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THE VALUE OF ASSISTED REPRODUCTIVE TECHNOLOGIES IN ENDOMETRIOSIS ASSOCIATED INFERTILITY

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Endometriosis, a common gynecological disease, is characterized by local and systemic inflammation, which causes pelvic pain and infertility and eventually, increased utilization of assisted reproductive technologies (ART). This methods, especially in vitro fertilization (IVF), represent efficient and useful means for women affected by endometriosis and infertility. Despite the fact that older studies suggest that in vitro fertilization outcomes are negatively affected by endometriosis, with lower pregnancy rates, recent studies show no significant differences compared to controls. Moreover, there is no clear evidence to support that treatment administration for endometriosis prior to in vitro fertilization will improve success rates, though some studies encouraged the administration of pre-in vitro fertilization cycle suppressive medical therapy in a subset of endometriosis patients. There is controversial evidence regarding removal of endometriomas as it may not have any benefit and may have a deleterious impact on ovarian reserve and response. The correct management of these patients with endometriosis associated infertility should focus on early recognition of disease, and prompt referral to assisted reproductive techniques as needed. The assisted reproductive technologies are considered the most successful in achieving conception in endometriosis patients struggling with infertility.

Key words: endometriosis; infertility; assisted reproductive technologies

INTRODUCTION

Endometriosis has been estimated to affect up to 10–15% of reproductive aged women and has been widely associated with infertility[1]. However, the exact mechanisms that lead to fertility impairment have not been identified[2]. The fecundity rate in normal reproductive age couples without infertility is estimated to be around 15% to 20%, compared to the fecundity rate in women with untreated endometriosis which vary from 2% to 10% according to several controlled studies[3,4]. Yet, there is a percentage of women with endometriosis that will conceive without difficulty, and others will have a substantially longer time to conception.

A retrospective cohort study over a three year period demonstrated a significantly lower incidence of pregnancy among women with endometriosis-associated infertility compared to unexplained infertility (36% versus 55%)[5]. Studies suggested that negative impact on fertility is demonstrated by distorted pelvic anatomy[6], altered microenvironment[7-9], impaired ovarian reserve, reduced ovarian response[10-12], as well as affected endometrial receptivity[13-15].

Serum AMH (Anti-Mullerian Hormone) is considered to be a useful predictor of ovarian response in endometriosis[16-19]. In assisted reproductive technologies, serum AMH levels represent an excellent method for the evaluation of follicular cohort and prediction of ovarian response in case of controlled ovarian stimulation (COH), even better than FSH (Hormone folliculo-stimulante) or age[20-22]. Despite the diminished ovarian reserve caused by ovarian failure, studies considered that endometriosis will not have an impact on embryo quality and on the implantation rate[23].

The assisted reproductive technologies and, more specifically, in vitro fertilization (IVF) represent the most common and successful methods to help women with endometriosis associated infertility achieve conception. Studies concerning the outcomes of IVF in women with endometriosis as well as in those with other causes of infertility, are controversial as some reported poor IVF outcome in women with endometriosis, while others reported high success

rates[24,25]. This article will discuss endometriosis-associated infertility, the role of ART in endometriosis, as well as benefits and indications of the medical and surgical treatment associated to ART in endometriosis.

PATHOGENESIS OF ENDOMETRIOSIS AND INFERTILITY

The pathogenesis of endometriosis is still unknown but there are a number of possible theories involved such as: retrograde menstruation, coelomic metaplasia, metastatic dissemination, altered immunity and stem cells as newer domain.

Retrograde menstruation

Retrograde menstruation is the oldest and most accepted theory, proposed by Sampson in the 1920's and states that the retrograde flow of endometrial cells via fallopian tubes into the peritoneal cavity during menstruation is the main factor in causing endometriosis. However, retrograde menstruation occurs among 76%–90% of women with normal fallopian tubes and few will actually develop endometriosis. In order to support Sampson's theory further studies demonstrated that factors that contribute to menstruation obstruction, such as congenital abnormalities (imperforate hymen and iatrogenic cervical stenosis), increase the risk of developing of endometriosis[26-27].

Coelomic Metaplasia and Metastatic Dissemination

In the 1960's, Ferguson proposed that coelomic metaplasia may also be a significant factor in the development of endometriosis. Metaplastic changes in the coelomic epithelium, in response to an undetermined stimulus, can eventually lead to transformation into endometrial cells. Menstrual tissues spreads through lymphovascular system and causes endometrial implants outside the pelvic cavity[28].

Altered Immunity

It is considered that endometriosis involves alterations in certain immune cells, components of cell-mediated immunity, which will determine the survival and growth of displaced menstrual tissues. A lot of studies showed decreased cytotoxicity to endometrial cells, as a consequence of defective NK-cell activity[29,30]. In addition, the presence of recruited immune cells within the peritoneal cavity will trigger other proinflammatory cytokines and growth factors, potentiating the process of inflamation[31]. The nature of endometriosis-associated inflammation contributes in a substantial way to a hypersensitivity to inflammation across multiple organ systems.

Stem cells

Over the last decade, studies observed the ability of stem cells to differentiate into endometrial cells, with further implication in the development of ectopic endometrial implants. This is considered to be a novel mechanism of endometriosis, with a lot of implication in the origin and progression of this disease. The potential advantages of these processes in reproductive biology is of great interest, as they can be exploited for new medical treatments[32,33].

Endometriosis associated infertility

The proposed mechanisms of how endometriosis adversely impacts fertility are of great interest, as they can offer solutions for the treatment of this disease. In endometriosis there are a lot of significant modifications with negative impact on fertility. The pelvic anatomy is modified by a lot of adhesions, with adverse impairment on: oocyte release or pick-up, sperm motility, fallopian tube activity, embryo transport and endometrial function[34,35].

Apart from these, there is abnormal peritoneal function, increased inflammatory activity and angiogenesis, reduced immune surveillance and clearance of endometrial cells, and increased production of autoantibodies against endometrial cells[36]. Understanding the involvement of inflammatory cytokines, growth and angiogenic factors in the development of endometriosis may be very helpful to evaluate the pathogenesis and spontaneous evolution of this condition.

ART AND ENDOMETRIOSIS

Recent studies stated that endometriosis patients who underwent IVF/ICSI (Intracytoplasmic sperm injection) reached comparable results compared to infertile patients with tubal-factors.

A systematic review and meta-analysis published by Hamdan et al in 2015 including 36 studies and 4852 patients concluded that ART outcomes were comparable among women with or without endometriosis (OR 0.94; CI0.84-1.06). However, women with severe endometriosis had lower live birth rate, clinical pregnancy rate, and mean number of oocytes compared with women with no endometriosis[37].

Another systematic review published in 2015 by Kawwass comparing ART outcomes in United States between 2000- 2011 which included 1,589,079 ART cycles reported comparable pregnancy outcomes per transfer among women using ART for endometriosis-associated vs. male factor infertility, despite decreased oocyte yield and higher medication dose[38]. Additionally, a report on the Society of Assisted Reproductive Technology data showed that the average delivery rate per retrieval of patient's undergoing IVF-ET (in vitro fertilization-embryo transfer) was higher for women with endometriosis (39.1%) compared to women with all causes of infertility (33.2%)[39].

In the systematic review published by Barbosa et al in 2014 including 92 studies in the review and 78 in the meta-analysis suggested that women with endometriosis

undergoing ART have practically the same chance of achieving clinical pregnancy and live birth as do women with other causes of infertility[40].

Other study published in 2013 compared IVF/ICSI outcomes among patients with endometriosis and tubal infertility. A number of 431 cycles were performed for patients with endometriosis (152: stage I-II endometriosis and 279: stage III-IV endometriosis). This study suggests similar pregnancy outcomes in patients with different stages of endometriosis and patients with tubal infertility[41].

Olivennes et al reported favorable results in women affected by endometriosis with a 30% delivery rate per embryo transfer in 360 IVF cycles performed on 214 endometriosis patients in contrast to a 37.5% rate in 166 cycles performed on 111 controls with tubal disease[42].

In a retrospective cohort study published in 2012 on 2245 infertile women with various stages of endometriosis and tubal factor infertility IVF or intracytoplasmic sperm injection was performed. The results showed similar success rate of IVF and intracytoplasmic sperm injection between patients with different stages of endometriosis and those with tubal infertility, excepting those with endometrioma[43].

On the other hand, several early studies demonstrated significantly compromised rates of fertilization, implantation and pregnancy rates among patients with endometriosis compared to controls, which had mainly tubal diseases.

A review published in 2002 by Barhart et al analyzed twenty-two published studies and reported that patients with endometriosis-associated infertility undergoing IVF had significantly decreased pregnancy rates of almost one half compared to women with other indications for IVF. They concluded that endometriosis does not only affect the receptivity of the endometrium but also the development of the oocyte and embryo[44].

A retrospective, database-searched cohort study performed in 2012 on women who underwent IVF/intracytoplasmic sperm injection between January 2006 and December 2010 stated that endometriosis patients suffer a decreasing IVF pregnancy rates mainly caused by reducing oocytes number and fertilization rate, regardless of the severity of the disease[45]. Another systematic review and meta-analysis published in 2013 included 27 studies and 8984 patients and reported that the presence of endometriosis stage III and IV is associated with poor implantation and clinical pregnancy rates[46].

Comparable ART outcome	**Negative outcome**
Hamdan M.et al. *Obstet Gynecol*. 2015[37]	Barnhart et al. *Fertil Steril.* 2002[44]
Kawwass J.F. et al. *Fertil Steril*. 2015[38]	LIN et al. *Chinese Medical Journal.* 2012[45]
American Society for Reproductive Medicine/ Society for Assisted Reproduction registry 2012[39]	Harb et al. *BJOG*. 2013[46]
Barbosa et al. *Ultrasound Obstet Gynecol*. 2014[40]	Pop-Trajkovic et al. *Taiwan J Obstet Gynecol*. 2014[54]
Dong X et al. *International Journal of Clinical and Experimental Pathology*. 2013[41]	Coccia ME et al. *Acta Obstet Gynecol Scand*. 2011[55]
Olivennes et al. *Fertil Steril*. 1995[42]	Paula Kuivasaari et al. *Hum. Reprod*. 2006[56]
Opøien HK et al. *Fertil Steril.* 2012[43]	
Singh N. et al. *Journal of Human Reproductive Sciences*. 2014 [47]	
Matalliotakis et al. *Fertil. Steril*. 2007[48]	
Kuivasaari P et al. *Hum Reprod.* 2005[49]	
Bukulmez O et al. *European journal of obstetrics, gynecology, and reproductive biology*. 2001[50]	
Al-Azemi M et al. *Hum Reprod.* 2000[51]	
Pal L et al. J *Assist Reprod Genet*. 1998[52]	
Bergendal A et al. *Journal of Assisted Reproduction and Genetics.* 1998[53]	

Table 1. Impact of endometriosis on oocyte quality and IVF outcomes

ASSOCIATING SURGICAL MANAGEMENT TO ART IN TREATING ENDOMETRIOSIS

In vitro fertilization and embryo transfer (IVF-ET) are useful tools to treat women with endometriosis associated infertility. Apart from this, laparoscopic treatment represents the gold standard for symptomatic patients with endometriosis and a combined approach using both laparoscopy and IVF-ET can offer the best outcomes as it improves the overall pregnancy rate.

A retrospective observational study on 107 infertile patients with endometriosis who both benefited from laparoscopic and IVF-ET or just laparoscopy reported that pregnancy rate achieved after the integrated laparoscopy-IVF approach was 56 %. Patients who benefited only from laparoscopic treatment of endometriosis had a significantly lower pregnancy rate (37.4%)[57]. A study published in 2011 including 29 patients with endometriosis associated infertility and with history of prior IVF failures, reported that 22 conceived after laparoscopic treatment of endometriosis. Authors encouraged laparoscopic approach after multiple IVF failures, in the absence of tubal occlusion and male factor infertility[58]. A retrospective study published in 2001 evaluated ovarian response during IVF cycles after laparoscopic ovarian cystectomy. They reported that laparoscopic cystectomy did not have a negative impact on the number of oocytes and embryos obtained[59].

Another retrospective study was published in 2015 by Centini et al on 115 patients in order to evaluate the impact of laparoscopic excision of lesions on deep endometriosis-related infertility. They evaluated fertility outcome after laparoscopic treatment of deep endometriosis by spontaneous conception and by assisted reproductive technology (ART) and reported an overall pregnancy rate of 60%: 38.5% (n = 27) spontaneously and 21.4% (n = 15) by ART[60]. Additionally, a systematic review and meta-analysis including 33 studies reported that surgical treatment of endometrioma did not have a negative impact on IVF/ICSI outcome compared with those who did not receive surgical intervention. Taking into consideration that endometrioma has a detrimental impact on ovarian reserve, there is mandatory need for an individualized treatment of women with endometrioma, as surgery in inexperienced hands can even worsen the prognostic[37]. A retrospective case-control study analyzing 428 first-attempt in vitro fertilization (IVF) cycles, which involved 254 women with a previous or present diagnosis of ovarian endometriosis resulted in similar pregnancy, implantation and live birth rates[61].

On the other hand, previous surgical intervention for endometriosis can negatively impact IVF outcomes, as reported a study performed on two hundred eighty-five infertile women who had previous laparoscopy. Women with previous surgical intervention for endometriosis had a significantly lower number of live births compared to those with endometriosis but no previous surgery[62]. Alborzi et al. in a prospective study on 193 patients with endometriomas undergoing laparoscopic cystectomy reported a significant decline in AMH up to 9 months after laparoscopic cystectomy[63].

Another randomized control trial of 101 women with minimal to mild endometriosis reported no difference in live birth rates between women who underwent laparoscopic treatment of endometriosis either by ablation or resection compared to diagnostic laparoscopy alone (19.6% versus 22.2% over one year, OR 0.75, 95% CI 0.30–1.85)[64].

However, Roman et al published in 2013 a retrospective non-comparative pilot study including 55 patients treated during 28 months, where endometrioma ablation was performed with plasma energy. The results showed from a number of 33 women who wished to conceive that 67% became pregnant, spontaneously in 59% cases. Plasma energy is considered to have an important role in the management of infertile women with ovarian endometrioma, especially the cases with bilateral endometrioma and history of ovarian surgery[65].

The surgical technique used in treating endometrioma can be more or less efficient on endometrioma recurrence, but at the same time can damage more the ovarian reserve. Somigliana et al. in 2011 compared two surgical techniques: excision/stripping surgery to vaporization/coagulation technique. Results confirmed that excision/stripping surgery technique is more efficient for obtaining lower recurrence rate of ovarian endometriomas, but at the same time may result in higher damage to ovarian reserve[66].

Therefore, considering laparoscopic treatment of endometriosis associated infertility may be of great benefit, especially for symptomatic patients, suspicious aspect, rapid growth and risk of rupture in pregnancy. Priority for cystectomy should have patients for those in whom removal of the endometrioma may improve access to ovarian follicles when taking into consideration assisted reproductive technologies[67]. A lot of studies do not encourage routine removal in order to improve fertility rates, which eventually will contribute to negatively affect the ovarian reserve.

IMPROVING IVF OUTCOME BY USING MEDICAL THERAPY IN ENDOMETRIOSIS

Medical management is widely used in treating patients with endometriosis as it proved its beneficial effects in improving the quality of life. Medical therapies such as: oral contraceptives, progestins, androgens, and gonadotropin releasing hormone agonists, however contribute in a significant in reducing the reproductive activity, due to their contraceptive effects. A lot of controversies arise when taking into consideration this method, especially when the patient is anticipating a possible conception. A Cochrane review of 23 trials including over 3000 women reported no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wish to conceive[68].

However, large body of literature evaluated the benefits of prolonged use of GnRHa prior to initiation of gonadotropin stimulation for the assisted reproductive

technologies, in order to increase the preganancy rate in patients with endometriosis associated infertility.

Sallam et al performed a Cochrane Database analysis including 163 endometriosis patients undergoing 3 to 6 months of pre-cycle GnRHa treatment and demonstrated a fourfold increases in the odds of clinical pregnancy (OR: 4.28; 95% CI, 2.0 to 9.15)[69].

De Ziegler et al recently evaluated the role of a 6- to 8-week course of oral contraceptives in patients with endometriosis proposed for IVF. The treatment administration resulted in higher pregnancy rates per retrieval than in controls (35% versus 12.9%, $p = 0.01$)[70].

Rickes and colleagues evaluated the outcomes of 110 patients with endometriosis stage II to IV: 55 patients received GnRH-a for 6 months after surgery and subsequently underwent up to 3 cycles of ART, and 55 patients received 3 cycles of ART alone immediately after surgery. The pregnancy rate per patient was higher among patients who received follow-up treatment with GnRH-a. Ultralong GnRH-a therapy increases the pregnancy rate of ART in patients with severe endometriosis[71].

In a prospective randomized multicenter trial, published by Surrey et al. in 2002, evaluated 41 patients with surgically confirmed endometriosis and infertility, in order to see the effect of a 3-month course of GnRH agonist administered immediately before IVF-ET. 25 patients were administered a three-month course of a GnRHa prior to ovarian stimulation and IVF and 26 were treated with standard ovarian stimulation prior to IVF. The group administered a prolonged course of GnRHa resulted in higher implantation rates (42.7% versus 30.4%) and significantly higher ongoing pregnancy rates (80% versus 53.9%) than the group with standard ovarian hyperstimulation[72].

A study performed by Ferrero et al analyzed peritoneal fluid samples from patients who beneficed from a 6 month GnRH-a treatment prior to surgery, compared to controls who did not receive prior treatment. They concluded that several inflammatory molecules present in peritoneal fluid are down-regulated during treatment with GnRH-a and encourage administration of this drug in order to reduce the inflammation in the peritoneal cavity[73].

The majority of retrospective studies are in favor of using prolonged downregulation with GnRH agonist before starting ovarian stimulation prior to IVF, in order to improve reproductive outcome in women with endometriosis.

CONCLUSIONS

IVF/ICSI can be considered as an effective approach for managing endometriosis-associated infertility. There is good evidence to suggest that surgery followed by IVF-ET is more effective than surgery alone. Despite the risk of negative outcomes on ovarian reserve, an appropriate surgical technique by a skilled specialized surgeon, can offer incredible results with spontaneous conception. When patients fail to conceive spontaneously, after a maximum of 1 year from surgery, ART can be taken into consideration as the integrated approach increases the overall pregnancy rate.

An individualized approach of women with endometriosis and infertility prior to IVF/ICSI may significantly improve the following outcomes. Another important aspect is to accurately evaluate the patient before any intervention is planned, meaning ovarian function and reserve, tubal functionality, male function, uterine cavity, and other possible diseases and infections. A lot of interest arises from the administration of a prolonged course of GnRHa, prior to IVF, as lot of studies showed significant improvement of cycle outcome and pregnancy rates.

However, surgical approach should be reserved to a number of well selected cases, as endometriomas should not be resected to enhance IVF outcome. The most recent evidence suggests that IVF should directly be proposed to asymptomatic infertile patients, especially the older ones with a diminished ovarian reserve, those with bilateral endometriomas, or those with prior surgical treatment.

Nevertheless, there is a constant need for additional studies concerning this field, especially regarding surgical techniques that are less harmful for the ovary. Furthermore, designed prospective randomized trials concerning the best moment to benefit for IVF techniques will be extremely useful.

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