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Short Commentary

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Infertility Associated with Ovarian Endometriomas: Surgery or *In-Vitro* Fertilization?

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Abstract

Ovarian endometriomas are frequently associated with female infertility. The choice of treatment in these cases is one of the most discussed topics in Reproductive Medicine, and the approach to the patient should be tailored based on different parameters. Management options include surgery, *In-Vitro* Fertilization (IVF), or a combination of both. Laparoscopic excision of the ovarian endometrioma should be the treatment of choice when there is associated pain. Surgery should be performed following appropriate techniques to reduce the possible damage to the ovarian reserve. Pregnancy rates around 50% have been consistently reported after surgery, which compare favorably with those obtained with IVF. IVF may be preferred in case of associated male or tubal factor, in case of a reduced ovarian reserve, or if previous surgery has failed, particularly if there is no associated pain, and when the ultrasonographic features of the ovarian cyst are reassuring. Sometimes IVF may be preceded by surgery, when a difficult access to follicles at pick-up, due to the size and location of the ovarian cyst, or to severe adhesions, is anticipated.

Keywords

Endometrioma, Endometriosis, *In-Vitro* Fertilization, Infertility, Laparoscopy

Introduction

Pelvic endometriosis is present in 25%-50% of infertile women [1-3]. In 17%-44% of these women, an endometrioma may be present [3-5]. The scenario of an infertile woman with an endometrioma is therefore a very common one in clinical practice. Unfortunately, many issues regarding the management of the infertile patients with an ovarian endometrioma are not addressed in Randomized Clinical Trials (RCTs), and the choice of treatment in these cases represents therefore a very challenging situation for the clinician.

In case of endometrioma-associated infertility, treatment options include expectant management, surgical excision, or *In-Vitro* Fertilization (IVF). Medical therapy suppresses ovulation and has no role in the infertile patient [1,4-6]. The only exception is for medical treatment administered before IVF, which has been associated with better results for subsequent IVF [7].

Recent guidelines from the European Society of Human Reproduction and Embryology (ESHRE) [6] suggest that, in stage III-IV endometriosis associated with infertility, clinicians should consider operative laparoscopy,

instead of expectant management, to increase spontaneous pregnancy rates, although there are no RCTs comparing reproductive outcome after surgery and after expectant management. This suggestion is based on prospective cohort studies showing crude spontaneous pregnancy rates of 57-69% for moderate and 52-68% for severe endometriosis, which compare favorably with 33% and 0% respectively for moderate and severe endometriosis after expectant management [6,8]. However, concerns have been raised in recent years as to the possible damage to the ovarian reserve as a consequence of excisional surgery [9]. Consequently, the ESHRE guideline [6] "recommends that the clinician counsels the pa-

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tient with an ovarian endometrioma regarding the risks of a reduced ovarian function after surgery". Given these concerns, some authors advocate direct referral to IVF in case of endometrioma-associated infertility [8,10]. Surgery before IVF, in fact, has not been demonstrated to improve live birth rates compared to direct referral to IVF [3].

In this article we will briefly review the pros and cons of the surgical excision of an ovarian endometrioma, with the aim of addressing the question of which approach, surgery or IVF, should be considered as the first treatment option for patients presenting with associated infertility.

Surgery: The Pros

As outlined above, surgery yields satisfactory results in terms of postoperative pregnancy rates. A meta-analysis by Vercellini, et al., [11], pooling the results of several uncontrolled case series, reports a cumulative pregnancy rate of 50% after surgery for endometriosis, and represents probably the highest level of scientific evidence that is available in the absence of RCTs. The 50% pregnancy rate after surgery compares favorably with the 29% clinical pregnancy rate per oocyte pick-up reported by the ESHRE for IVF [12], which corresponds approximately to a 21-22% term pregnancy rate per initiated cycle. In addition, spontaneous pregnancy after surgery is not at higher risk for multiple gestations, and subsequent pregnancies following the first one after surgery do not need additional treatments.

Besides these results in terms of pregnancies, surgery allows also immediate postoperative pain relief, as documented in a recent meta-analysis [13]. Therefore, when infertility is associated with pelvic pain, surgery represents the only approach that may be effective on both pain and fertility. Medical therapies, in fact, may only treat pain, whereas IVF may only resolve the fertility issue.

In case of non-reassuring sonographic features, or in case of fast-growing cysts, surgery should be considered mandatory [5], in order to obtain tissue for histology and exclude an ovarian malignancy. However, even in case of carefully selected patients, with reassuring sonographic features with the typical aspects of an ovarian endometrioma, final histology may reveal an unexpected malignancy in approximately 0.9% of the cases [14]. Therefore, among the pros of surgery, there is also the possibility of obtaining a surgical specimen for histology diagnosis, which rules out the rare cases of unexpected malignancy [6].

As a final consideration on the advantages of surgery, the presence on ovarian endometriomas may determine the derangement of normal ovarian anatomy, and sometimes, a difficult access to follicles at pick-up, due to the size and location of the ovarian cyst, or to severe adhe-

sions, may be anticipated. In these particular cases, even smaller cysts may need surgery before IVF in order to gain an easier access to the follicles [15].

Surgery: The Cons

Besides the generic risks associated with a surgical procedure, laparoscopic excision of an ovarian endometrioma has been specifically associated with a damage to the ovarian reserve, as demonstrated by a decrease of 38% in Anti-Mullerian Hormone (AMH) levels after surgery [9]. Also, worse responses to gonadotropin stimulation for *In-Vitro* Fertilization (IVF) have been reported by many authors after surgery [16]. Additionally, in case of bilateral ovarian endometriomas, premature ovarian failure after surgery has been reported in 2.4% of the patients [17]. Studies on the histology of the excised cyst specimen demonstrated that some ovarian tissue is inadvertently removed with the cyst capsule [18], and this may partly explain the reduced ovarian reserve after surgery. Also, additional damage may be exerted on the remaining ovary by excessive bipolar coagulation [13]. This worrying postsurgical scenario may however be less worrying if, for example, ovarian reserve is evaluated with Antral Follicle Count (AFC) rather than AMH. In a recent meta-analysis [19], in fact, no change in AFC has been reported after surgery.

Conclusion

The management of an ovarian endometrioma associated with infertility should be tailored on each patient, after careful consideration of various parameters, such as age and ovarian reserve of the patient, previous treatments for the disease, the presence of associated pain, and associated infertility factors. Recently, a multiparametric score to guide the clinician in the choice of treatment of the ovarian endometrioma has been developed [5].

Surgery should be preferred in case of non-reassuring features or rapid growth of the cyst at sonography, or when moderate to severe pain symptoms are present. Surgery should be performed following appropriate techniques to reduce the possible damage to the ovarian reserve [20]. IVF may be preferred in case of associated male or tubal factor, in case of a reduced ovarian reserve, or if previous surgery has failed. If surgery is withheld, and the patient is directly referred to IVF, or managed expectantly, the possibility of an unexpected ovarian malignancy still exists, and close follow-up with serial ultrasound scans is mandatory. The patient should be accurately counseled as to the pros and cons of both approaches, and a shared decision should be reached. Due to the lack of robust scientific evidence in the context of endometrioma-associated infertility, RCTs are strongly needed.

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