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Review Article

Comprehensive review of the latest evidence available on endometriosis and subfertility

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ABSTRACT

Endometriosis is a chronic inflammatory condition affecting women of reproductive age group, often resulting in subfertility and chronic pelvic pain. The multifactorial nature of endometriosis-associated infertility is influenced by a complex interplay of genetic, hormonal, menstrual, inflammatory and immunological factors, which together define the phenotypic presentation of the disease. These factors complicate natural conception and impact the success of Assisted Reproductive Technology (ART) cycles. While medical management, typically contraceptive, offers symptomatic relief, it may not address the underlying issues that impede natural conception. Surgical intervention, particularly for ovarian endometriosis, has the potential to enhance spontaneous conception rates but also carries the risk of reducing ovarian reserve. This presents a dilemma in fertility preservation, especially when considering assisted reproductive technologies (ART). The current evidence on the efficacy of surgery in improving ART outcomes remains inconclusive, underscoring the need for an individualized and holistic approach in treatment planning. Such an approach is crucial in optimizing reproductive outcomes for women with endometriosis. A systematic search of the literature was conducted to gather the latest evidence on endometriosis and subfertility. Databases searched included PubMed, Scopus, Web of Science and Cochrane Library. While excising endometriomas may help restore pelvic anatomy and increase spontaneous pregnancy rates, there is also a substantial risk of reducing ovarian reserve due to damage caused during the procedure. In particular, cystectomy has been associated with a significant reduction in anti-Müllerian hormone (AMH) levels, a key marker of ovarian reserve.

Keywords: Assisted reproductive technology cycles, Anti-Müllerian hormone levels, Deep endometriosis, Endometriosis fertility index, Follicular stimulating hormone, Ovarian tissue cryopreservation, Pouch of douglas

INTRODUCTION

The exact prevalence of endometriosis is uncertain, with estimates ranging from 2% to 10% in the general female population and up to 50% in infertile women.[1] It is estimated that 6–10% of women, mainly of reproductive age, are affected by the condition, with a reported higher prevalence in specific subgroups, such as those affected by infertility. Ovarian endometriomas can be found in up to 17-44% of women with endometriosis and are often associated with the severe form of the disease. Around 30% of infertile women have a higher prevalence of getting diagnosed with endometriosis.[2] Whilst not all women with endometriosis are symptomatic, endometriosis-associated pain and infertility are the

clinical hallmarks of the disease, affecting not only women with endometriosis but also their partners and families. An impact of endometriosis and particularly pain symptoms, has been shown on quality of life, but also on a range of activities and life domains, including physical functioning, everyday activities and social life, education and work, sex, intimacy and intimate partnerships and mental health and emotional wellbeing.[3]

Finally, a study done by Zondrvan et al, showed that endometriosis has a bearing on society in general, e.g., through direct and indirect healthcare costs comparable to other common diseases such as type 2 diabetes, rheumatoid arthritis and Crohn's disease.[3] The mainstays of management typically involve long-term hormonal treatments, which, while effective in controlling symptoms, often have contraceptive effects. This presents a unique challenge in the context of fertility, where preserving the ability to conceive is paramount.

POTENTIAL MECHANISMS FOR ENDOMETRIOMA-ASSOCIATED INFERTILITY

Ovarian reserve

The presence of ovarian endometriomas, significantly in both ovaries, can impact the ovarian reserve and the response to fertility treatment drugs. The decrease in follicles may be due to damage caused by the inflammation linked to endometriosis and increased tissue oxidative stress leading to fibrosis.[4]

Anatomical distortion

Endometriosis is linked to inflammation and pelvic distortion. Severe endometriosis can cause tubal damage, which may affect egg capture and transport, leading to decreased conception rates. Up to 30% of women with endometriosis have tubal pathology such as obstruction, adhesions or hydrosalpinx.

Chronic inflammation: Peritoneal fluid from women with endometriosis contains increased numbers of immune cells, including macrophages, mast cells, natural killer cells and T cells, along with elevated levels of growth factors, chemokines and cytokines. This heightened inflammatory state can impact the quality of oocytes and impair ovarian function, resulting in defective folliculogenesis and fertilization.[5]

Chronic inflammation

Peritoneal fluid from women with endometriosis has been found to contain increased numbers of immune cells, including macrophages, mast, natural killer and T cells and elevated levels of growth factors, chemokines and cytokines.[6,7] The enhanced inflammatory state can affect the quality of the oocytes and impair ovarian function, resulting in defective folliculogenesis and fertilisation.[8]

Dyspareunia

Deep endometriosis can also be a significant cause of dyspareunia, which can lead to impairment of sexual function, relationships and psychological well-being.

MANAGEMENT

Investigation

Endometriosis is a prevalent and often debilitating gynecological condition characterized by symptoms such as dysmenorrhea, chronic cyclical or non-cyclical pain, deep dyspareunia and subfertility. The non-specific nature of these symptoms frequently complicates the diagnostic process, leading to delays in referral and confusion with other conditions such as pelvic inflammatory disease (PID) and irritable bowel syndrome (IBS). This diagnostic challenge is further compounded by symptoms like dyschezia and deep dyspareunia, which may indicate the presence of deep infiltrating endometriosis.

Diagnostic evaluation should be conducted in a systematic, expeditious and cost-effective manner to identify all relevant factors.[9] Ovarian reserve tests include biochemical analysis and ultrasound imaging of the ovary.

Biochemical tests that aim to depict the biology of the ovary include basal FSH and estradiol measurements and anti-Mullerian hormone concentrations. Basal FSH and estradiol should be measured together in the early follicular phase between menstrual cycle days 2-4. Anti Müllerian hormone can be measured at any point in the menstrual cycle. Transvaginal ultrasound can assess the follicular phase antral follicle count (AFC) and ovarian volume.[9]

Women in need of donor sperm to achieve pregnancy, including single women and women in a same-sex relationship, also warrant a fertility evaluation, as the presence of endometriosis will inform the decision for intrauterine insemination (IUI) or in vitro fertilization (IVF). Same-sex female couples may also elect to pursue reciprocal IVF, where the oocytes are removed from one partner and are used to create embryos, which are subsequently transferred to the other partner who carries the pregnancy.[10] Both women need to be evaluated thoroughly, as the presence of severe endometriosis may guide the decision about which partner will contribute the oocytes and which partner will carry the pregnancy.[11]

Traditionally, the gold standard for diagnosing endometriosis has been laparoscopic identification of lesions with histological verification, a method endorsed by the European Society of Human Reproduction and Embryology (ESHRE). However, this approach, while precise, presents several drawbacks, such as operative risks, limited access to specialized surgeons and significant financial implications. Recent advances in imaging technologies now offer non-invasive alternatives

for diagnosing certain forms of endometriosis, signaling a shift towards less invasive diagnostic methods. As highlighted by the current ESHRE guidelines, imaging techniques such as advanced ultrasound (USS) and MRI have emerged as first-line investigations, particularly for detecting deep endometriosis (DE). Both modalities demonstrate high sensitivity and specificity for DE, though they are less effective for diagnosing superficial endometriosis. The choice of imaging modality depends on the clinician's expertise and the availability of equipment, emphasizing the need for a nuanced approach to diagnosis.

STAGING AND SCORING ENDOMETRIOSIS

The Endometriosis Fertility Index (EFI) was created to predict the likelihood of spontaneous pregnancy in women three years after undergoing surgery for endometriosis.[12] This comprehensive score takes into account factors such as the patient's age, duration of infertility, pregnancy history, description of lesions observed during surgery (ASRM, AFS endometriosis score) and a post-operative functional score (LF score).

The EFI is calculated by adding the surgical and historical factors and ranges from 0 to 10. Research has shown that women with higher EFI scores have a greater rate of spontaneous pregnancies. For instance, the cumulative non-ART pregnancy rate at 36 months was found to be 10% (95% CI: 3, 16; p<0.001) for women with an EFI of 0-2 and 69% (95%CI: 58, 79; p<0.001) for women with an EFI of 9-10.[13]

In 2017, the world endometriosis society (WES) described the EFI as a strong and clinically valid tool for predicting fertility after surgery for endometriosis. As a result, the French college of gynaecologists and obstetricians (CNGOF) recommends the use of EFI for guiding post-operative strategies. However, it's important to note that the EFI is a predictive tool, not a treatment decision-making tool. Therefore, clinical interpretation is required to determine the best approach for post-operative.[14]

Medical management of endometriosis to achieve spontaneous conception

A meta-analysis of medical treatments for endometriosis found no benefit in using ovulation suppression for endometriosis-related infertility.[16] ESHRE guidance is that ovarian suppression should not be prescribed to improve subfertility related to endometriosis.

GnRH-a therapy works by suppressing ovarian hormone production, leading to a hypoestrogenic state that can reduce the size of endometriotic lesions. However, its effectiveness in enhancing fertility remains controversial. To date, no prospective, double-anonymized, placebo-controlled study has provided convincing evidence that GnRH-a therapy improves fertility in women with endometriosis.[17] A meta-analysis of 25 clinical trials compared laparoscopic ablation alone and in combination with ovulation suppression therapies, including GnRH-a. The analysis concluded that suppressive therapy does not significantly improve fertility outcomes in women with endometriosis. Similarly, Adamson et al, recommended against the use of medical therapy, including GnRH-a, for treating minimal and mild endometriosis when infertility is the sole symptom.[18]

Surgical management of minimal or mild endometriosis: implications for enhancing spontaneous conception

The effectiveness of surgical intervention in women with minimal or mild endometriosis (rASRM stage 1 or 2) for improving natural conception rates remains debated.

A landmark RCT involving 341 women aged 20 to 39 years with minimal or mild endometriosis. They were followed for 36 weeks after the laparoscopy or, for those who became pregnant during that interval, for up to 20 weeks of pregnancy. The study demonstrated that surgical intervention, specifically the excision or ablation of superficial endometriotic lesions, significantly improved natural fertility outcomes compared to diagnostic laparoscopy alone. The cumulative probability of conception in the surgery group was 30.7%, compared to 17.7% in the diagnostic laparoscopy group, a statistically significant difference (p=0.006).[18]

This evidence is backed by a recent Cochrane systematic review, which analysed data from three randomized controlled trials (RCTs) involving 528 participants. When compared to diagnostic laparoscopy alone, it remains uncertain whether laparoscopic surgery reduces overall pain associated with minimal to severe endometriosis. No data were reported on live births.

However, there is moderate-quality evidence that laparoscopic surgery increases viable intrauterine pregnancy rates, with an odds ratio (OR) of 1.89 (95% CI 1.25 to 2.86). The evidence was graded as moderate quality.[19] ESHRE recommends that laparoscopy could be offered as a treatment for endometriosis-related subfertility for early-stage endometriosis, as it improves the rate of ongoing pregnancy.

Surgical management of moderate to severe endometriosis (RASRM stage 3 or 4) for spontaneous conception

The decision to surgically manage endometriomas in women undergoing infertility treatment is fraught with controversy. On the one hand, surgical intervention is often pursued with the hope of enhancing fertility by restoring pelvic anatomy. However, it remains contentious whether addressing the endometrioma itself translates into improved fertility outcomes. While surgery can correct anatomical distortions, it may not address the underlying inflammatory and biomolecular changes that impact fertilization and implantation.

Furthermore, surgical treatment raises concerns about reducing ovarian reserve and the risk of requiring an oophorectomy.[20] Studies have shown that while cystectomy may reduce the risk of recurrence and increase the likelihood of spontaneous conception, it can also lead to a significant decrease in the number of ovarian follicles and a sustained reduction in AMH levels, which are essential markers of ovarian reserve. For instance, a study reported a 39% decrease in AMH levels following cystectomy and Raffi et al, observed a 24% reduction in antral follicle count (AFC) post-surgery in women who had undergone previous ovarian surgery.[19,20]

Despite these risks, cystectomy has been shown to be more effective than drainage or ablation for achieving spontaneous pregnancies. Hart et al, summarized two RCTs involving 88 women, which demonstrated that excisional surgery had a significantly higher success rate for spontaneous pregnancy compared to drainage or ablation (OR 5.24, 95% CI 1.92-14.27.[21] However, the risk of ovarian damage remains a significant consideration, particularly in women with a history of ovarian surgery.

Given these complexities, the management of endometriomas should be individualized, considering factors such as pain, cyst size and the risk of malignancy. It is recommended that surgical treatment be performed by a gynaecologist with specific expertise in endometriosis and fertility to minimize the impact on ovarian reserve and ensure a comprehensive approach to future fertility management.[22]

Alternative surgical techniques, such as CO2 laser or plasma energy ablation, have shown promise in reducing ovarian damage while maintaining satisfactory fertility outcomes, but further RCTs are needed to establish their efficacy. Daraï et al, (2013) reported favorable outcomes with CO2 laser ablation, including a 20% recurrence rate and a 45% pregnancy rate in women with endometriomas, though the sample size was small and more research is needed.[23.24] In conclusion, while surgical management of moderate to severe endometriosis can improve fertility outcomes, it must be approached with caution and decisions should be tailored to the individual patient, with careful consideration of the potential risks and benefits.

SURGICAL TREATMENT PRIOR TO IVF

The ESHRE guidelines suggest that cystectomy for endometriomas larger than 3 cm does not improve IVF pregnancy rates. However, surgery may still be considered before ART for managing endometriosis-associated pain, improving access to follicles during oocyte retrieval or addressing concerns about malignancy.

The decision to perform surgery for an endometrioma before ART should be based on a thorough assessment of various factors. These include the woman's age, ovarian reserve, the presence and extent of endometriomas, symptoms, any suspicious radiological findings, the extent of extraovarian disease and past ovarian surgeries. In cases where women are asymptomatic, of advanced reproductive age, have reduced ovarian reserve, bilateral endometriomas or a history of previous ovarian surgeries, it may be more beneficial to proceed directly with IVF. This approach can avoid potential risks of further compromising ovarian function and delaying treatment.25

Surgery may be the first-line treatment for highly symptomatic women, those with a healthy ovarian reserve, unilateral and large cysts. It should also be considered for cysts with suspicious radiological and clinical features. Endometriomas may be linked to extraovarian disease, such as intestinal disease and deeply infiltrating endometriosis. While surgical excision of endometriotic nodules can provide symptomatic relief, there is no evidence that it improves reproductive outcomes. However, it is important to note that this surgery may pose significant risks and women should be appropriately counselled before undergoing it (ESHRE 2023).[15]

Surgical treatment of endometriomas before ART does not improve live birth rates. A retrospective study comparing ART outcomes in women with untreated endometriomas versus those who had laparoscopic removal of endometriomas found no significant difference in live birth rates per embryo transferred (23.7% vs. 26.1%, p=0.80).[26] Additionally, cystectomy is linked to a poorer response to ovarian stimulation and a higher risk of cycle cancellation compared to not performing surgery (13.7% vs. 0%, p=0.18.[27]

ART AND OVARIAN STIMULATION FOR WOMEN WITH ENDOMETRIOSIS

AMH and AFC are critical markers used to predict ovarian response during controlled ovarian stimulation, but their effectiveness can vary, particularly in women with endometriomas. Research indicates that AFC might be a more sensitive predictor than AMH in severe endometriosis.[28]

Despite similar AMH levels, women with endometriomas often experience a lower oocyte yield. This issue is further compounded in cases of severe endometriosis, where patients may require nearly double the standard gonadotropin doses to achieve comparable oocyte numbers but still obtain fewer oocytes overall.[29]

The choice of ovarian stimulation protocol, whether agonist or antagonist, generally does not influence pregnancy or live birth rates significantly. However, a study has shown that women with mild endometriosis might achieve a higher live birth rate with an agonist protocol compared to an antagonist protocol, though this advantage does not extend to those with moderate or severe endometriosis.[29] Additionally, long-term downregulation with agonists prior to ART has been found to offer uncertain benefits in terms of live birth rates, as supported by a Cochrane review.[30]

Other downregulation methods, including combined oral contraceptives and progesterones, have not been shown to improve live birth rates.[31] Dienogest, a specific progesterone derivative, demonstrated potential benefits in one study by enhancing clinical pregnancy and live birth rates in women with endometriosis, but these findings were not consistently replicated and, in some cases, showed reduced cumulative live birth rates. Thus, while the evidence on optimizing ART protocols for women with endometriosis is mixed, individualized treatment strategies remain essential for improving reproductive outcomes.[32]

APPLICATION OF FERTILITY PRESERVATION IN ENDOMETRIOSIS

Women with severe endometriosis and bilateral endometriomas face an increased risk of diminished ovarian reserve and premature ovarian insufficiency. The improvement in cryopreservation techniques for oocytes, embryos and ovarian tissue has allowed for the possibility of FP in patients with endometriosis. Fertility preservation strategies, such as oocyte and embryo cryopreservation, are essential components of patient counselling and family planning.

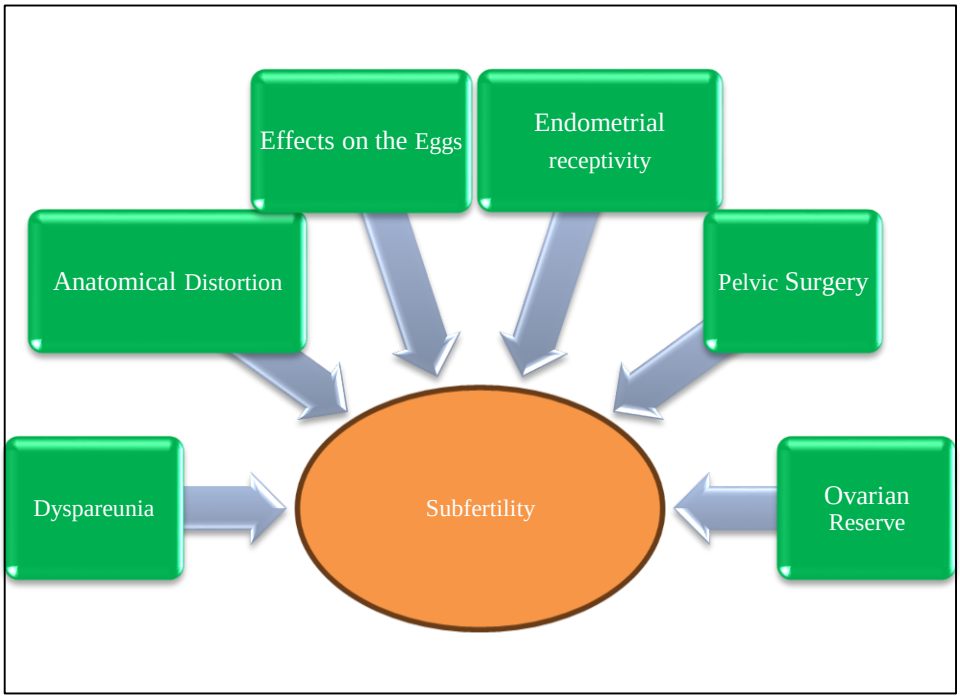

Figure 1: Mechanisms for endometrioma-associated infertility.

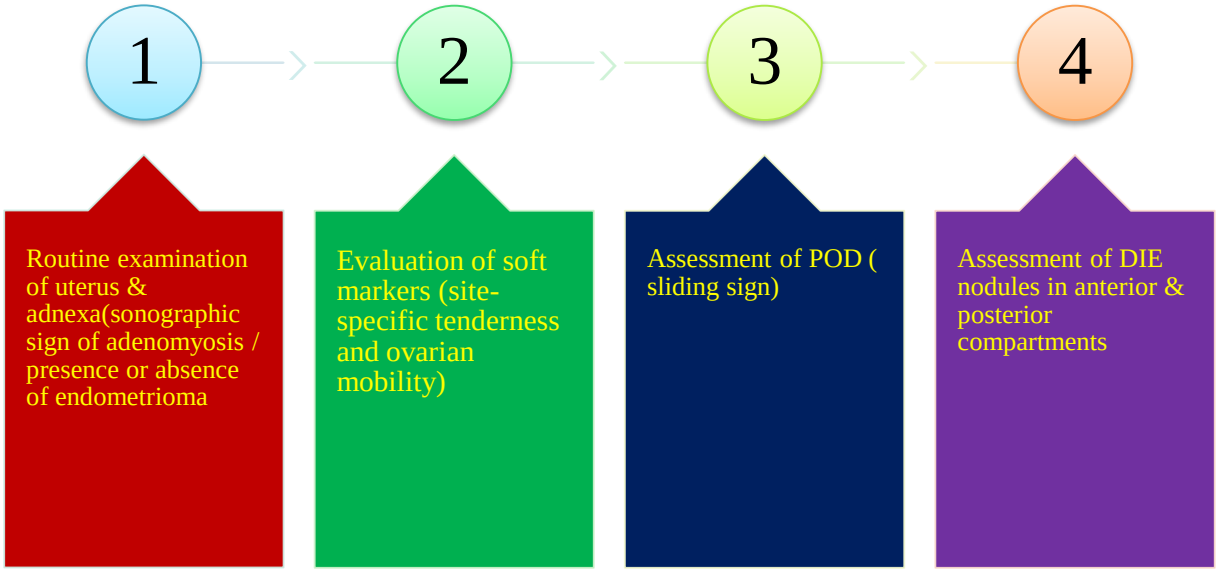

Figure 2: Four basic sonographic steps when examining women with suspected or known endometriosis.[3]

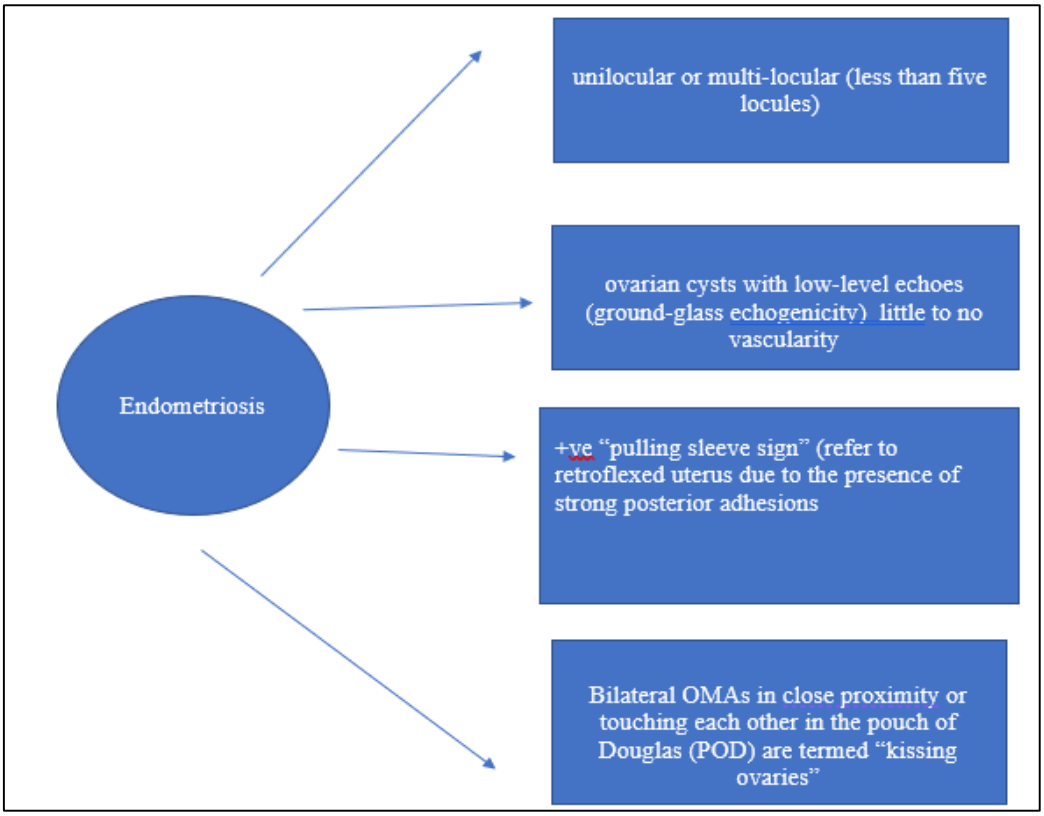

Figure 3: USG diagnosis of endometriosis.[3]

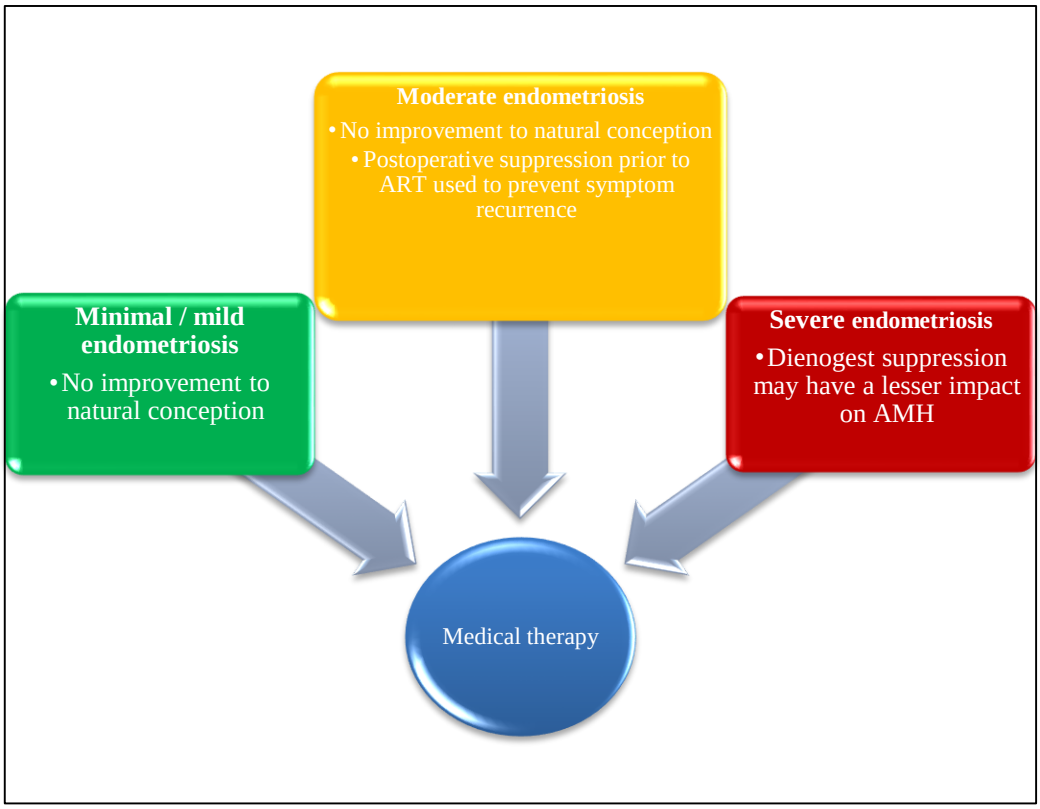

Figure 4: Medical management recommended for endometriosis in context of infertility NICE 2024, GTG, ESHRE 2023.

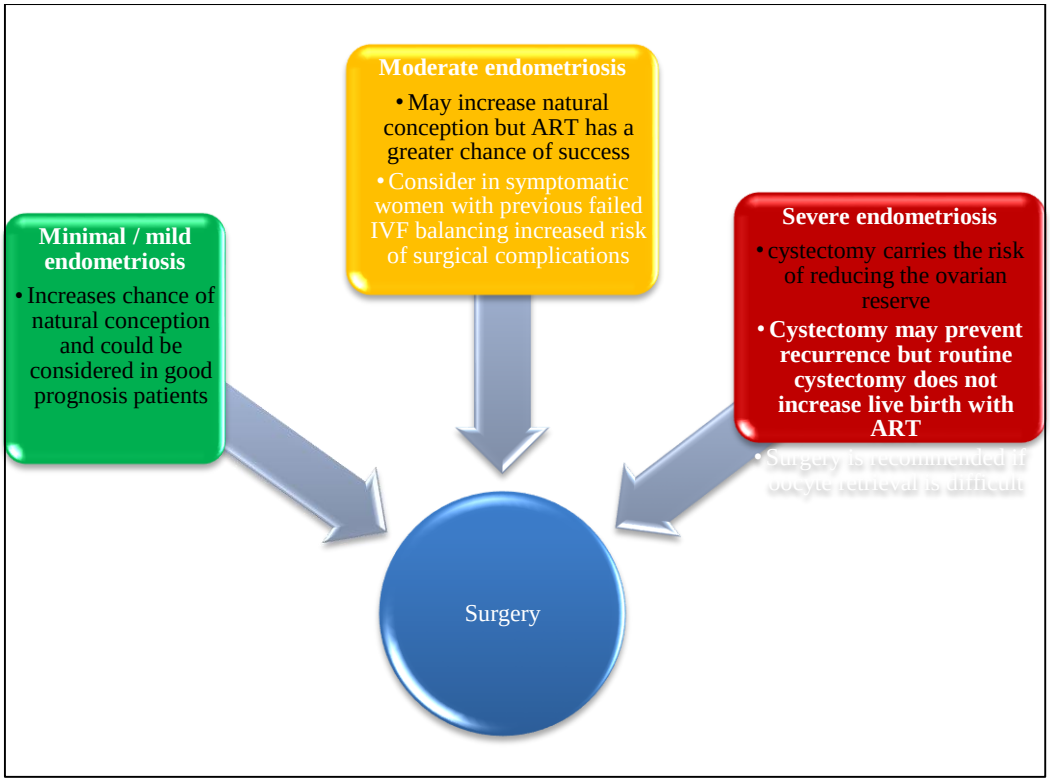

Figure 5: Surgical management recommended for endometriosis in context of infertility NICE 2024, GTG, ESHRE 2023.

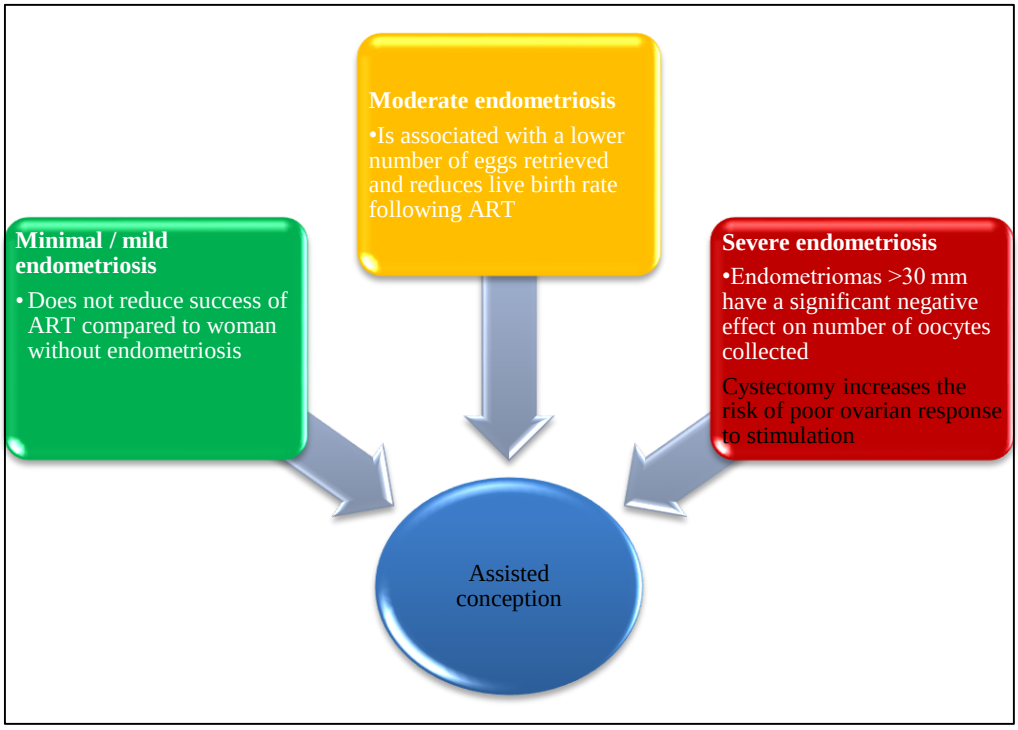

Figure 6: Management of different types of endometriosis prior to assisted conception recommended by NICE 2024, GTG, ESHRE 2023.

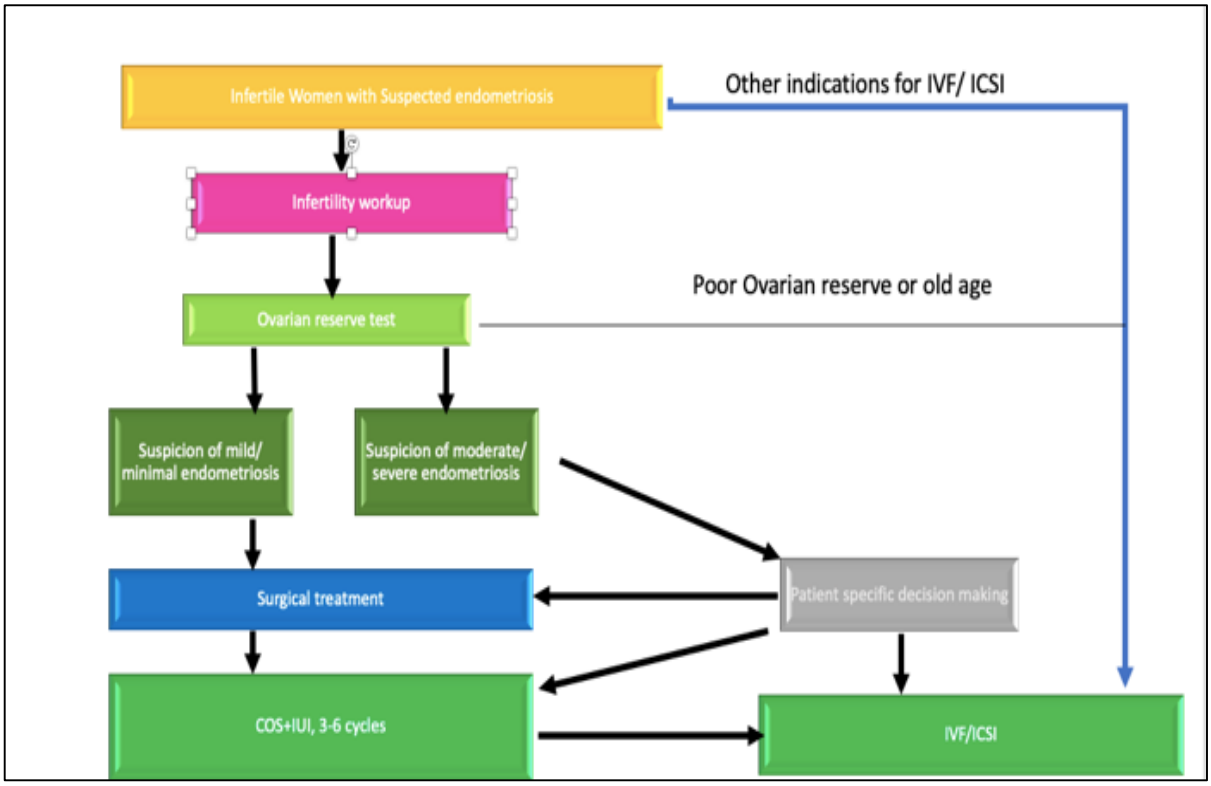

Figure 7: Algorithm for decision of treatment method.

A multicenter study involving 1044 women with endometriosis found that oocyte vitrification resulted in a 46.5% return rate when attempting pregnancy. Notably, 97.7% of participants had advanced stages of endometriosis (III-IV). The study also highlighted that oocyte yield was higher in women who did not undergo ovarian surgery compared to those who had unilateral or bilateral cystectomy.

The cumulative live birth rate per patient was 46.4%, with no significant differences in outcomes between women with different stages of endometriosis or those under or over 35.[34]

In patients with endometriomas, Ovarian Tissue Cryopreservation (OTCP) can be performed by extracting ovarian tissue surrounding these benign cysts. The endometrioma cyst wall often contains follicles, though their number can be reduced during the cyst removal.

Histological analysis of the cyst wall typically shows that follicle counts are higher in younger patients and healthy ovarian cortex fragments may be preserved during endometrioma removal.[35,36]

Despite its promise, clinical data on OTCP in women with endometriosis remains limited. In a pioneering study from 2005, Donnez et al, reported two cases involving fresh ovarian tissue transplantation in patients with severe endometriosis who underwent left oophorectomy for recurrent disease.[37] Ovarian cortex strips were taken from the remaining healthy ovarian tissue and transplanted into a highly vascularized peritoneal window beneath the contralateral ovary's hilus. Three months later, both patients showed healthy grafted tissue with primordial follicles and active angiogenesis, leading to a successful pregnancy in one case after multiple IVF attempts.[37]

Further longitudinal analysis by Oktay et al, involving 59 women included a notable case where a 28-years-old with presumed endometriosis had ovarian fragments cryopreserved and transplanted into the left pelvic peritoneum a year later, achieving regular ovulatory cycles until her last follow-up nine months post-procedure.[38]

A recent report highlighted two 21-years-old women who underwent cystectomy and ovarian cryopreservation due to large endometriotic cysts. Post-surgery, these patients experienced a significant decline in AMH levels, indicating reduced ovarian reserve.

Histopathological examination revealed lower follicle density than anticipated, which underscores the possibility of pre-existing reduced ovarian reserve in patients with endometriosis.[39]

Overall, while OTCP offers a valuable option for fertility preservation in a range of clinical scenarios, ongoing research and clinical data are essential to understand its efficacy fully and to optimize outcomes for patients undergoing this procedure.

Table 1: ESHRE Recommendations on endometriosis management 2023.[15]

ESHRE	Recommendations	Observations
Minimal to mild endometriosis rASRM stage I/II	Clinicians are not recommended to routinely perform surgery prior to ART to improve live birth rates in women with rASRM stage I/II endometriosis, as the potential benefits are unclear.	Intrauterine insemination (IUI) with ovarian stimulation, instead of expectant management or IUI alone, as it increases pregnancy rates.
Ovarian endometrioma	Clinicians are not recommended to routinely perform surgery for ovarian endometrioma prior to ART to improve live birth rates, as the current evidence shows no benefit and surgery is likely to have a negative impact on ovarian reserve. Surgery for endometrioma prior to ART can be considered to improve endometriosis-associated pain or accessibility of follicles.	The extended administration of GnRH agonist prior to ART treatment to improve live birth rate in infertile women with endometriosis is not recommended, as the benefit is uncertain.
Stage III/IV endometriosis	The decision to offer surgical excision of deep endometriosis lesions prior to ART should be guided mainly by pain symptoms and patient preference as its effectiveness on reproductive outcome is uncertain due to lack of randomized studies.	There is a risk of reduction in ovarian reserve after surgery. In case of extensive endometriosis/ large endometrioma clinicians should discuss the pros and cons of fertility preservation with women with endometriosis. The true benefit of fertility preservation in women with endometriosis remains unknown.

Table 2: Factors influencing ART outcomes.[33]

Factors	Outcomes
Age and number of oocytes	Younger women (≤35 years) generally have better outcomes with a higher cumulative live birth rate
Cycle characteristics	Studies indicated that conducting multiple stimulation cycles can increase the number of cryopreserved oocytes
Surgical history	Women who had prior ovarian surgery for endometriomas had reduced oocyte yield. A study showed a significant decrease in retrieved and mature oocytes in those who had undergone surgery compared to those who had not.
AMH levels and symptoms	Higher serum Anti-Müllerian Hormone (AMH) levels are associated with a better response to ovarian stimulation and a higher number of retrieved oocytes. Conversely, the presence of more clinical symptoms, such as chronic pain, can negatively impact ovarian response.
Ovarian reserve	AMH levels, ovarian reserve and the total dose of gonadotropins used for stimulation play crucial roles in determining the number of oocytes retrieved. Women with a higher AMH level typically have a better ovarian response.

Table 3: Difference between protocols use for ovarian stimulation.[31-33]

Parameters	Mild to moderate endometriosis	Severe endometriosis
Ovarian response predictors	AMH & AFC	AFC more sensitive to AMH
Agonist and antagonist protocol	Standard dose, higher live birth rate with agonists (42.8% versus 26.7%)	Require double dose, No difference in live birth rate in either protocol
COCP/progesterones downregulation	No increase in live birth rate	No increase in live birth rate
Dienogest down regulation	improvement in clinical pregnancy and live birth rate	Observations study showed the reduced cumulative live birth rate

CONCLUSION

Endometriosis presents a complex and varied clinical challenge, particularly for women who wish to preserve their fertility. In younger women with mild endometriosis and a good ovarian reserve, surgical intervention may offer a window for natural conception or facilitate less invasive treatments, such as superovulation and IUI. However, for older women or those with more severe forms of the disease, ART are likely to provide the most viable path to achieving a live birth.

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