

Opinion

Should Endometriosis-Associated Ovarian Cancer Alter the Management of Women with an Intact Endometrioma in the Reproductive Age?

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Abstract: Endometriosis-associated ovarian cancer (EAOC) is an evolving clinical entity believed to develop from ovarian endometriosis. Continuous efforts are nowadays invested in exploring its pathogenesis and causality. Since endometrioma is a widespread sub-type of the disease, malignant transformation to EAOC during reproductive age may cause much concern and affect its management. The summary relative risk of developing EAOC in women with endometriosis is 1.93-fold compared to women without endometriosis, but its lifetime risk is relatively low, equivalent to 2.1%. EAOC is an age-dependent disease with a mean age of 51.64 ± 3.24 years at diagnosis; 30.68% of patients are below 50, presumably premenopausal. Only 2.10% and 0.017% of cases are below 45 and 40 years, apparently in reproductive age. The evidence is reassuring and implies that managing an intact endometrioma should not be altered in most women of reproductive age. Particular attention should be focused on sporadic cases with an enlarging endometrioma, atypical findings on transvaginal ultrasound (TVUS), and characteristic magnetic resonance imaging (MRI) features.

Keywords: endometriosis; endometrioma; endometriosis-associated ovarian cancer; reproductive age



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1. Introduction

Endometriosis is a chronic, prevalent, and inexplicable disease involving the female procreative organs and affecting women of reproductive age with an estimated prevalence of up to 1 in 10 women [1]. The incidence of endometriosis may increase to 40–60% in women with chronic pelvic pain [2,3]. While endometriosis is a leading cause of infertility, it also involves fertile women with an estimated prevalence of 25–40% and 0.5–5%, respectively [4]. An endometriotic cyst is the most pathognomonic and diagnosed form of the disease, with an estimated incidence of up to 55% of affected women [5].

Until recently, endometriosis was considered an estrogen-dependent disease, believed to resolve at menopause. However, epidemiological evidence indicates that endometriosis is associated with an increased risk of ovarian malignancy, today termed endometriosis-associated ovarian cancer (EAOC), which may extend beyond the menopausal transition [6]. In a recent well-undertaken systematic review and meta-analysis, ovarian cancer-specific analysis indicates a summary relative risk (SRR) of 1.93 (95% CI = 1.68–2.22) in women with endometriosis [7]. The strongest association is for clear cell ovarian and endometrioid ovarian cancer histotypes with an estimated SRR of 3.44 (95% CI = 2.82–4.42) and 2.33 (95% CI = 1.82–2.98), respectively. Furthermore, it is apparent today that EAOC is merely associated with endometriotic cysts [8]. However, further studies are required to explore the association between extra-gonadal endometriosis, specifically superficial and deep infiltration subtypes of the disease.

The pathogenesis of the malignant transformation of endometriosis is still under active investigation. Multifactorial factors have been implicated, including genetic, inflammatory, immunologic, and hormonal mechanisms [9]. Recently, advanced methodologies have

reported a strong genetic relationship between endometriosis and EAO, suggesting a causal relationship [10]. Nonetheless, further studies are essential to substantiate the causal connection to the specific histotypes of EAO.

The association between endometriosis and EAO and recent evidence of causality, specifically in women with intact endometrioma, may cause much concern for women of reproductive age. Furthermore, translating this new evidence into clinical practice also seems challenging regarding patient counseling and EAO early detection [11]. This may be even more defying in women with infertility or others, postponing live birth or planning for a future pregnancy. This perspective discusses these issues by revising epidemiology, risk factors, and EAO clinical manifestations. In addition, it briefly summarizes the discussion between conservative and surgical approaches to endometrioma management in infertile women. Furthermore, it explores whether the risk linked with EAO should change policy management in women with intact endometrioma.

2. Lifetime Risk of EAO

According to the most recent data from the National Cancer Institute in the USA, a part of the National Institutes of Health (NIH), the lifetime risk of developing ovarian cancer is 1.1% [12]. Considering the 1.93 ovarian cancer SSR in women with endometriosis [7], it is estimated that the lifetime risk of EAO would be 2.1%. These figures seem reassuring in women with endometriosis since their lifetime absolute risk remains low compared to other lifetime risks of breast, lung, and colon cancers, of 12%, 6%, and 4%, respectively.

3. Age at Diagnosis of EAO

Age distribution among women of EAO at diagnosis has not been well delineated. Overall, women with EAO are often older than those with intact endometrioma while younger than others with non-EAO, such as highly progressive serous ovarian carcinoma. The development of EAO in reproductive age seems infrequent. While several case reports describe sporadic women with EAO at a young age [13–16], most seem to develop later. Previous cohort studies, including a modest number of patients, have shown contrasting rates of premenopausal EAO diagnoses ranging between 30 and 70% of cases [17–21]. A recent systematic search of cohort studies targeting age at diagnosis of patients with EAO disclosed 25 eligible papers and 1082 women [22]. The mean age at diagnosis was 51.64 ± 3.24 years; 30.68% were below 50 years, presumably premenopausal. At the same time, only 2.1% and 0.017% were below 45 and 40 years, respectively, apparently during the reproductive age.

4. Clinical Manifestations of EAO

Though clinical manifestations of a benign endometrioma may resemble those of EAO, suspicions should be increased in particular situations. The chronological age of each case is crucial since it has been repeatedly shown as an independent risk factor in cases with EAO [17,22–25], especially in women above 45 years. Relapsing or worsening pelvic pain in women with an intact endometrioma should be addressed and investigated. A rapidly enlarging or enlarged endometrioma above 9 cm should be investigated. Furthermore, nulliparity and hyperestrogenism (endogenous or exogenous) are risk factors for EAO development [26]. Further exploration, analysis, and assessment of risk factors that may guide patients and doctors to detect a malignant transformation of an intact endometrioma are essential. Furthermore, it may provide clues for appropriate screening and early detection of EAO in this setting [27].

Serum CA-125 is largely reliable for high-grade serous ovarian cancer, mainly in the postmenopausal period. However, it has a very low sensitivity for stage I disease, in those with epithelial cancer subtypes other than high-grade serous adenocarcinoma, and in the premenopausal period [28]. Furthermore, serum CA-125 may be increased in cases with benign endometrioma [29]. As such, it does not seem to promote EAO diagnosis [30]. In contrast, very high CA-125 levels should arouse concern for adnexal

cancer in premenopausal women and provoke suspicions of malignant transformation in women with ovarian endometriosis [28,31].

Transvaginal ultrasound (TVUS) is crucial in differentiating a benign endometrioma from EAOC. A benign endometrioma typically has a homogenous cystic 'ground glass' appearance, while EAOC is usually a large (above 9 cm) unilateral cyst with solid parts, papillations, and vascularization [30]. With increasing age in premenopausal women, benign endometrioma may show atypical structures containing multilocular cysts, papillations, and solid features. The ground glass appearance also becomes less common, while cyst diameter remains the same [32]. The expertise of the TVUS performer appears of high significance in atypical cases.

In cases with atypical TVUS features, counting for 5–25% of patients [33], a supportive magnetic resonance imaging (MRI) role becomes indispensable. Computerized tomography scans have no added value in these cases [30]. Classical benign endometriomas on MRI typically display features of T2-weighted image shading [33]. Conversely, the disappearance of shading, or hypointensity, within the endometrioma on T2-weighted images, combined with the enhanced solid portion of the endometrioma and an enlarged unilocular cyst, suggests malignant transformation [34–36].

Since atypical TVUS findings may eventually result in benign findings, MRI performance in this setting is essential. Therefore, the final decision on a conservative or surgical intervention in a young woman should contain all the above findings and be discussed in a multidisciplinary forum, considering each case's age and reproductive aspirations.

5. Surgery or Conservative Management for an Intact Endometrioma

The optimal approach to treating intact endometrioma, with no signs of malignant transformation, is a broad and long-standing topic that has been intensively discussed. There are pros and cons for each course, surgical or conservative. The discussion nowadays focuses on women of reproductive age, especially with endometriosis-associated infertility or, in others, postponing motherhood or alternately planning a future pregnancy.

Several issues previously in dispute concerning the impact of an intact endometrioma on ovarian reserve and pregnancy achievement seem to be gradually coming to a resolution. Today's main argument focuses on the effect of an intact endometrioma on oocyte competence and ovarian reserve since *in vitro* studies are not conclusive and clinical studies continue to be controversial [37]. Conversely, it is acknowledged today that endometriotic cystectomy impairs ovarian reserve and may adversely affect future reproductive life spans [38–40]. A recent systematic review, including 12 prospective studies and 783 women, found a significant reduction in serum AMH levels in 9–12 months following endometriotic cystectomy, equivalent to 39.5% and 57.0%, in unilateral and bilateral cases, respectively [39].

Moreover, robust evidence is still lacking to show that endometriotic cystectomy may improve infertility outcomes [41,42]. Furthermore, there is no improvement in clinical pregnancy or live birth rates in women undergoing endometriotic cystectomy before ART treatment [43,44]. Likewise, intact endometrioma has no adverse impact on clinical pregnancy or live birth rates in the ART setting [43,45].

Conjointly, evidence from interrelated clinical issues associated with the impact of endometrioma on ovarian reserve and pregnancy achievement seems to favor the conservative approach to treatment. This policy should be espoused especially in infertile women or women planning for a future pregnancy. Additional targeted randomized controlled studies are mandatory to substantiate these recommendations further. Meanwhile, iatrogenic adverse and sustained effects on the ovarian reserve with little gain should be avoided. Furthermore, exploring minimally invasive surgery approaches to minimize the negative impact on ovarian reserve should be pursued.

6. When Should Surgery Be Considered for an Intact Endometrioma?

In the reproductive age, especially in women desiring future pregnancies, surgery may be considered in cases where endometriosis-associated pelvic pain is refractory to medical treatment [37]. Furthermore, surgery may be advisable in the ART setting when the risk of endometrioma complications, particularly infection, is considerable [46]. Surgery should also be considered in patients undergoing IVF when developing follicles during oocyte retrieval cannot be reached [38]. This risk of incomplete oocyte retrieval is almost 3-fold in women with intact endometrioma compared to those without [47]. Endometrioma aspiration in these cases would be a reasonable alternative. Furthermore, repeated IVF failure may be an argument for re-evaluation, considering the surgical approach in infertile women with endometrioma. However, evidence suggesting a negative impact on oocyte competence in these cases remains weak [46,48]. Therefore, individual case-by-case management should be considered.

Although an endometrioma diameter ≥ 4 cm was considered, in the past, to be an indication for surgical treatment in infertility-associated endometriosis [49], the new ESHRE guidelines do not relate to endometrioma diameter as an indication for surgery [11]. Furthermore, women of reproductive age developing clinical manifestations suggestive of EAOC or showing reminiscent signs of the disease on TVUS should undergo MRI [30]. Apparent MRI characteristics of EAOC at reproductive age, although it seems to be a sporadic event, necessitate surgical intervention for proper diagnosis and effective treatment.

7. Conclusions

Endometrioma-associated ovarian cancer is an evolving distinct clinical entity believed to develop from endometrioma, and as such, it may raise much concern among patients and doctors alike. Endometrioma is a widespread finding in women of reproductive age, estimated to arise in up to 1 in 18 women. Although the risk of EAOC is increased by 1.93-fold in women with endometrioma, the lifetime risk remains relatively low. Furthermore, EAOC is an age-dependent disease; 30.68% of cases are diagnosed as premenopausal. In contrast, among all women with EAOC, only 2.10% and 0.017% are detected below 45 and 40 years, equivalent to 2 in 100 and 2 in 10,000 cases, respectively.

The available evidence is reassuring and suggests that endometrioma management should not be altered in women of reproductive age. However, further investigations are essential to expound on EAOC pathophysiology and explore the causality of the disease development. In the clinical setting, particular attention should be directed to symptomatic women with an enlarged or enlarging endometrioma and atypical findings on TVUS. In these cases, an MRI is mandatory to differentiate between benign endometriomas and EAOC. In selected cases, surgery may be inevitable to offer a proper diagnosis and management.

Future exploration, analysis, and assessment of risk factors that may detect a malignant transformation of endometrioma to EAOC are essential for adequately managing these women. Machine learning, based on artificial intelligence and computer science, may have the potential in such cases [50]. A risk-predicting model, taking into account all available epidemiological, clinical, diagnostic, and histopathological characteristics of endometrioma versus EAOC, cases should be explored. Such a powerful tool may guide practitioners to manage, follow up, and detect EAOC in its early stages, and counsel patients on the best treatment plan.

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