addition to being costly and emotionally stressful[23].

There is also a scenario in which surgery is a mandatory adjunct to IVF: hydrosalpinx. Evidence and recommendations from the ASRM support salpingectomy or proximal occlusion prior to IVF in communicating tubes, since tubal reflux reduces implantation and IVF success[24]. From this pathophysiological concept, IVF offers a direct route that avoids the hostile peritoneum, does not sacrifice ovarian tissue, and shortens the time to pregnancy, while surgery is selectively indicated for significant pain, oncological safety, or to remove specific barriers to IVF such as hydrosalpinx. This is currently the position of the reference guidelines and the pattern that best aligns the biology of the disease, prognosis, and reproductive outcome[18, 21, 22].

Clinical results of IVF in endometriosis

Several studies have shown that, although IVF success rates may be somewhat lower in women with endometriosis compared to other infertility factors, the treatment offers a significantly higher cumulative probability of clinical pregnancy and live birth than surgical or expectant management. A meta-analysis by Liang et al.[21] showed that removal of endometriomas prior to IVF does not improve pregnancy or live birth rates, while it may reduce the number of oocytes retrieved. In line with this, recent studies confirm that direct access to IVF is associated with better overall results and a shorter time to pregnancy[12, 22].

In patients with minimal or mild endometriosis, laparoscopy can relatively improve pregnancy rates. In women under 35 years of age, it is recommended to attempt spontaneous conception for a short period (6 to 12 months) before considering IVF; in women of advanced reproductive age, they should proceed directly to IVF, where better results are achieved[3, 18]. In moderate or severe disease, the indication for IVF is even stronger, since anatomical distortion and ovarian damage reduce the chances of natural conception, and surgery provides little benefit compared to early IVF[10, 22].

Although some deep endometriosis (DE) is progressive, 50% of the disease appears stable over time, and progression is reduced with hormonal treatments (21% vs. 12%). Hormonal treatment can reduce the size of DE lesions by 1 cm^3, with reductions occurring after 6 months and remaining stable for up to 3 years. Most hormonal therapies improve symptoms and quality of life, regardless of changes in DPE size, with combined contraceptives and progestogens being the most studied. DPE may present a higher risk of ovarian and extraovarian cancer than previously hypothesized. Hormonal treatments improve symptoms and reduce the progression of DPE[25].

Recommendations from international guidelines

The ESHRE 2022 guideline explicitly states that

surgery should not be performed routinely with the aim of improving IVF outcomes, except in specific situations such as refractory pain, suspected malignancy, hydrosalpinx, or technical difficulties with follicular puncture[18]. For its part, the ASRM recommends not delaying assisted reproduction in women with endometriosis and poor prognostic factors, emphasizing the importance of reproductive timing[26]. More recently, the British Fertility Society has also emphasized that IVF is the first-line treatment option in cases of endometriosis associated with infertility, especially in patients with reduced ovarian reserve or advanced maternal age[27].

Strategies for optimizing IVF

The management of IVF in endometriosis requires specific adaptations. Controlled ovarian stimulation must be individualized, taking into account the lower ovarian reserve present in many patients, especially those with a history of endometrioma surgery. Cryopreservation of oocytes or embryos can be a valuable strategy for preserving fertility in young women with progressive endometriosis[12]. In cases of hydrosalpinx, salpingectomy or proximal occlusion prior to IVF is mandatory, as evidence shows that tubal fluid significantly reduces implantation and pregnancy rates[24].

Clinical results

In summary, IVF offers a therapeutic approach that maximizes the chances of pregnancy and live birth in women with endometriosis, while avoiding the cumulative risks of repeated surgery. Current scientific evidence and clinical practice guidelines agree that assisted reproduction, and IVF in particular, is the cornerstone of managing infertility associated with endometriosis. Surgery should be reserved for strictly selected indications.

Conclusions

In vitro fertilization (IVF) has emerged as the most effective and appropriate tool for overcoming the reproductive barriers imposed by endometriosis. By avoiding the hostile pelvic microenvironment, IVF maximizes the probability of clinical pregnancy and live birth, while reducing the risk of ovarian reserve loss associated with repeated surgical procedures.

Recent studies and meta-analyses confirm that surgery prior to IVF does not improve reproductive outcomes compared to direct IVF, and that the benefits of lesion resection should be reserved for specific indications[10, 21, 22]. Scientific societies, including ESHRE, ASRM, and the British Fertility Society, converge on a clear recommendation: IVF should be considered the first line of treatment in women with endometriosis and infertility, especially in those with advanced age, low ovarian reserve, or long periods of infertility[27].

Surgery should only be indicated in selected cases, aimed at pain control, oncological safety, or optimization of IVF when anatomical barriers exist, such as hydrosalpinx[18]. Consequently, modern management of infertility associated with endometriosis requires a patient-centered approach, where IVF is positioned as the therapeutic pillar. Prioritizing assisted reproduction over routine surgery not only responds to the biological and clinical logic of the disease, but also to the fundamental objective of maximizing the chances of achieving a live birth in the shortest possible time, without losing sight of innovations in preclinical diagnosis and treatment that will change the practice of fertility in this group of patients.

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