Endometriosis

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Contributor: Ana Sofia Pais , Sun-Wei Guo

Endometriosis is an inflammatory condition characterized by the presence of endometrial-like tissue outside the uterus. It affects mostly women of reproductive age and approximately 30–50% of women with endometriosis may present infertility.

Endometriosis retrograde menstruation endometrial determinism mutation root treatment

1. Introduction

Between 17% and 44% of endometriosis patients have endometriotic ovarian cysts (endometrioma), which are bilateral in about 19–28% of cases [1][2]. The aetiopathogenesis of endometrioma is still uncertain and several hypotheses have emerged. Hughesdon [3] and Brosens et al. [4] demonstrated the formation of a pseudocyst by invagination of the ovarian cortex following the bleeding of a superficial endometriotic implant and the accumulation of menstrual debris. According to Nezhat et al. [5], endometrioma results from the transformation of a functional cyst. More recently, Donnez et al. [6] confirmed the involvement of metaplasia of invaginated coelomic epithelium in the origin of endometrioma.

Recommendations on the different surgical options available for ovarian endometrioma have recently been published by the working group of the European Society for Gynaecological Endoscopy (ESGE), the European Society of Human Reproduction and Embryology (ESHRE) and the World Endometriosis Society (WES) [7]. In summary, the available approaches for conservative surgical treatment of ovarian endometrioma are cystectomy, ablation or a combined technique.

Laparoscopic ovarian cystectomy is performed by the stripping technique, in which the drained endometrioma and ovarian cortex are pulled apart and haemostasis is applied on the ovarian cyst bed [8]. Traction and counter-traction must be performed using appropriate instruments with low to moderate force to avoid excessive bleeding.

In the ablative approach, endometrioma is fenestrated, drained and washed out and the cyst wall is then destroyed with an energy source, such as a CO_2 laser, bipolar coagulation or plasma energy [8]. Care must be taken to ablate the entire surface of the cyst wall in order to reduce the risk of residual ovarian endometrioma. The entire depth of the cyst capsule must not be ablated as endometriotic tissue is present only superficially, with a mean depth of 0.6 mm [9].

In cases of large ovarian endometrioma, a three-step approach could be suggested, requiring a first laparoscopy for draining the cyst, followed by 3 months of gonadotropin-releasing hormone (GnRH) agonist therapy [6][10]. At the end of the medical treatment, a second laparoscopy is performed in order to ablate the reduced ovarian endometrioma [6][7].

In order to avoid two laparoscopic procedures, Donnez et al. [10] described a combined technique in which 80–90% of the endometrioma is excised according to the cystectomy technique, and a CO_2 laser is then used to vaporize the remaining 10–20% of the endometrioma close to the ovarian hilus. Indeed, in this region of the ovary, dissection is usually more difficult and is associated with a higher risk of bleeding which needs coagulation close to the ovarian vessels.

Surgical treatment of endometrioma improves patients' symptoms, such as pain, but the most appropriate approach for reproductive outcomes is still controversial, according to the Royal College of Obstetricians and Gynaecologists (RCOG) [11]. The guidelines from the ESHRE and a Cochrane review state that ovarian cystectomy is the preferred technique in terms of recurrence and spontaneous pregnancy rate after surgery [12][13]. In infertile women with stage I/II endometriosis according to the revised American Fertility Society (rAFS) classification of the American Society for Reproductive Medicine (ASRM), ESHRE recommends performing an operative laparoscopy rather than only a diagnostic laparoscopy [12]. On the other hand, ASRM proposed that in the initial stages and in women under than 35 years, expectant management or superovulation/intrauterine insemination can be considered as first-line therapy [14]. For stage III–IV disease, both societies agree with the benefit of surgical therapy [12][14]. However, the safety of this option has been questioned as it may cause ovarian damage, with a negative effect on ovarian reserve.

Ovarian reserve is defined as the functional potential of the ovary and reflects the number and quality of the follicles in the ovaries at any given time. Anti-Müllerian hormone (AMH) is a reliable marker of ovarian reserve [15]. AMH is a glycoprotein secreted by granulosa cells of primary, pre-antral and antral follicles, but it is not produced by primordial follicles. After the AMH peak at 24 years old, it gradually decreases to become undetectable at menopause [16][17].

The risk of postsurgical ovarian failure has reopened the debate between excision and ablation [18]. The deleterious effects of the presence of endometriosis in the ovarian reserve itself as well as the risk of affecting the ovarian reserve by the surgical procedures are taken into account when deciding whether or not to operate on patients who want a pregnancy [19][20][21][22]. Therefore, in many centres, patients are directly referred to in vitro fertilization (IVF) instead of offering them an appropriate surgical procedure associated with the possibility of getting pregnant spontaneously. Therefore, as endometriosis is mainly found in women of reproductive age, the impact of endometrioma and its treatment on ovarian function must be evaluated in order to maintain the best chances of pregnancy.

2. Impact of Surgical Management of Endometrioma on AMH Levels and Pregnancy Rates

The benefit of endometrioma excision for pain management is consensual, but surgical excision for the sole purpose of improving reproductive outcomes is controversial [8]. Ovarian involvement with endometriosis might have a negative impact on ovarian reserve [22][23][24]. That fact, alongside the risk of postsurgical ovarian failure, has reopened the debate between excision and ablation [18].

The reduction of ovarian reserve after surgery for endometrioma is inevitable, regardless of the technique. Both excisional and ablative approaches lead to a postsurgical decrease of up to 60% in AMH levels. However, studies comparing the two techniques show a higher and significant decrease after cystectomy [25][26].

The decline in ovarian reserve after ovarian surgery is multifactorial. Healthy ovarian tissue may be unintentionally removed during ovarian cystectomy due to the absence of a clear histologic cleavage plane, which can result in loss of follicles. This justifies the theory that ovarian reserve is better preserved by ablation than by cystectomy. However, other proposed mechanisms for the ovarian reserve decline include thermal damage caused by bipolar coagulation, ovarian vascular injury and postoperative inflammatory response [18][27][28][29]. Therefore, bipolar electrocoagulation should be kept to a minimum, especially for patients with reproductive goals [29]. With the use of a CO_2 laser, the glandular epithelium and the underlying stroma [10][26] are destroyed without reaching the fibrous capsule surrounding the endometrioma or healthy neighbouring ovarian cortex. The CO_2 laser would provide better control of the depth of vaporization, remaining superficial compared to bipolar electrocoagulation [26][30]. This is an advantage as it would not be necessary to destroy the entire fibrous capsule by vaporization, as only 1.0–1.5 mm of the inner lining would be sufficient [31]. The CO_2 laser as well as plasma energy are techniques for sparing ovarian tissue with a shallower thermal diffusion [30][32]. Their low thermal energy avoids excessive ischaemic damage while providing high precision and optimal coagulation, reducing the need for electrocoagulation or suturing [18][30]. Thus, CO_2 technology may be used to treat endometrioma with minimal damage to the adjacent healthy ovarian tissue and it might be an alternative treatment in women with a desire for pregnancy.

Excision of the ovarian cortex could be involved in the reduction of ovarian reserve just after surgery, but a continuous decrease could be attributed to other factors, such as vascular compromise by excessive coagulation or adhesiolysis as well as postsurgical inflammation [27][23][33][34].

The number of studies that have evaluated changes in ovarian reserve after cystectomy over a period longer than 6 months is limited, but it seems that the decrease in AMH following surgery for endometrioma is temporary and can be recovered. This can be explained by surgery-related reversible mechanisms related to ovarian vasculature and inflammation-mediated injuries. After ovarian injury, compensatory mechanisms may include the recruitment and growth of primordial follicles and the excessive activation of granulosa cells [28]. This leads to rearrangements of the cohort of follicles, including follicles producing AMH, which can explain the “recovery” in the ovarian reserve. The delay in this recovery is explained by the approximate 180-day duration of folliculogenesis from the primordial follicles to the pre-ovulatory follicles [33]. A similar pattern of AMH recovery has been reported in young women after chemotherapy, in which a complete restoration of AMH levels was observed [23][35]. However, some studies showed that ovarian reserve cannot be fully restored in all patients after surgery for endometrioma, indicating some elements of permanent damage. Since the literature on the late postoperative period is scarce, recovery of the

ovarian reserve should be interpreted with caution [2]. Furthermore, factors like AMH decline with age and endometriosis must be considered [22][36].

Bilaterality, size of endometrioma, stage of endometriosis and patient's age are independent factors that should be also considered when planning a surgery in patients who are interested in preserving their fertility [2][37]. Bilateral endometriomas, stage III/IV endometriosis and patients over the age of 35 have a higher impact on postsurgical AMH levels. For large cysts, a proportional loss of healthy ovarian tissue with the diameter of the cyst can explain the higher decrease of AMH levels [38][39]. Additionally, for endometriomas with more than 5 cm, ablative treatment seems to have low impact in postoperative AMH levels than excisional surgery [40]. For recurrent endometrioma, a second surgery is associated with higher loss of ovarian tissue and is more harmful to the ovarian reserve [41]. Indications for surgery for recurrent endometrioma should thus be considered with caution and excisional surgery must be avoided [41]. Medical treatment may be the first option, but when surgery may still be indicated, an ablative approach can be considered, as recurrence rates are similar [42].

All of these factors will allow clinicians to select therapies to prevent further decline of ovarian reserve, especially for infertile patients with ovarian endometrioma [43]. Therefore, surgery should be performed when mandatory, such as pain refractory to medical therapy, pain associated with otherwise unexplained infertility and in the case of non-reassuring features of the cyst on preoperative ultrasound [44]. Individual reproductive plans and oocyte or ovarian tissue cryopreservation should be discussed with patients before surgery. Ideally, surgery can be postponed until the reproductive project is complete [2].

The decline of AMH levels after surgery is higher in patients with ovarian endometrioma than in those with other benign tumours [45][46][24][47]. This is in line with the impact per se of endometriosis in ovarian reserve and the fact that it is also present when surgery is performed by a specialised surgeon [23][24][44]. The likelihood of spontaneous pregnancy after surgery is also lower in patients with endometrioma [45].

According to the ESHRE guideline, there is evidence to suggest that ovarian cystectomy via stripping is the preferable surgical technique for management of endometrioma, compared with other excisional/ablative techniques in terms of the pregnancy rate [12][13]. However, studies carried out later show a higher overall pregnancy rate after the ablative approach than the excisional (67–73% vs. 30–67%) [34][32]. This fact is in line with the lowest impact on AMH levels.

Favourable preoperative ovarian reserve and its postoperative maintenance together may be implicated in postsurgical pregnancy after surgery for endometrioma [43][48]. The potential risk of postsurgical poor ovarian response could be predicted by using optimal cut-off points of presurgical AMH levels (2.1 ng/mL of unilateral endometrioma; 3 and 3.5 ng/mL for bilateral endometrioma at 3 and 6 months after surgery, respectively) [43]. The cut-off value to predict spontaneous pregnancy rates after endometrioma cystectomy is approximately 3.5 ng/mL, with higher AMH levels associated with a higher pregnancy rate [48][49][50]. Thus, after cystectomy, better ovarian reserve with optimal rearrangement of the follicle cohort may be related to subsequent pregnancy [51]. In patients at

risk, alternative management of cystectomy should be foreseen. However, AMH is a quantitative but not qualitative surrogate for oocytes [43].

In patients with stage III and IV endometriosis submitted to ablative surgery, the probability of pregnancy and the risk of decreasing ovarian reserve is similar in patients with high and low preoperative AMH levels [52]. Therefore, a young patient suffering from severe endometriosis with a decreased ovarian reserve and a preoperative AMH level below normal could benefit from surgical management. This surgery could restore the capacity of spontaneous pregnancy in this population and may be an alternative to ART [52].

3. Conclusions

In conclusion, measurement of AMH should be included in the evaluation of reproductive-age women with endometriosis. The indication of surgery for an ovarian endometrioma should be thoroughly discussed with the patient, with particular emphasis on the issue of possible damage to the ovarian reserve. The endometrioma ablation procedure, even if performed in patients with a decreased ovarian reserve, is beneficial in terms of pregnancy.

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