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REVIEW ARTICLE

Gynecology

Managing endometrioma to optimize future fertility

Maebh Horan[1,2,3] | Louise Glover[1,3] | Mary Wingfield[1,2,3]

[1]Merrion Fertility Clinic, Dublin 2, Ireland

[2]Department of Obstetrics and Gynecology, National Maternity Hospital, Dublin 2, Ireland

[3]School of Medicine, University College Dublin, Dublin 4, Ireland

Correspondence
Maebh Horan, MRCPI MRCOG, Merrion Fertility Clinic, 60 Lower Mount Street, Dublin 2, Ireland.
Email: horanm2@tcd.ie

Abstract

The management of endometriomas in women wishing to preserve their fertility is complex. While surgery can help to achieve pregnancy in some, it may also have a detrimental effect on a woman's ovarian reserve. The present article reviews the impact of endometriomas on fertility and the different management approaches that should be considered in women who wish to preserve their fertility. This study also reviews the role of assisted reproduction in the setting of endometriomas, and the evolving role of oocyte cryopreservation for this benign but progressive disease. Using evidence from the latest guidelines and major publications, we emphasize the need to consider the woman's future fertility when navigating the diverse range of management strategies available, and outline an evidence-based framework to help facilitate fertility-friendly discussion, counseling and management of this complex disease.

KEYWORDS
endometrioma, endometriosis, fertility, fertility preservation

1 | INTRODUCTION

Endometriosis is a chronic disease, affecting approximately 10% of women of reproductive age.[1] It is defined by the presence of endometrial glandular epithelium and stromal implants in extra-uterine locations, found at laparoscopy in up to 50% of women with pain and infertility and up to 80% of those with chronic pelvic pain.[1] Histopathological diagnosis requires the presence of two or more of the following histological features: endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-laden macrophages.[2] Three forms of pelvic endometriosis are described: superficial implants, endometriomas, and deep infiltrating endometriosis. While these should be considered separate entities,[2] they may occur independently or in combination. Disease phenotype exhibits different effects on fertility. Ovarian endometriotic cysts or endometriomas are of particular relevance to fertility due to the negative impacts of both the disease and its treatment on prognosis. Emerging evidence shows that assisted reproduction techniques, prior to or alongside surgery, offer effective treatment of infertility in the setting of endometrioma. It is therefore important for clinicians, especially those in non-fertility settings, to be aware of options for preserving reproductive potential in these women. The focus of this review is management of women with endometrioma, the majority of whom will be classified as stage III/IV (moderate to severe) endometriosis, as defined by the American Society of Reproductive Medicine (ASRM).[3]

2 | ENDOMETRIOMA: DIAGNOSIS AND HISTOLOGY

2.1 | Endometrioma diagnosis

Diagnosis of endometrioma is often made based on ultrasound findings of a unilocular, or multilocular ovarian cyst, with internal homogenous low-level echogenicity of the cyst content and no solid component or internal vascularity.[4] Definitive diagnosis require laparoscopy and histological sampling. Endometriomas have been described as representing an invagination of the ovarian cortex, with functionally active endometriotic implants and neovascularisation

located on the surface of this inverted cortex.[2] A histological study of 70 endometriomas demonstrated that they have a fibrotic capsule, with endometrial tissue present on up to 60% (range 10–98%) of the internal surface of the cyst wall. This endometriotic tissue penetrated into the cyst wall for a mean depth of 0.6 mm (range 0.1–2.0 mm). [5]

2.2 | Endometrioma and ovarian reserve and function

Infertility is a common complication in moderate to severe disease.

Endometriomas are reported to affect up to 17–44% of infertile women with endometriosis and are typically associated with more severe disease (ASRM). [6] A study of unilateral endometrioma by Horikawa et al (2008) demonstrated that the frequency of ovulation in ovaries affected by an endometrioma is reduced compared to the frequency in a contralateral unaffected ovary. The mean ovulation rate in affected ovaries was 34.4 ± 6.6% rather than the expected rate of 50% and this was further reduced to 16.9% ± 4.5% following ovarian cystectomy.[7]

Endometriomas are also associated with diminished ovarian reserve, due to both the endometrioma per se and surgical interventions to treat and excise the cyst. One study investigating the longitudinal decline of Anti-Mullerian Hormone (AMH) levels over a 6-month period revealed an increased rate of decline in women with endometriomas compared with controls.[8]

Kitajima et al. demonstrated that follicular density was significantly lower in the ovarian cortex of ovaries with endometriomas, with more fibrosis and subsequent loss of cortex-specific stroma.[9] This work further described accelerated depletion of follicles, indicating upregulated and enhanced follicular recruitment, but also increased follicular atresia, resulting in exhaustion of primordial follicles.[9] Investigation of follicular survival and activity in xenografted ovaries by Dolmans et al. led to the development of the "burnout" hypothesis. This describes a focal inflammation leading to fibrosis and destruction of the normal ovarian cortex, which in turn causes enhanced follicular recruitment and atresia, eventually leading to burnout of dormant follicles.[10]

Endometriomas contain free iron, reactive oxygen species, proteolytic enzymes, and inflammatory molecules in much higher concentrations than benign ovarian cysts. These are proposed to lead to fibrous changes in the adjacent ovarian cortical tissue, with subsequent loss of ovarian follicles.[11]

3 | MANAGEMENT OF ENDOMETRIOMAS

There are conservative, medical, surgical, and assisted reproduction approaches to the treatment of endometriomas. Management options are influenced by several factors including symptoms, clinical signs, radiological and investigative findings, patient characteristics and desire for pregnancy. Herein, we focus primarily on the management of those presenting with endometriomas who wish to conserve and optimize their chances of pregnancy either at the time of presentation or at some time in the future. It is important to consider the male partner from the outset as assisted reproduction will be most effective, or indeed the only viable option, if there is a significant sperm factor. Sperm abnormalities are found in up to 50% of couples accessing ART,[12] and while it may seem obvious to those practicing assisted reproduction, it is imperative that semen analysis is performed for the partner of any woman contemplating surgery for an endometrioma (Figure 1). Similarly, assisted reproduction may be required if there is an additional tubal factor.

3.1 | Conservative Management

Depending on individual patient characteristics and fertility prognostic factors including female age, duration of infertility, ovarian reserve tests, surgical history (particularly previous ovarian surgery) and semen parameters (if the patient has a partner), a conservative approach to the management of an endometrioma may be reasonable initially. As mentioned earlier, Horikawa et al. reported reduced ovulation in ovaries affected by endometrioma, especially in the presence of a larger endometrioma >4 cm. However, this study had only 28 participants, with the authors conceding that further studies are required.[7] In contrast, a larger study from the University of Milan, assessed ovulation in seventy women with unilateral endometrioma over six menstrual cycles.[13] Ovulation was similar between healthy and affected ovaries, with 43% of patients conceiving spontaneously during the study period. It must be acknowledged that these patients had no other infertility risk factors. This supports a period of conservative management in younger women with unilateral endometriomas who are asymptomatic and have no history of subfertility. Guidelines produced in 2017 on behalf of the Royal College of Obstetricians and Gynaecologists (RCOG) support this view and advise against surgical treatment for those with an incidental finding of endometrioma.[6]

3.2 | Medical Management

While hormonal medical treatments such as the oral contraceptive pill, progestagens and GnRH agonists may help women with dysmenorrhea and pain and may help prevent recurrences, they are counterproductive for infertility due to their effects on ovulation and endometrial function. In general, they should not be used in women who are actively trying to conceive, except in selected symptomatic women awaiting assisted reproduction or surgical treatment.

3.3 | Surgical Management

The role of surgery for women with endometriomas and infertility is complex. Pregnancy rates of up to 50% have been reported after unilateral endometrioma surgery.[6] However, as already discussed, there is increasing evidence highlighting the fertility risks of surgery, which can

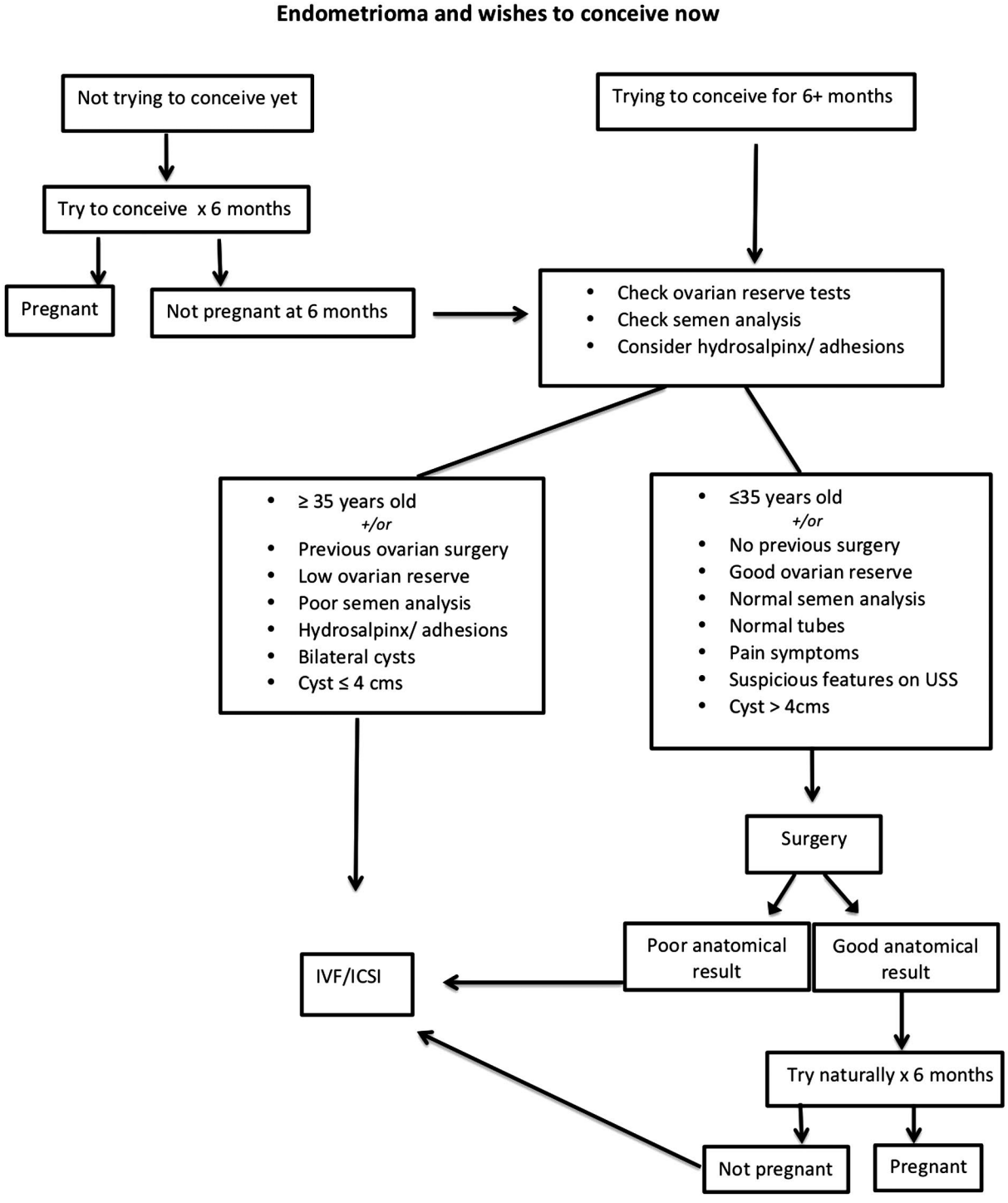

FIGURE 1 Clinical support algorithm for management of women with endometrioma who wish to conceive

cause a significant post-operative reduction in ovarian reserve. This can have a devastating effect on future reproductive potential, particularly in the case of repeated endometrioma surgeries. To optimize fertility, meticulous technique must be used to reduce inadvertent, iatrogenic ovarian tissue damage. Damage can result from removing normal ovarian cortex, or from excessive use of electro-cautery to achieve hemostasis.[14] Studies have shown that experienced surgeons remove less healthy ovarian tissue at the time of ovarian cystectomy.[15]

There is no standardized surgical approach to the management of endometriomas, although several different surgical techniques are described. A 2008 Cochrane review compared excisional surgery to cyst drainage and ablation of the cyst capsule, using recurrence of endometrioma and pain symptoms as primary outcomes. This review reported that when surgical management is indicated, cystectomy seems to be the more effective approach in terms of lower cyst recurrence rates, lower recurrence of pain symptoms and an increase

in spontaneous pregnancy rates. However, this review looked only at the results of two randomized studies.[16] Guidance from the RCOG recommends ovarian cystectomy as opposed to ablative treatment or cyst drainage but highlights the risk to ovarian reserve.[15]

More recently, the European Society for Gynaecological Endoscopy (ESGE), the European Society of Human Reproduction and Embryology (ESHRE), and the World Endometriosis Society (WES) provided recommendations on surgery in women with endometriosis. They describe three surgical methods for the treatment of endometrioma—ovarian cystectomy, laser or plasma energy ablation and electrocoagulation. These can be performed individually or as a combined technique.[17] This guidance does not recommend one surgical approach above another, but rather focuses on minimizing trauma to healthy ovarian tissue and selecting a surgeon with the relevant expertise.

Although endometriotic cystectomy is associated with lower recurrence rates,[18] it is proven to negatively impact ovarian reserve and function. Studies show decreases in systemic AMH levels, number of follicles responsive to ovarian stimulation, and age at menopause,[11,14] as well as decreased ovulation frequency.[7] Muzii et al. in 2005 reported that tissue excised near the ovarian hilum contained follicles within the excised specimen in up to 69% of cases.[19] The impact of surgery is even more evident in bilateral disease, with one study reporting a low but definite risk of premature ovarian insufficiency after bilateral ovarian cystectomy.[20]

A study examining the use of the combined cystectomy and ablative techniques by Donnez et al. assessed antral follicle counts (AFC) and ovarian volume of operated and non-operated ovaries in patients with and without endometriosis. They described a low recurrence rate of 2%, as well as preserved ovarian volumes and AFC.[21] This was in part attributed to the fact that the risk to ovarian follicles is highest near the hilum as well as the increased complexity of cystectomy here due to absence of a clear cleavage plane.[19] This combined technique describes a partial cystectomy, which removes the majority of the endometrioma, up until the cleavage plane is less visible, with subsequent use of laser or ablation to treat the residual cyst. A multicenter randomized trial comparing this technique to traditional cystectomy, found similar recurrence rates and comparable AFC post-operatively between groups. However, the sample size was small and may not be large enough to detect clinically significant differences.[22]

Although excisional surgery for endometriomas remains the gold standard, based on available data, a combined approach may offer a viable alternative, particularly when the cleavage plane at the ovarian hilum is distorted.

3.4 | Recurrence of endometrioma and repeated surgery

Recurrence of endometrioma following surgical management is reported to be as high as 16–50%.[23] Repeated surgery has a greater deleterious effect on ovarian reserve and may be more harmful to healthy ovarian tissue than the primary surgery.[24] Importantly, repeated surgery does not seem to improve fertility outcomes. Women failing to conceive after a single operative procedure should therefore be counseled to avoid further surgery and to consider other options, including assisted reproductive technologies (ART) such as in vitro fertilization (IVF). A study evaluating the efficacy of repeat operative management of infertility in women with moderate or severe endometriosis found a cumulative pregnancy rate (CPR) of only 24% nine months after repeat surgery, compared to 70% after two IVF cycles following the primary surgery.[25] This supports IVF as an effective alternative for women in whom primary surgery has failed to restore fertility. The debate regarding surgery or ART in the management of women with endometrioma is discussed further below.

3.5 | Assisted reproductive technology (ART)

Endometriosis affects approximately 10–25% of patients requiring assisted reproduction, and ART is a widely established and effective treatment in the management of endometriosis-associated infertility.[1] The ESHRE guideline development group recommends the use of ART for infertility associated with endometriosis, especially in the setting of compromised tubal function or associated male factor infertility.[26]

Numerous studies have assessed the impact of disease on ART outcomes and investigated the mechanisms behind endometriosis-associated infertility. Unfortunately, despite continued advances in the field of ART, evidence suggests that endometriosis has a negative impact on all stages of reproduction, including the number and quality of oocytes retrieved, oocyte fertilization, embryo implantation and early and later pregnancy outcomes.[27]

A large retrospective cohort study demonstrated that women with endometriosis were 24% less likely to achieve a live birth when compared to controls. This effect became more pronounced with increasing severity of disease.[28] Previous work showed similar live birth rates (LBR) in women with milder disease, but poorer outcomes in more severe disease. Those with stage III–IV endometriosis had a 30% lower LBR, 40% lower clinical pregnancy rate (CPR) and lower mean number of oocytes retrieved at the time of oocyte collection compared with women with no disease.[29] A population-based study analyzing 347,185 ART cycles from 2008–2010 found that women with endometriosis in isolation have similar LBRs to other infertility diagnoses. However, women with endometriosis and additional diagnoses (eg male factor), or reproductive tract alterations, had the lowest chance of live birth.[30] These studies highlight the remarkable heterogeneity of the disease, and the importance of accurate classification for reproductive outcome comparison.

3.6 | Surgery or ART in women with endometriomas and subfertility?

Surgical treatment of endometrioma prior to ART is widely practiced, even though there is little robust evidence to provide adequate

guidance to clinicians.[26] Those proposing a surgical approach in the first instance advocate that earlier diagnosis and treatment limits the development of fibrotic changes and preserves vascularity of the ovarian bed. Moreover, operating on smaller cysts may cause less inadvertent ovarian tissue trauma, with some older studies showing a beneficial effect for obtaining a pregnancy within 12 months postoperatively.[31]

Multiple studies have demonstrated that endometrioma excision prior to IVF does not confer a significant benefit to pregnancy rates or IVF outcomes, and that cystectomy in fact reduces the response of the patient to ovarian stimulation.[32,33] Hamden et al. reported that the presence of endometriomas does not adversely affect IVF outcomes in terms of LBR, but these women have lower oocyte yields per ART cycle and higher cancellation rates than those without endometriotic cysts.[32] In a subgroup analysis of women with ASRM III/IV endometriosis, surgical treatment prior to IVF/ICSI was associated with lower LBR, clinical pregnancy rates, and mean number of oocytes retrieved. This study concluded that there was insufficient evidence to recommend surgery routinely as a means of improving ART outcomes.[29] Younis et al. reinforce this approach, concluding that cystectomy, particularly bilateral cystectomy, results in significantly decreased ovarian reserve and reduced potential reproductive lifespan without obvious reproductive advantage.[33] This study advocates delaying surgery if possible until after a woman's reproductive aspirations are achieved. Another systematic review of IVF/ICSI outcomes found similar LBR, CPR and miscarriage rates (MR) in women with and without endometrioma. However, women with endometrioma had an almost three times higher cycle cancellation rate, and women who had surgical treatment of their endometrioma required higher gonadotrophin doses during stimulation.[32] Somigliana et al. demonstrated that the risks associated with ovarian stimulation and oocyte retrieval in the presence of an endometrioma were modest and did not surmount the risks of iatrogenic harm to ovarian reserve from surgery.[34]

Certain scenarios arise where most reproductive specialists now advise consideration of ART prior to surgical treatment. These include women at higher risk of impaired fertility, such as women over 35 years with low ovarian reserve tests, women with bilateral endometriomas, and women with endometriomas who are asymptomatic.[35] As previously discussed, this also holds true when endometriosis is present in conjunction with male factor infertility, or the presence of severe tubal disease, conditions that we know require ART for conception.

There are circumstances in which surgical intervention is still indicated. Surgery should be considered to treat concomitant endometriosis associated pain symptoms. Acute pain with large endometrioma also remains an indication for surgery, especially with suspected cyst accident such as torsion.[36] Given the relationship between endometriosis and epithelial ovarian cancer, surgery should be considered to facilitate complete pelvic assessment and histopathological diagnosis,[36] where there are concerning sonographic features. Surgery with the goal of restoring the anatomical and functional integrity of reproductive organs will remain an indication for patients who decline ART or for those who simply cannot afford it.

In conclusion, the management of infertility in a woman with endometrioma is complex. Careful balance needs to be achieved between the benefits and risks of surgery as opposed to ART. Involvement of the patient (and her partner, where applicable), is essential in deciding the optimal course of action in each situation. Resources should also be provided to facilitate access to ART for all.

3.7 | Fertility Preservation (Oocyte cryopreservation)

Fertility preservation (FP) techniques can offer women the chance to conceive using their own oocytes after age-related or other decline in fertility.[37] Advances in FP strategies, particularly oocyte vitrification, have facilitated greater uptake for both medical and non-medical indications.

Oocyte cryopreservation (OC) is now routinely carried out for young women diagnosed with cancer who are at high risk of fertility loss due to gonadotoxic cancer treatment. It would seem prudent that FP should also be considered for women with benign conditions known to have potential adverse impacts on fertility, such as endometrioma.

However, there remains a lack of clinical consensus and guidelines for the identification of patients with endometriosis who should be counseled to consider FP, and it is unclear whether conversations around FP are routinely taking place prior to ovarian surgery.[38] This applies particularly to women who present with pain symptoms or an asymptomatic mass to non-reproductive medicine specialists.

Optimizing fertility is highly time sensitive, so it is vital that a woman's age be taken into account as part of a fertility risk assessment. Evidence suggests women diagnosed with endometriosis at a younger age have a greater risk of recurrence of their disease. Moreover, the quality and number of vitrified oocytes is anticipated to be higher in younger women, potentially avoiding the need for repeated cycles of cryopreservation.[37] Studies have shown that younger age and the number of oocytes retrieved and vitrified are both related to successful outcomes in future IVF cycles.[37] The largest study to date analyzing OC in women with endometriosis found a significantly lower oocyte yield and cumulative LBR (28.4%) in women over 35 years compared to women under 35 years (61.9%).[37] Another notable finding was the significant difference in CLBR between nonsurgical (70%) and surgical (50%) endometriosis patients under 35 years, attributed to the increased number of oocytes collected and a subsequent increase in CLBR in patients who had not undergone surgery prior to ART. Importantly, the high return rate for use of these frozen oocytes in a cycle of fertility treatment and the high success rate (overall CLBR/patient of 46.4%) observed, reflect the difficulties patients with endometriosis often encounter in trying

to achieve natural pregnancies. This highlights the need for consideration of fertility preservation at a younger age and prior to surgery to optimize outcomes.[37]

Embryo and oocyte vitrification are the most common FP techniques. Embryo vitrification requires a male partner (or sperm donor) and has ethical and legal implications in the case of death or separation. In contrast, oocyte vitrification preserves a woman's reproductive autonomy, allowing a patient to procreate with a chosen partner in the future.[39] A recent review of FP in patients with endometriosis showed that in most cases, mature oocyte vitrification was the FP procedure of choice.[39]

An individualized approach to fertility assessment, optimization and prioritization should be strongly considered as the standard of care for women with endometriosis, particularly endometriomas. Like other diseases which we know can negatively impact future reproductive capacity, FP should be considered and included in presurgical counseling for women of reproductive age who have not yet completed their family (Figure 2).

3.8 | Evaluation of ovarian reserve

Antral follicle count (AFC) and anti-Mullerian hormone (AMH) are the most commonly used ovarian reserve markers. Performing ovarian reserve evaluation in women with endometriosis can provide early recognition of subfertility risk, and low preoperative AFC or AMH may guide surgeons to pursue less aggressive techniques to minimize harm to fertility potential. ESHRE recommend performing ovarian reserve tests when future fertility is of concern.[17] It would seem reasonable to perform ovarian reserve testing prior to surgical treatment of endometriomas in all women who have not yet completed their family,[24] particularly in those with added risk factors for impaired ovarian reserve (Figure 2). A study by our own group demonstrated that women undergoing ovarian reserve testing greatly value knowing their ovarian reserve, regardless of the result.[40] This supports the approach of performing a personalized risk assessment for women, which has been demonstrated to have a much stronger impact on women's behavior, and may help guide changes in reproductive planning.[40]

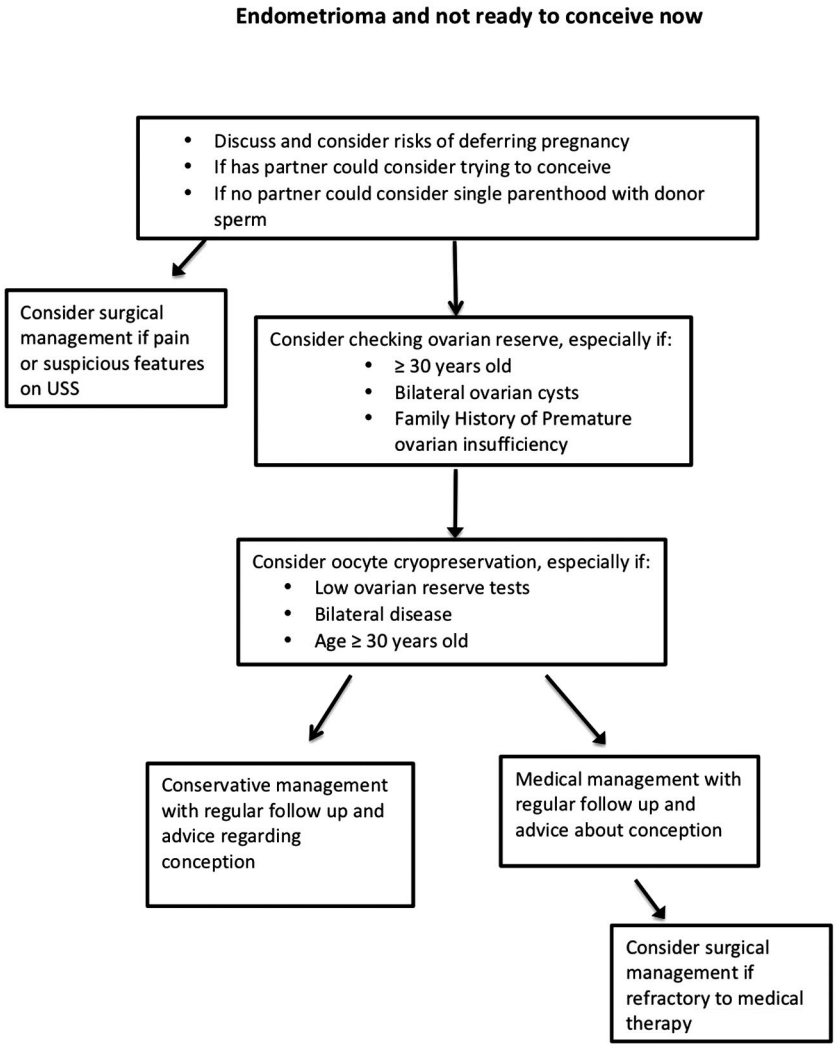

FIGURE 2 Clinical support algorithm for management of women with endometrioma who are not trying to conceive

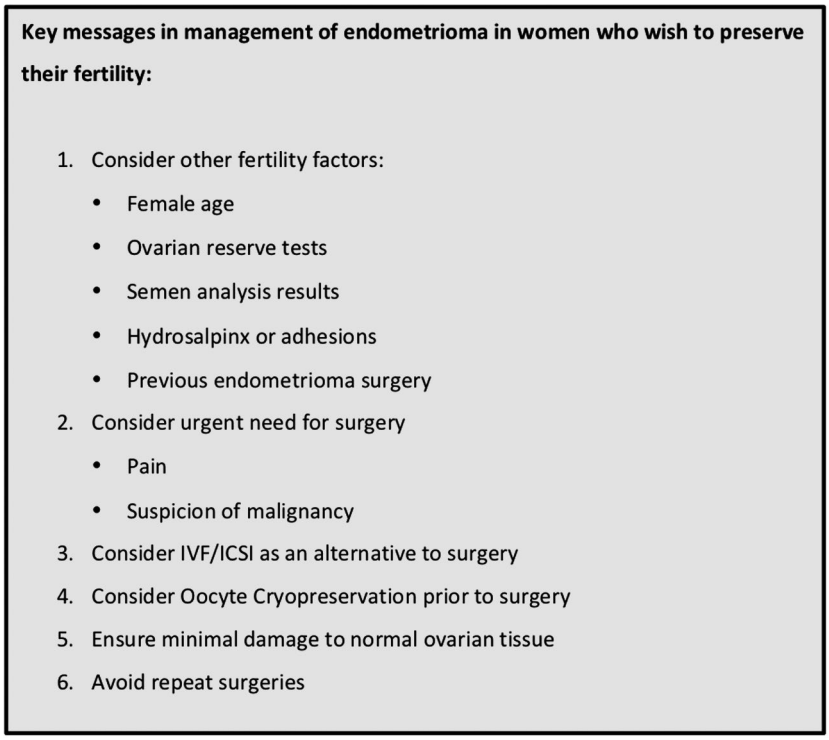

FIGURE 3 Key messages for the management of endometrioma in women who wish to preserve their future fertility

4 | CONCLUSION

The management of endometrioma in young women is complex. It is important to advocate at all clinical management levels for consideration of the woman's fertility needs and reproductive choices both at the time of initial treatment and in the future. Our approach to the management of endometriosis must be patient centered, with careful consideration and awareness of the impact of the disease and its management on current and future reproductive potential (Figure 3).

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CONFLICTS OF INTEREST

The authors declare no conflict of interest in any of the work submitted here.

AUTHOR CONTRIBUTIONS

MH and MW conceived and designed the study, MH performed the literature review and wrote the manuscript. All authors contributed to editing and critical discussion of the manuscript.

ORCID

Maebh Horan https://orcid.org/0000-0003-3684-6860

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