Counseling Endometriosis Patients in Fertility Clinics Guidelines Based Approach

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Abstract

Endometriosis is a gynecological disease, affecting young women and is a main cause of pain and infertility. Due to the advances in reproductive medicine, a lot of endometriosis patients seek counseling in fertility clinics. They are worried about their reproductive capability and are often scared by the information they have access to on social media. On the other hand, the clinicians in those centers are overwhelmed by thousands of publications which capture different sometimes contradicting management approaches. The above mentioned is a challenge to a proper counseling in fertility centers. In our manuscript, we provide a concise review about counseling of endometriosis patients in fertility clinics based on different international guidelines, published between 2010 and 2019. This provides the clinicians with up-to-date recommendations regarding infertility issues. Moreover, we enriched our manuscript with a section for counseling endometriosis patients seeking for fertility preservation. We summarized the best approach for counseling in one flow chart that can ease the mission of the clinicians. To the best of our knowledge this constitutes the first effort to put different guidelines together for counseling of endometriosis patients in fertility clinics.

Keywords: Endometriosis; Infertility; Counseling; ART; Cryopreservation

Introduction

Endometriosis is a common gynecological disorder affecting 10% of women in their reproductive age. It is estimated that 176 million women world-wide suffer from endometriosis. Its prevalence increases dramatically affecting 30 - 40% of women when looking at women with infertility [1-3]. The diagnosis of endometriosis depends basically on a good operative laparoscopy to detect the characteristic endometriotic lesions [1]. Nevertheless, a typical complaint of dys-syndrome (dysmenorrhea, dyspareunia, dyschezia and dysuria) should raise the suspicion of endometriosis. Sometimes it manifests in atypical non-cyclic chronic abdominal pain. An interval of 4 - 10 years usually elapses before the final diagnosis of endometriosis is made [4].

Nowadays, endometriosis patients constitute a large proportion of women seeking counseling for infertility in fertility clinics. Many of those patients come with a confirmed histopathological diagnosis of endometriosis, being referred by their gynecologist for further fertility treatment. Others may have a recurrence of the disease. Lastly, specialists in the fertility clinics are confronted with patients, counseled by Dr. Google. On the other side, the doctors are overwhelmed with around 26000 publications on PubMed (last update in December 2019), all concerning endometriosis in different aspects. We feel that there is a great demand of a concise review for those specialists in the field of fertility counseling and treatment.

What is counseling?

Counseling is, according to the American Counseling Association, defined as, "a professional relationship that empowers diverse individuals, families, and groups to accomplish mental health, wellness, education, and career goals" [5]. People search for counseling
when their concerns cannot be dealt with any more effectively. The same applies to our endometriosis patients, who come with a lot of concerns not only about their reproductive performance but also about a compromised social, physical and sexual life. Counseling should be goal-based, aiming at changing the way of thinking, feeling and behaviour of the person seeking counseling.

**Which endometriosis patients do come to fertility clinics?**

There are two types of endometriosis patients in the fertility clinics. The first type has an imminent child wish with a current partner. The other one has a delayed child wish, as she is single or first wants to accomplish her career. Therefore, we included in our review both endometriosis-related fertility treatment as well as endometriosis-related fertility preservation. The first group is further subdivided into patients expecting spontaneous conception and those who are candidates of assisted reproductive technologies (ART).

**International guidelines in endometriosis diagnosis and management**

To provide a practical guide for fertility specialists, we considered the most-up-to-date guidelines, which were published 2010 - 2019 namely:

- The interdisciplinary S2k guidelines (German guidelines): Diagnosis and treatment of endometriosis, published in August 2013 [7].
- Society of Obstetricians and Gynecologists of Canada (SOGC) guideline: Endometriosis, diagnosis and management, published in July 2010 [8].

**Classifications of endometriosis**

To avoid confusion of the readers by the different terminologies of endometriosis, two major endometriosis classifications were considered in this review:

- The revised American Society of Reproductive Medicine (rASRM) [9] (Figure 1A) and
- The ENZIAN classification of deep-infiltrating endometriosis (DIE) [10] (Figure 1B).

**Figure 1:** (A) revised classification of endometriosis by the American society of reproductive medicine (rASRM) [9]. (B) ENZIAN classification of deep infiltrating endometriosis according to the endometriosis research foundation [10].

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Besides, a phenotypic localization of endometriosis lesions is also considered. This classifies endometriosis according to its localization into three groups; superficial endometriosis (SEM), deep-infiltrating endometriosis (DIE) and ovarian endometriotic cyst (endometrioma). DIE is defined as any endometriosis involving rectovaginal septum, rectum, vagina, ureter, urinary bladder, sacro-uterine ligaments or parametrium [7] or endometriosis lesions extending deeper than 5 mm [11].

**Endometriosis patients expecting spontaneous conception**

This group includes all women who wish to get pregnant, having a partner whose semen analysis is normal. Furthermore, the fallopian tubes should be patent, tested either by hysterosalpingography, sonohysterography or by laparoscopy (chromopertubation). A major concern of those patients is whether the treatment of endometriosis would improve their chance to get pregnant.

**Superficial endometriosis:** ESHRE (Grade A), S2k, SOGC (Grade I) and NICE highly recommend a laparoscopic excision of all visible endometriotic lesions with stage I and II according to rASRM. This should include an excision and or ablation of the lesions. Both showed the same beneficial effect on improving the pregnancy rates. Adhesion lysis should also be considered to restore the pelvic anatomy. Furthermore, ESHRE outweighs the benefit of using CO₂ laser vaporization over the standard monopolar electrocoagulation (Grade C) to achieve higher cumulative pregnancy rates. The excision may be considered especially for a histological diagnosis of the disease [7].

Patients with moderate to severe endometriosis (stage III and IV) will benefit from laparoscopic excision compared to an expectant management (ESHRE, Grade B).

Furthermore, controlled ovarian stimulation (COS) and intrauterine insemination (IUI) in minimal and mild endometriosis provide higher pregnancy rate than COS alone or IUI alone. Patients are encouraged to start COS and IUI as soon as possible after surgical excision of endometriosis, as the first 6 postoperative months show a high pregnancy rate (ESHRE, Grade C).

Ovarian suppression drugs to modulate the growth of endometriotic lesions won’t add any further beneficial effect over the surgery alone, so that both ESHRE (Grade A) and S2k discouraged clinicians from prescribing those drugs neither pre-operative nor post-operative. In a recent study of Furness *et al.* the addition of those drugs to the surgical excision did not provide any obvious improvement either in pain, recurrence rate or pregnancy rates [12].

**Deep-infiltrating endometriosis:** Diagnosis of DIE necessitates a complete gynecological exam including rectovaginal palpation and imaging by trans-vaginal or trans-rectal ultrasonography. A trans-abdominal ultrasonography to exude hydronephrosis secondary to ureteric involvement by endometriosis is mandatory according to S2k guidelines. MRI, cystoscopy, colonoscopy, rectoscopy and rectal endosonography can be considered as secondary diagnostic tools [4]. Excision of DIE (e.g. rectovaginal nodule, bowel endometriosis) has clear advantages in patients suffering from dyschezia, dysmenorrhea, dysuria or other pain symptoms secondary to DIE. Excisional surgery remains controversial concerning improvement of pregnancy rates and other fertility parameters (SOGC, Grade II).

If surgery is considered in patients without additional pain symptoms, the implications of this type of surgery should first be discussed with the patient desiring to get pregnant. Major concerns should be clarified regarding postoperative complications, possibly longer hospitalization, and delayed fertility treatment and if higher spontaneous pregnancy rate is realistic (NICE).

ESHRE guideline states that radical excision of endometriosis in infertile patients with severe resistant pelvic pain or severe segmental bowel stenosis combined with segmental bowel resection leads to a higher pregnancy rate than those operated without segmental bowel resection. This should be cautiously considered as it was not statistically significant.

Nevertheless, and based solely on a single prospective controlled study, excision of rectovaginal endometriosis does not seem to provide a higher pregnancy rate than expectant management alone (ESHRE guideline).

It is noteworthy, that recent studies showed a spontaneous pregnancy rate of 42%- 53% following rectal shaving or disc resection/segmental resection of colon/rectal endometriosis, in follow-up studies of up to 48 months [13-16]. Moreover, postoperative complications in colo-rectal endometriosis patients do not seem to reduce the spontaneous pregnancy rate [14], and disc resection combined with

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segmental resection in case of multiple endometriotic nodules show a pregnancy rate of almost 70% [17]. The same is described for urinary bladder/ureter-endometriosis with 40% spontaneous pregnancy rate following resection [18].

**Endometrioma:** Endometriosis can manifest as a blood-filled ovarian cyst. It is mostly easy to diagnose using high resolution transvaginal ultrasonography, with a characteristic ground glass appearance. Until recently management of endometrioma was controversial regarding implications for fertility.

ESHRE recommends a laparoscopic cystectomy in favor of higher pregnancy rate (Grade A) compared to a drainage or fenestration with electrocoagulation of the cyst wall. The same recommendation was emphasized by the NICE guidelines. This approach ensures a lower recurrence rate, in addition to a histopathological diagnosis to exclude any suspicious component in the cyst. A new consensus about the surgical treatment of ovarian endometrioma was developed by the European Society for Gynecological Endoscopy (ESGE), the European Society of Human Reproduction (ESHRE) and the World Endometriosis Society (WES), summarized in figure 2 [19].

Another controversy was raised about the threshold cyst diameter for a laparoscopic intervention. Although both ESHRE and NICE guidelines lack a clear recommendation, the SOGC set it at a diameter bigger than 3 cm.

The pro and cons of an operative procedure should be discussed with the patients. Every ovarian surgery destroys some of the ovarian reserve, especially remarkable when the cysts are deeply located and adherent to the sound ovarian cortex or hilus respectively. Postoperative adhesion formation is another concern. Such approach can also delay the fertility treatment for a while. Nevertheless, endometrioma can be associated with superficial endometriosis and DIE. The removal of superficial endometriosis and possibly also DIE will be beneficial for improving the pregnancy rate.

Hormonal treatment of endometrioma will not be effective in eliminating them or in compensating for an incomplete removal of the cyst (S2K guidelines).

**Endometriosis fertility index (EFI):** Surgically diagnosed endometriosis patients are often overwhelmed with the disease staging according to rASRM. Minimal (stage I), mild (stage II), moderate (stage III) and severe endometriosis (stage IV) is not essentially
meaningful for the reproductive capabilities of those women. This urged Adamson and Pasta to develop EFI [20]. It considers both the historical part as well as the operative findings and American Fertility Society (AFS) scores of the endometriosis patients. Three historical factors are essential in this index: age, duration of infertility and previous pregnancy with the current partner. The age is a good predictor for the ovarian reserve, while a previous pregnancy with the current partner excludes a male factor of infertility.

The surgical factors incorporate the AFS endometriosis score, AFS total score and least function score (LFS). The latter involves an estimation of the function of the tubes, fimbria and the ovaries, graded in 5 categories, while the former considers the widely used rASRM classification of endometriosis (Figure 3).

![Figure 3: Endometriosis fertility index (EFI) - Surgery form [20].](image)

The different EFI score categories are predictive of the spontaneous pregnancy rate using non-IVF treatment (intra-uterine insemination is considered as a non-IVF treatment), and EFI was further validated by external studies [21]. Self-criticized by the authors themselves, the EFI lacks a score for a uterine factor.

Endometriosis patients’ candidates for ART

Deep-infiltrating endometriosis: ESHRE guidelines addressed the question if surgical excision of DIE nodule would improve the pregnancy rate following ART. The panel could not establish effectiveness associated with an operative approach to excise DIE nodule to an improved pregnancy rate (Grade C). In S2k guidelines, in recurrent endometriosis ART is superior to repeated surgery in terms of pregnancy rate.

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**Endometrioma:** In contrast to endometriosis patients expecting spontaneous conception, an ovarian cystectomy of an endometrioma does not associate with improved pregnancy rate (ESHRE, Grade A). An expectant management of endometrioma will preserve the ovarian reserve and avoids a delay of ART. Nevertheless, endometrioma bigger than 3 cm, those which are associated with pain, or looking suspicious should be completely excised to improve pain and to exclude malignancy respectively (ESHRE, GPP). Another indication to an ovarian cystectomy is a large endometrioma hindering feasible oocyte retrieval during ART (ESHRE, GPP).

The fear of a possible contamination of the follicular fluid by the cyst content of an incidentally punctured endometrioma could affect the quality of oocyte and the developing embryo. Again, an incidental puncture of an endometrioma can interfere with oocyte retrieval, prolonging the procedure, and even may necessitate changing of the suction needle. Pros and cons of an ovarian surgery should be thoroughly discussed with those patients (see above).

All patients with endometriomas should be counseled about a possible acceleration of the age of menopause after a cystectomy. According to the study of Coccia et al [22], the bilaterality of the disease is considered a risk factor for an early menopause around 42 years old. However, unilateral endometrioma lack a similar effect, as the contralateral ovary compensates [23]. Moreover, the sum of the endometrioma diameter is another factor to be considered, especially in bilateral endometrioma. It shows an inverse relationship with age of menopause, so that the bigger the sum of the cyst diameters is, the earlier the patient will go into menopause. This relationship does not exist in unilateral disease.

**When to begin ART in endometriosis patients?**

ESHRE panel recommends a 3-6 months pituitary down-regulation using Gonadotrophin analogue (GnRH Agonist) prior to ART. This approach is associated with improved pregnancy rate (ESHRE, Grade B).

However, adjunct pituitary suppression for 3 months in mild endometriosis improves neither the number of retrieved MII oocytes nor the pregnancy rate. This protocol necessitates however higher doses of gonadotrophins and longer stimulation [24,25].

A delayed start of ART due to planned surgical excision of endometriosis/ endometrioma is not associated - even under controlled ovarian stimulation during IVF/ICSI - with increased cumulative recurrence rate of endometriosis (ESHRE, Grade C).

**Endometriosis and oocyte quality/embryo quality**

In a prospective study, oocytes retrieved from endometriosis patients were of lower quality than in endometriosis-free patients, though there was no difference in the retrieved number of oocytes. This effect seems to be endometriosis-stage dependent, being worse in severe cases. This observation can be extrapolated to the higher fertilization failure rate observed in the conventional IVF compared to ICSI. So, in severe endometriosis (stage III and IV) ICSI may be a better option for those patients than the conventional IVF. However, once oocytes were fertilized, there was no difference in the resulting embryos [25]. In another study, embryos from endometriosis patients exhibit altered morpho kinetics that can be indicative of poorer embryo quality in comparison to embryos resulting from ART in non-endometriosis patients [26].

However, oocytes retrieved from an ovary harboring a small endometrioma did not exhibit any morpho kinetic difference to the sibling oocytes from the healthy contralateral side. Furthermore, both were indifferently fertilized and the resulting embryos were morpho kinetically similar and both resulted in similar clinical pregnancy rate [27]. Furthermore, once fertilization occurs there is no difference in the implantation rate between endometriosis and non-endometriosis patients [23,28].

**Endometrioma and ovarian cancer**

Infertile patients with endometrioma are often kept in fertility treatment for many years. This usually raises a big concern about a possible malignant transformation of the endometrioma. In this regard, it is necessary that clinicians should reassure their patients that the prevalence of an ovarian carcinoma is still lower than 1% (SOGC, Grade II-2). In another study, the prevalence was found slightly higher (1.8%) compared to the general population (1.3%) [29]. Unfortunately, there is no effective screening program for ovarian malignancies. Endometriosis patients should be reassured that according to the above data there is no need for additional exams such as
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sonography or CA 125 in light of the minimal risk of ovarian malignancy in endometriosis patients. It is noteworthy that CA 125 is usually found consistently elevated in endometriosis patients (S2k).

Endometriosis and pregnancy outcome

It is not infrequent, that an infertility-specialist will be faced with unique concerns about a possible detrimental effect of endometriosis on the pregnancy outcome. Actually, the aforementioned guidelines did not include any statements in this regard. Reviewing the recent publications in this area revealed a lot of controversies.

In previous studies, the miscarriage rate was not increased in the endometriosis patients [25,30]. Furthermore, another study did not show any significant detrimental effect of endometriosis on the pregnancy outcomes. Nevertheless, one year later and in a study by Kohl Schwartz et al, a significantly increased miscarriage rate was noted in endometriosis patients [31].

Another group came up with the conclusion that endometriosis is an independent risk factor for placenta previa [32]. Moreover, endometriosis is associated with increased risk for preterm premature rupture of membrane [33].

To draw a final statement about a possible effect of endometriosis on the pregnancy outcome we are still in need of large randomized controlled trials.

Should fertility preservation be offered as an option to endometriosis patients?

To answer the question, two relevant publications are shortly discussed, where endometriosis patients present to fertility clinics for fertility preservation options.

Cryopreservation of oocytes

Elizur et al. 2009 presented a single 25-years old woman, who had undergone four times laparoscopy with unilateral salpingectomy due to severe symptomatic endometriosis. Meanwhile, the patient presented with a remarkably reduced ovarian reserve with antral follicle count of three. Three cycles of controlled ovarian stimulation (twice in agonist and once in antagonist protocol) ended up with vitrification of a total of 21 oocytes [34].

Ovarian cortex cryopreservation and transplantation

A case report of two young patients with history of unilateral recurrent endometrioma and with previous history of one or more cystectomies was first described by Donnez et al. During an inevitable oophorectomy, an ovarian cortex biopsy was orthotopically transplanted on the contralateral side in a peritoneal pouch underneath the ovarian hilum of the unaffected ovary during the same surgery. Four months later, a second-look laparoscopy revealed macroscopically a functioning graft, and on biopsy a neovascularization was seen with viable primordial and primary follicles as well as an evidence of spontaneous ovulation. One of the patients achieved a live birth after the 3rd trial of IVF [35].

A proper counseling should cover different aspects

A proper counseling of those patients should cover a group of aspects:

1. Endometrioma per se compromise the follicle density in the ovarian cortex of the affected ovary and diminish the viable follicles, especially when presenting with a diameter of more than 4 cm. Moreover, fibrosis is more evident in affected ovaries. This also affects the homogenous distribution of the follicles in the ovarian cortex. These effects are age- and endometrioma size-independent [36-38]. AMH is a good reliable marker for primordial follicles in endometriosis patients. It can predict the follicular density in ovarian tissue cryopreservation. Endometriosis patients regardless of its localization suffer from significantly decreasing AMH with age when compared to non-endometriosis patients [39]. Family history of premature ovarian failure (POF) and history of endometriosis are risk factors for low AMH-levels, and hence a compromised ovarian reserve [40].

2. Although a young age is mostly associated with a good ovarian reserve and good quality of oocytes, the longevity of those patients represents a high risk for the recurrence of the disease. It is estimated that 20% and 50% of endometriosis patients will have a disease recurrence 2 and 5 years after surgery, respectively [41].

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3. The prescription of oral contraceptive pills after cystectomy reduces the disease recurrence [6]. This can in turn prevent the damaging effect of the endometrioma on the primordial follicles.

4. How many oocytes can be cryopreserved in order to get (later) a baby? It is stated that a woman less than 35 years of age aiming at social freezing (fertility preservation without medical indication) should cryopreserve 20-25 oocytes in order to later take home a baby. This in turn necessitates multiple treatment cycles, which are not only costly but also time consuming. High doses of FSH/LH hormones are usually needed and the oocyte yield can be variable [34].

5. Although cryopreservation of fertilized oocytes either by slow freezing or vitrification is nowadays a routine practice in all fertility centers, the data regarding cryopreservation in endometriosis patients are still scarce and randomized controlled trials are needed.

6. Patients should not take the success of oocytes freezing for granted, although there are great advances in oocyte vitrification. As soon as an imminent child wish appears, they should turn to the next fertility clinic.

**Conclusion (Figure 4)**

*Figure 4:* Flow chart for a proper counseling of endometriosis patient either with child wish or desired fertility preservation. EFI: Endometriosis Fertility Index, ART: Assisted Reproductive Technique, SEM: Superficial Endometriosis, DIE: Deep Infiltrating Endometriosis, AFC: Antral Follicle Count, OC: Oral Contraceptives, RCTs: Randomized Controlled Trials.

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- All patients with fertility issues having endometriosis should be staged according to rASRM, ENZIAN (in case of DIE) and EFI [11].
- Spontaneous conception in endometriosis patients can be improved by laparoscopic excision of superficial endometriosis lesions by expert operators. Neither pre- nor post-operative hormonal treatment exhibits any beneficial reproductive outcome. EFI is a clinical predictive tool for spontaneous conception which can be considered in the routine praxis.
- A high spontaneous conception rate following excision of colo-rectal or urinary endometriosis is recently shown to be achievable.
- In ART patients, excision of endometriosis did not show clear advantages concerning improvement of pregnancy rate, unless an endometrioma hinders the oocyte retrieval, causing pain or looking suspicious. Then cystectomy is recommended.
- In ART patients, endometriosis patients need a longer stimulation with higher gonadotrophin doses; however cumulative endometriosis recurrence rates are not increased after IVF/ICSI.
- Whether endometriosis compromises either the oocyte or the embryo quality remains unclear.
- Ovarian cancer in endometrioma is a rare event, so that there is currently no need for a prophylactic salping oophorectomy or a routine CA-125-measurement.
- Association of endometriosis and compromised pregnancy outcomes are debatable and need further studies.
- Fertility preservation can be offered but still remains premature for a standard clinical practice.

Disclosure

No possible conflict of interests for all authors.

Author Contributions

M.G. Ibrahim conceived the study question, drafted the manuscript, together with all other authors critically discussed and reviewed the manuscript and provided a proof for publication.

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