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Fertility preservation options in women with endometriosis

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Endometriosis is a common, chronic condition in reproductive age women. Although some women may be asymptomatic, most women present with dysmenorrhea, dyspareunia, pelvic pain and/or infertility. Despite the fact that a causal relationship between endometriosis and infertility has not been clearly established, the fecundity rate of untreated women with endometriosis is lower than normal couples. However, suppressive medical therapy for endometriosis has not been shown to improve fecundity rates and may only result in a delay in the use of more effective treatments to achieve pregnancy. In the other hand, surgery for severe endometriosis can be useful to treat infertile women, but several studies reported a lower ovarian reserve after excision of ovarian endometriomas, due to incidental excision of normal ovarian tissue together with the endometrioma wall. Therefore, fertility preservation procedures should be considered to reproductive-age women at risk of impaired fertility related to endometriosis progression or endometriosis surgical treatment. The purpose of this document was to review the current literature regarding fertility preservation techniques for patients diagnosed with endometriosis.

KEY WORDS: Fertility preservation - Endometriosis - Embryo disposition.

Endometriosis is a common, chronic condition characterized by the growth of endometrial glands and estroma outside the uterine cavity. Typically, ectopic endometriotic implants are found on the peritoneal surface, within the ovary or invading the rectovaginal septum. Several studies suggest that the prevalence of endometriosis among infertile women is 25% to 50% and that 30% to 50% of women with endometriosis are infertile.[1] The true prevalence of endometriosis is difficult to quantify as very wide ranges have been reported in the literature. Although some women may be asymptomatic, most women present with dysmenorrhea, dyspareunia, pelvic pain and/ or infertility. Its symptoms are associated with work absenteeism, social isolation, and high costs of therapy.

Despite the fact that a causal relationship between endometriosis and infertility has not been clearly established, the fecundity rate of untreated women with endometriosis is lower than normal couples.[2] In fact, one of the objectives of endometriosis treatment is to improve fertility in infertile women. However, suppressive medical therapy for endometriosis has not been shown to improve fecundity rates and may only result

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in a delay in the use of more effective treatments to achieve pregnancy.[3] In the other hand, surgery for severe endometriosis can be useful to treat infertile women, but several studies reported a lower ovarian reserve after excision of ovarian endometriomas, due to incidental excision of normal ovarian tissue together with the endometrioma wall.[4] Therefore, fertility preservation procedures should be considered for reproductive-age women at risk of impaired fertility related to endometriosis progression or endometriosis surgical treatment.

The purpose of this document was to review the current literature regarding fertility preservation techniques for patients diagnosed with endometriosis.

Embryo and oocyte cryopreservation

The most established methods for fertility preservation in women are oocyte and embryo cryopreservation. These procedures both require controlled ovarian stimulation with gonadotropins, which usually takes two weeks from the onset of the menstrual cycle to complete. Oocyte retrieval is undertaken usually by vaginal ultrasound assistance under sedation or general anesthesia. The mature oocytes retrieved can be cryopreserved unfertilized or can be fertilized by in vitro fertilization (IVF) resulting in embryos that can be cryopreserved in different stages of development. Recently, with important development of cryopreservation technique, studies shows similar pregnancy rates between frozen and fresh embryo transfers.[5] In addition, mature oocyte cryopreservation is no longer considered an experimental technique, and there is good evidence that fertilization and pregnancy rates are similar to IVF with fresh oocytes when vitrified/warmed oocytes are used as part of IVF for young women.[6]

The use of oocyte cryopreservation as a strategy for fertility preservation in a woman with endometriosis was previously reported in a case of a 25-year-old woman with history of previous right oophorectomy and at risk of losing her remaining ovary due to severe and symptomatic endometriosis. The patient underwent three cycles of ovarian stimulation for oocyte retrieval and 21 mature oocytes were cryopreserved.[7] Thus, fertility preservation should be part of the preoperative counseling in young women with severe endometriosis.

There are, however, several studies suggesting that women with endometriosis who are treated with IVF or intracytoplasmic sperm injection (ICSI) have a lower pregnancy and implantation rates when compared to women with tubal factor infertility.[8] This occurs mostly because of the poor quality of oocytes in women with endometriosis.[9, 10] In an attempt to increase pregnancy and implantation rates in these patients, clinical and surgical approaches have been proposed to treat endometriosis prior to the use of assisted reproduction technology.

Of all the clinical approaches that have been used to improve the IVF success rates in women with endometriosis, gonadotrophin releasing hormone agonists (GnRHa) seem to be the most promising.[11] A Cochrane meta-analysis of three randomized controlled trials came to the conclusion that treating women with endometriosis for three to six months with GnRHa before IVF or ICSI increases the odds of clinical pregnancy four-fold.[12] However, whether this therapy is equally beneficial for mild and severe stages of endometriosis and whether one type of agonist is superior to another cannot be determined from the present studies. It is also unclear whether the improvement in the pregnancy rate is due to the production of better oocytes (and hence embryos) or better endometrial receptivity.[12]

The management of women with asymptomatic ovarian endometriomas before IVF/ICSI remains challenging, because the impact of endometriotic cysts on assisted reproductive technology (ART) outcomes is still controversial. There are no randomized trials comparing laparoscopic excision or cyst aspiration to expectant management before IVF/ICSI cycles. Thus, each case have to be analyzed independently and the risks and benefits have to be balanced be-

fore the treatment decision.[13] However, if the endometrioma is large (>4 cm), surgery should be considered to confirm the histological diagnosis, to improve access to follicles during oocyte retrieval, and possibly to improve ovarian response.[14]

Ovarian tissue cryopreservation and transplantation

Ovarian tissue transplantation is an experimental technique for fertility preservation. It consists in re-implantation of fresh or cryopreserved ovarian tissue aiming the recovery of ovarian function and,[15] in some cases, the restore of fertility.[16-18] Ovarian tissue can be transplanted orthotopically or heterotopically.[19]

The transplantation of cryopreserved ovarian tissue in a patient with endometriosis was first reported in a case of a 29-year-old woman, with history of previous ovarian surgery and diminished ovarian reserve, who had undergone ovarian tissue cryopreservation for endometriosis and risk of losing her remaining ovary due to repeated ovarian surgery. After a orthotopic ovarian tissue transplantation in a peritoneal pocket created in the left pelvic ovarian fossa, this patient had ovulation documented after ovarian stimulation and her ovarian endocrine function documented up to 9 months after the transplantation.[20, 21]

Autotransplantation of fresh ovarian tissue in patients with endometriosis was reported in two women aged 25 and 27-year-old, both with history of large left unilateral endometrioma submitted to surgical treatment. The finding of frozen pelvis in the left part of the pelvis, with compromised vascularization of the left ovary, indicated the need of left oophorectomy in both cases. However, before left ovarian removal, biopsies were taken from residual healthy ovarian tissue. Part of this tissue was cryopreserved and part of this tissue was transplanted in a peritoneal pocket created in the right pelvic ovarian fossa during the same surgery. In both patients, biopsies performed in a second-look laparoscopy showed the survival of primordial follicles and the presence of a neovascular network.[22]

In view of this data, ovarian tissue cryopreservation aiming future transplantation and ovarian tissue fresh transplantation are valuable techniques, as demonstrated by previous reports and should be proposed to all women at high risk of loss of ovarian reserve due to severe endometriosis or repeated ovarian surgery.

Surgical treatment in women with endometriosis

With respect to women with ovarian endometriomas, who are undergoing surgical treatment, two main risks have to be considered: 1) the risk of incidental excision of normal ovarian tissue together with the endometrioma wall; and 2) the risk of incomplete surgery with subsequent recurrence of endometrioma and the need of repeated surgery in the future. Although ovarian cystectomy appeared to be better than cyst drainage or ablation for the treatment of ovarian endometriomas,[23] in women who will undergo fertility treatment insufficient evidence exists to determine the favored surgical approach. Different surgical techniques for endometriomas treatment had been reported, all aiming better preservation of the ovarian parenchyma.

In one prospective study, 52 women under 35 years with endometriomas larger than 30 mm were treated with a combination of both cystectomy and ablative surgery (with CO2 laser). Ovarian volume and antral follicle count (AFC) were compared between operated ovaries and non-operated ovaries of patients with endometriosis and controls (women with male factor infertility). The ovarian volume and the AFC were similar in all subgroups.[24]

In other retrospective study, 30 women with no previous history of ovarian surgery and comparable baseline characteristics were divided in two groups for management of unilateral endometrioma larger than 30 mm in diameter. One group was treated with ablation using plasma energy

and the other was treated with ovarian tissue-sparing cystectomy. Those patients who underwent cystectomy showed a statistically significant reduction in ovarian volume and AFC when compared with women who underwent ablation using plasma energy.[25]

Both studies showed different approaches in the management of ovarian endometriomas aiming better preservation of the ovarian parenchyma. These approaches need to be fully investigated and more studies have to be conducted to validate these findings.

One case of fertility-sparing surgery was reported in a 38-year-old woman with deep infiltrating endometriosis of the cervix causing obstructive uropathy and diminished kidney function. Abdominal radical trachelectomy, insertion of a pigtail catheter in the left ureter and end-to-end anastomosis of the uterus with the vagina was performed to remove endometriotic lesion.[26] To our knowledge there is only one more case of radical trachelectomy for management of endometriosis involving the cervix.[27]

Conclusions

Endometriosis is a common condition in women of reproductive age, which may result in a diminished ovarian follicular reserve. Women with endometriosis should be counseled about fertility preservation strategies, particularly those with advanced age, disease progression or who are undergoing ovarian surgery. In addition, experienced surgeons should perform the surgical treatment of ovarian endometriomas in order to better preserve the ovarian parenchyma.

Riassunto

Opzioni di conservazione della fertilità nelle donne affette da endometriosi

L'endometriosi è una comune patologia cronica delle donne in età riproduttiva. Sebbene in alcune possa essere asintomatica, la maggior parte delle donne manifesta dismenorrea, dispareunia, dolore pelvico e/o infertilità. Nonostante non sia stata chiaramente definita una relazione causale tra endometriosi e infertilità, la percentuale di fecondità delle donne non trattate affette da endometriosi è inferiore rispetto alle coppie normali. Tuttavia, la terapia medica soppressiva per endometriosi non ha dimostrato di migliorare la percentuale di fecondità e può determinare solo un ritardo nell'adozione di trattamenti più efficaci di ottenimento della gravidanza. D'altro canto, l'intervento chirurgico per endometriosi grave può essere utile per il trattamento di donne sterili, ma diversi studi hanno riferito una bassa riserva ovarica dopo l'asportazione di endometriomi ovarici, a causa dell'asportazione accidentale di tessuto ovarico normale insieme alla parete degli endometriomi. Pertanto, è necessario prendere in considerazione procedure di conservazione della fertilità per le donne in età riproduttiva a rischio di fertilità compromessa, correlata alla progressione dell'endometriosi o al trattamento chirurgico dell'endometriosi. Lo scopo di questo documento era l'esame della letteratura attuale relativa alle tecniche di preservazione della fertilità per le pazienti con diagnosi di endometriosi.

PAROLE CHIAVE: Fertilità, conservazione - Endometriosi - Embrione, disposizione.

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