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Review Article

Fertility Preservation in Women with Endometriosis

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Abstract

Endometriosis (E) typically affects women of reproductive age, and surgery may be required to relieve pain symptoms. However, the excision of ovarian endometriomas, even in the hands of expert surgeons, may reduce ovarian reserve. Fertility preservation (FP) aims to enhance a woman's chance of having biological children. Counselling and shared decision making is an integral part of endometriosis management and fertility preservation, especially at early stages of the disease and prior to surgical intervention. Limited evidence to recommend routine FP in all E patients. Good evidence to recommend FP in young (preferably 35); with advanced stages of endometriosis and at high risk for diminished ovarian reserve. Ideally prior to surgical management. or if they are at high risk of recurrence. The evidence supports oocyte cryopreservation as an effective method of FP.

Keywords: Endometriosis

1. Introduction

- **Endometriosis**

While several mechanisms have been implicated in the pathogenesis of endometriosis (E) related infertility, including distorted pelvic anatomy, inflammatory mediated changes, and decreased endometrial receptivity, iatrogenic injury from surgical treatment is one of the most impactful factors when considering fertility preservation (FP) [1]. Endometriosis typically affects women of reproductive age, and surgery may be required to relieve pain symptoms. However, the excision of ovarian endometriomas, even in the hands of expert surgeons, may reduce ovarian reserve [2], (up to 30% in unilateral versus up to 44% in bilateral endometriomas) [3]. Serum AMH significantly decreases after surgery, and whenever necessary, second surgery for endometriomas significantly impairs ovarian reserve.

Response to ovarian stimulation (OS) for IVF treatments is decreased after surgical treatment of endometriomas [4]. Patients operated for bilateral endometriomas enter menopause earlier [5], and postsurgical ovarian failure may occur following the excision of bilateral endometriomas [6]. Finally, endometriosis per se may have a detrimental effect on ovarian reserve.

- **Fertility preservation**

Fertility preservation aims to enhance a woman's chance of having biological children. It has been widely used in patients undergoing gonadotoxic treatment for malignant diseases [4]; however, a multitude of non-gynaecological or gynaecological conditions may impair the ovarian reserve, therefore requiring FP. In the case of endometriomas, consideration for FP is especially prudent in a patient desiring future fertility since evidence overwhelmingly demonstrates the negative impact of surgery, including damage to the ovarian cortex with decrease in ovarian reserve [7].

2. Reproductive Counseling

Counselling and shared decision making is an integral part of E management and FP, especially at early stages of the disease and prior to surgical intervention [8].

1. The provider should elucidate the patient's goals for E treatment, in addition to current & future fertility goals, including the number of desired children.
2. Patients should be well-informed regarding limited evidence to recommend routine FP in all E patients. If the patient is young and at high risk for diminished ovarian reserve, there is promising evidence to recommend its use. The evidence supports oocyte cryopreservation as an effective means to preserve fertility in E patients in young patients, especially when performed prior to surgical management. Young patient (preferably 35) with advanced stages of E ideally prior to surgical management [9]. or if they are at high risk of recurrence are counselled for FP. They should be counselled that the two main factors impacting LBR are the number of oocytes vitrified and age. It is recommended that women 35 year of age should cryopreserve at least 10–15 oocytes to achieve a CLBR between 40 and 70%, which typically can be achieved in 1 or 2 COS cycles [10]. Women over 35 years of age should be counselled to strongly consider immediate spontaneous or IVF pregnancy and, additionally, counselled regarding worse outcomes secondary to age-related fertility decline.

3. Patients should be counselled regarding the risks associated with IVF and/or surgery and the higher potential for procedural risks in patients with advanced disease secondary to distorted anatomy, pelvic adhesions, and large ovarian cysts [8].

4. It is important to counsel patients that oocyte cryopreservation does not guarantee pregnancy and that multiple COS cycles may be required to optimize egg banking

5. Patients need to be counselled on the financial aspects of FP.

6. Psychological and physical impacts of repeated cycles, surgery, and E-related pain should be addressed and provide the basis of an ongoing discussion with the patient [8].

3. Oocyte Cryopreservation

1. **Ovarian Stimulation**
   - **Pretreatment** before IVF: There is insufficient data to determine if women should discontinue hormonal therapies before the stimulation to have better outcomes regarding obtained oocytes, their quality, and pregnancy results. Typically, pretreatment before IVF involves either progestin (such as dienogest) or a GnRH antagonist, with neither showing clear superiority over the other [11].
   - **COS protocol:** No one is recommended, even though the use of GnRH antagonist protocol is associated with a slightly higher number of retrieved oocytes [12]. If an antagonist stimulation protocol is used, GnRH agonist triggering can be employed. This allows for a reduction in pain symptoms and a decrease in the rate of OHSS compared to HCG triggers [13]. The progestin primed ovarian stimulation (PPOS) protocol offered patients the flexibility to either continue their long-term oral progestin treatment and initiate the COS protocol with gonadotropin or to start an oral treatment with desogestrel simultaneously with COS on the first day of a natural cycle [14]. Similar days of stimulation were required in both antagonist and PPOS protocols. Similar number of retrieved oocytes and vitrified mature oocytes were obtained from either stimulation protocol. PPOS protocol exhibited significant cost-effectiveness advantages over the antagonist protocol.

Patients with E required higher total doses of gonadotrophins when compared to infertile women due to other causes [15]. However, it is unclear if women with E need more days of ovarian stimulation.

2. **Oocyte Retrieval** technique after COS is the same for FP or IVF cycle, but sometimes ovarian pick-up in a woman affected by E could be more challenging [9].
3. **Outcomes Of Fertility Preservation:** Infertile women with OMAs had significantly fewer oocytes retrieved when compared to infertile women due to other causes [16]. The number of retrieved oocytes was significantly higher in OMA patients 35 years or younger when compared to those over 35 [10]. As expected, evidence of prior E surgery decreased the yield of retrieved oocytes, with statistically significant results [15]. Cobo [10] found no difference between these two groups

In the study by Raad [18], patients with superficial E and OMAs had fewer oocytes retrieved compared to those with DIE. Cobo [10] found no difference when comparing stage I-II versus stage III-IV endometriosis. DIE (versus superficial endometriosis alone) was not associated with the number of retrieved oocytes, but age, prior ovarian surgery, and AMH level were associated with the number of retrieved oocytes [14]. However, the oocyte maturation rate was lowest in OMA cycles (72.5%) when compared to superficial E and DIE, respectively (83.1% and 83.3%) [18]. The presence of bilateral OMAs also decreased the oocyte maturation rates compared to unilateral OMAs [15]. When comparing OMAs to other benign cysts, it was evident that fewer oocytes were retrieved in women with OMAs (NS).

Closely related and associated with E, adenomyosis also needs to be considered since its presence negatively impacts the chances of live birth with ART treatment in E-associated infertility [4]. This may be explained by the local intra-endometrial oestrogen biosynthesis leading to progesterone resistance which negatively impacts implantation in adenomyosis and E.

4. **Return Rate:** Only the study by Cobo [10] has officially reported the return and pregnancy rate

after thawing in women with E after seeking FP. A high return rate of 46.5% was observed. In a smaller study, Santulli [17] reported a 1% return rate, with only two patients who returned to use their oocytes with both having a live birth after oocyte thawing. Nonetheless, the low return rate observed in this study is probably related to the fact that women used this treatment to potentially negate the effect of the disease on future fertility, without an immediate desire for pregnancy. It is also to be noted that the mean age of the population was over 4 years younger than that in the study by Cobo [10].

5. **Pregnancy Rates and Embryo Quality:** In general, there were higher oocyte survival rates, implantation rates, pregnancy rates, and CLBR in young (35 years) elective FP patients compared with E age-matched patients [19]. In E patients up to the age of 35 years, survival rate, implantation rate, CPR, and CLBR are significantly lower than age-matched women undergoing elective FP—an effect which was lost in women above the age of 35 years. As expected, the CLBR increased as the number of vitrified oocytes used increased. Age plays an important role in this context as the percentage CLBR per oocyte retrieved is always lower in E women >35 years compared to those 35 years [10]. There is no difference in CLBR when comparing E patients with women undergoing elective FP in age-matched groups, but CLBR was significantly higher in both E patients and elective FP patients when performed 35 years than when performed after the age of 35. The CLBR was statistically significantly higher in the nonsurgical group (72.5%) compared with the group of patients who underwent surgery (52.8%) [9].

Although there appears to be a decrease in the number of oocytes obtained in women with E, there seems to be no alteration in oocyte quality [20]. When comparing the stage of E, irrespective of age, there was a similar outcome in embryo score between both groups of E: stage I-II and III-IV [9]. The Cobo study [9] was limited by the fact that most patients within the cohort were diagnosed with stages III–IV of the disease (474 versus 11), and the women in the surgically treated group were significantly younger. Hence, extrapolations on these factors to the whole population of women with E is debatable.

6. **Number of Oocytes to Cryopreserve:** The number of oocytes to cryopreserve depends on patients' age—women under 38 years should aim to cryopreserve 15–20 oocytes, and women 38–40 years should aim to cryopreserve 25–30 oocytes [21], numbers which may be too large to accomplish considering merely patient age. In a more recent study, Hong [15] recommends that in general, at least 10–15 oocytes should be cryopreserved if the patient is willing to undergo FP to increase the chances of achieving a future pregnancy. The numbers needed to treat (NNT) is a simple tool that can be used to describe statistics to patients in clinics. The NNT corresponds to 16 women with E before surgical treatment, in whom cryopreservation must be performed to guarantee one supplemental live birth [22].

4. Ovarian Tissue Cryopreservation (OTC)

While previously having been primarily utilized for cancer patients prior to initiation of gonadotoxic therapy, more recently OTC has also been used for other conditions that may adversely impact ovarian function and cause POI. In some cases, OTC may be a reasonable option for patients with E [23]. Those who are unable or choose to forego IVF or patients who may require an oophorectomy.

Techniques:

1. **Ovarian Cortical Tissue Cryopreservation:** A small volume of cortical tissue containing primordial follicles is removed and then cut into 0.3–2 mm thick pieces & cryopreserved [23]. Once restoration of fertility is desired, auto-transplantation of the ovarian tissue is performed either in an orthotopic or heterotopic fashion.

A. In orthotopic transplantation, the tissue is attached to the remaining ovary or to the peritoneum of the ovarian fossa. This option may allow for spontaneous conception. Resumption of normal ovulatory cycles has been reported within 4–9 months [24]. A recent review reported 24 live births after orthotopic autotransplantation; however, it is difficult to interpret these results since most women had native ovarian tissue remaining [25].

B. In heterotopic transplantation: The cortical tissue is implanted in the arm, abdominal wall, or chest wall, and IVF is the only option to achieve pregnancy [26]. Successful oocyte retrieval and fertilization with heterotopic autotransplantation has been reported with one live birth; however, no spontaneous pregnancies have been reported [23].

2. Whole-Ovary Cryopreservation: An option for patients for whom ovarian failure is anticipated [27]. Currently, there are no reports of successful transplantation of a previously cryopreserved whole ovary. While there are favourable data to support OTC outcomes in women undergoing gonadotoxic treatment, aside from case reports, there is limited evidence of its efficacy in E patients.

Studies: The use of OTC in E was first described in 1999 by Oktay et al. in a patient who underwent orthotopic transplantation of ovarian tissue with subsequent return of ovulation; however, no pregnancy was achieved [28]. In 2005, Donnez et al. described a case of orthotopic OTC in a patient with a 9 cm endometrioma who achieved pregnancy with IVF [25]. Several studies support the use of OTC for indications other than E, including cancer. Shapira et al. in 2020, they reported 50 pregnancies (33 spontaneous versus 17 IVF) and 44 deliveries among 60 patients undergoing 70 auto-transplantations [29]. Overall, 50% of women were able to achieve at least 1 pregnancy with 41.6% attaining a delivery. In their cohort, they observed younger women were among those who became pregnant. Despite the promising outcomes of OTC used for other indications, further research regarding its efficacy, risks,

benefits, and cost-effectiveness in E patients is needed prior to more widespread use.

Advantages: Ability to perform it any time in the menstrual cycle and without ovarian stimulation.

Disadvantages: it requires two surgical procedures, the first to harvest the tissue, followed by auto-transplantation [23]. Access to OTC may be more limited compared to oocyte cryopreservation since the latter is more routine. Quality of oocytes may be impacted when obtained from ovarian tissue cryopreserved from an ovary involving an endometrioma, but more data are needed to address this concern.

Conclusions: Limited evidence to recommend routine FP in all E patients. Good evidence to recommend FP in young (preferably 35); with advanced stages of endometriosis and at high risk for diminished ovarian reserve. Ideally prior to surgical management. or if they are at high risk of recurrence. The evidence supports oocyte cryopreservation as an effective method of FP

Abbreviations

E: ENDOMETRIOSIS
FP: FERTILITY PRESERVATION
OS: OVARIAN STIMULATION
CLBR: CUMMULATIVE LIFE BIRTH RATE
COS: CONTROLLED OVARIAN STIMULATION
IVF: INVITRO FERTILIZATION
GNRH: GONADOTROPHIN RELEASING HORMONE
PPOS: PROGESTIN PRIMED OVARIAN STIMULATION
HCG: HUMAN CHORIONIC GONADOTROPIN
OMA: ENDOMETRIOMA
DIE: DEEP INFILTERATING ENDOMETRIOSIS
CPR: CLINICAL PREGNANCY RATE
NNT: NUMBER NEEDED TO TREAT
OTC: OVARIAN TISSUE CRYOPRESERVATION.

Declarations

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