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Endometriosis-Associated Ovarian Cancer: The Role of Oxidative Stress

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1. Introduction

Recent studies indicated that oxidative stress has a causal role in the carcinogenesis of mainly two histological subtypes of ovarian cancer, namely, clear cell carcinoma and endometrioid adenocarcinoma. Because of recurrent hemorrhage in endometrial cysts, excess of reactive oxygen species are produced due to iron deposition, which results in direct genomic mutation of the epithelial cells and exaggeration of oxidative stress by stromal cells such as macrophages. In endometriosis-associated ovarian cancer, genomic mutations in specific genes such as ARID1A, p53, K-ras, PTEN, PI3CA and Met have been reported. Mechanism of carcinogenesis, especially focusing on the precise role of oxidative stress, remains to be clarified. Development of novel drugs and methods for therapy or prevention of endometriosis-associated ovarian cancer is necessary.

2. Risk of cancer development in endometriosis

Endometriosis is a common disease affecting 10 to 15% of women of reproductive age (Irving, 2011). An association between endometriosis and cancer was reported as early as the 1920s in English publications. Sampson (Sampson, 1925) proposed that endometrial carcinoma of the ovary develops from endometrial tissue, based on classic microscopic observation using several strict criteria (i.e., the coexistence of benign and malignant tissue with a shared histologic relationship in the same organ and evidence against invasion from other sites or sources). Further studies were interrupted by World War II; however, in the late 1940s and 1950s, several groups published case reports that met Sampson's criteria (Scott, 1953; Postoloff & Rodenberg, 1955). Although none of the studies demonstrated any direct evidence, the consensus of the major researchers in the field at that time was that malignant transformation or transition occurred in ovarian endometriosis.

In 1990, Heaps et al. analyzed 195 cases that mostly fulfilled Sampson's criteria (Heaps, 1990). They found that the primary endometriosis site was most frequently the ovary (78.7%), followed by various other sites such as the pelvis, rectovaginal septum, colon or rectum, or the vagina. The most frequent histologic subtype was endometrioid adenocarcinoma in either of the primary sites, ovarian (69%) or extragonadal (66%), followed by clear cell carcinoma and sarcoma in 13.5% and 11.6% of ovarian tumors, respectively, and sarcomas in 25% of extragonadal tumors. More recently, an elevated risk of ovarian cancer development in endometriosis has been shown by statistical analyses. A

direct prospective study of 20,686 Swedish patients hospitalized with endometriosis between 1969 and 1983 with a mean follow-up period of 11.4 years demonstrated a standardized incidence ratio (SIR) of 1.9 and a 95% confidence interval [CI] of 1.3 to 2.8 (Brinton, 1997). Similar results were reported in a case-control study analyzing patients from the United States, in which the relative risk for ovarian cancer development in endometriosis patients was 1.7 (Ness, 2000). A nationwide case-control study of Australian patients with ovarian cancer revealed that endometriosis increased the risks of both endometrioid adenocarcinoma and clear cell carcinoma, with odds ratios of 3.0 and 2.2, respectively (Nagle, 2008). A recent retrospective study from Canada also showed a significant increase in the relative risk (rate ratio [RR], 1.6; 95% CI, 1.12 to 2.09) of ovarian cancer in patients with endometriosis (Aris, 2010). In line with these reports, a recent prospective study from Japan showed a significant and much greater elevation in the relative risk (SIR, 8.95; CI, 4.12 to 115.3) of cancer development in Japanese patients with endometrioma, or endometrial cyst of the ovary (Kobayashi, 2007). The reason for this discrepancy is unclear, but one possibility is that the endometriosis patients in the Japanese study included only those with clinically detectable ovarian endometrial cysts. It is also important to note that Danazol (17- α -ethinyltestosterone), a synthetic androgen that has been used to treat endometriosis, has been revealed to be an independent risk factor for the development of ovarian cancer. A negative correlation between oral contraceptive use and ovarian cancer, regardless of histologic type other than mucinous tumors, was recently shown by a collaboration of various groups worldwide (Cottreau, 2003). These factors may also influence the relative risk of ovarian cancer development.

In addition to an epidemiologic approach, the retrospective pathological analysis of samples from ovarian cancer patients is also useful to confirm the presence of endometriosis associated with ovarian cancers of various histological types. A comprehensive review of 2,807 ovarian cancer patients from 15 independent publications from western countries from the 1970s to 1990s, including 3 articles from Japan, revealed that endometriosis was incidentally found in 14.1% of ovarian cancer patients (39.2%, 21.2%, 3.3% and 3.0% of clear cell, endometrioid, serous and mucinous carcinoma patients, respectively), with a tendency toward a higher incidence of endometriosis in Japanese patients with clear cell carcinoma (Yoshikawa, 2000).

3. Pathogenesis of endometriosis-associated ovarian cancer; the role of iron overload-induced oxidative stress

Endometrial cysts, or so-called chocolate cysts, are well-known lesions in endometriosis that contain fluid with an excess of free iron because of recurring hemorrhage in the cyst. It is interesting to note that Sampson mentioned in his first report of endometriosis-associated cancer that old hemorrhages should be considered additional evidence that meets his criteria (Sampson, 1925). Hemosiderin, heme, or iron deposition in endometriotic lesions have been assumed to trigger oxidative damage and chronic inflammation (Van Langendonck, 2002a; Van Langendonck, 2002b; Van Langendonck, 2004; Toyokuni, 2009). In particular, iron storage in macrophages is significantly increased in patients with endometriosis; and intracellular iron activates the nuclear factor- κ B pathway and exaggerates chronic inflammation (Lousse, 2009; Lousse, 2008). As a result, prominent oxidative stress, or an excess of reactive oxygen species, is consistently produced. This

process is thought to have a causative role in endometriosis development and progression, leading to carcinogenesis (Murphy, 1998; Ness & Cottréau, 1999; Ngo, 2009). Alternatively, the high concentration of free iron in endometrial cysts may directly provide oxidative stress that induces genomic mutation in epithelial cells (Yamaguchi, 2008), and whether the direct pathway or the indirect pathway involving macrophages has a major role in carcinogenesis remains to be resolved. Iron overload in experimental animals enhances epithelial cell proliferation (Defrere, 2006) and causes malignant tumors with genomic abnormalities (Hu, 2010), which suggests a similar mechanism leading to carcinogenesis in human endometriosis (Fig. 1). However, further studies are awaited to elucidate the precise role of iron-deposition induced oxidative stress in carcinogenesis of endometriosis-associated cancer.

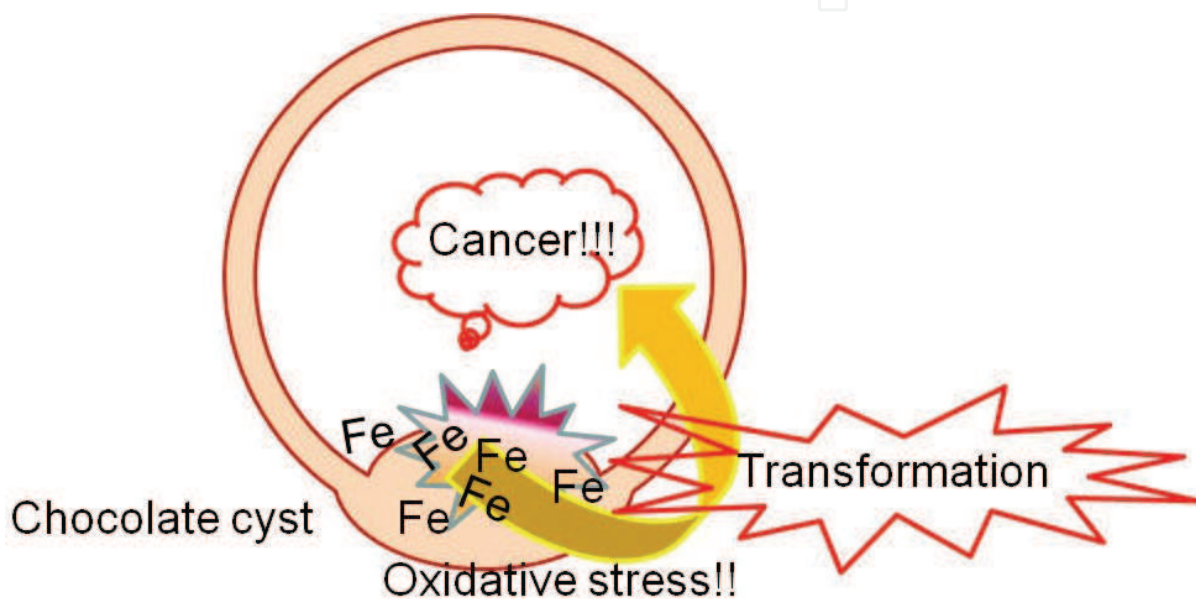


Fig. 1. A proposed mechanism of carcinogenesis in endometriotic (chocolate) cysts

4. Precancerous lesions in endometriosis

Endometriosis itself is generally considered a benign disease; however, endometriosis shares certain features with cancer, including the ability of cells from different lineages (i.e., epithelial cells, stromal cells, and the vasculature) to proliferate in ectopic sites. Thus, earlier studies have focused on the clonal or malignant potential of endometriosis by analyzing the loss of heterozygosity (LOH) at several candidate tumor suppressor gene loci. Positive results, such as the detection of LOH at the p53, p16 or PTEN gene, were observed in the majority of the endometriosis samples ((Jiang, 1996; Jiang, 1998; Sato, 2000), for review of other studies with similar results, see (Prowse, 2005)). Another approach, which assesses the clonality of endometriosis samples by analyzing methylation-related marker genes, also demonstrated the clonal nature of endometriosis (Jimbo, 1997). The findings, together with the LOH analysis, led to the conclusion that endometriosis was a neoplasm that may even have malignant potential. However, recent studies deny the malignant or neoplastic potential of endometriosis, demonstrating that most endometriosis tissues are not monoclonal (Mayr, 2003). Furthermore, neither LOH of

tumor suppressor genes, promoter methylation of oncogenes, nor oncogenic mutations of known tumor-related genes was frequently observed in the majority of the cases, further denying the neoplastic theory (Prowse, 2005; Vestergaard AL, 2011). In contrast with these results, a third approach (fluorescent in situ hybridization [FISH]) used to investigate chromosomal aberrations in endometriosis samples revealed a significantly elevated proportion of aneusomic (monosomic > trisomic) cells in endometriosis in multiple groups (Koerner, 2006) (Bischoff, 2002). However, both endometriosis tissue and normal endometrium also contain a certain proportion of aneusomic cells (Koerner, 2006), and telomerase expression, telomere elongation, higher expression of DNA replication markers and lower expression of DNA damage response markers are all observed in endometriosis tissue, but not in normal endometrium (Hapangama, 2008; Hapangama, 2009). Thus, it may be reasonable to conclude that although endometriosis is generally considered non-neoplastic, the relative rates of abnormal cells are higher in endometriosis than in normal endometrium.

In this case, then, which cells are premalignant? Is there a focal area representing the precancerous state of endometriosis that is morphologically distinguishable from other, presumably benign, areas? "Atypical endometriosis" is the term used to describe this state, which has been found in cases of extraovarian and ovarian cancer as atypical epithelium showing hyperchromatism and stratification continuous with the malignant tumor (Brooks&Wheeler, 1977; Lagrenade&Silverberg, 1988). Fukunaga et al. found atypical endometriosis in 61% of endometriosis-associated ovarian cancers, in contrast with 1.7% of benign endometriosis samples (Fukunaga, 1997). Immunohistochemical markers distinguishing atypical endometriosis from benign endometriosis have not been fully established, but staining patterns of Ki67, Bcl-2, and p53 have been reported as useful markers (Nezhat, 2002; Ogawa, 2000). Extraovarian endometriosis may also show atypical changes. Hyperplastic changes, including atypical hyperplasia and malignant changes, were observed in more than half of the adenomyosis cases associated with endometrioid adenocarcinoma arising from the endometrium (Jacques&Lawrence, 1990; Kucera, 2011), and histologically atypical hyperplasia has been reported in some cases of gastrointestinal endometriosis (Yantiss, 2000).

5. Histological characteristics of endometriosis-associated malignancies

Clear cell carcinoma (Fig. 2) and endometrioid adenocarcinoma are well-known histological subtypes in ovarian cancer associated with endometriosis (Fukunaga, 1997; Heaps, 1990; Modesitt, 2002; Ogawa, 2000; Yoshikawa, 2000). Endometrioid adenocarcinoma is the most frequently observed phenotype in western countries (Heaps, 1990; Modesitt, 2002); however, clear cell carcinoma predominates in the Japanese cases (Ogawa, 2000; Yoshikawa, 2000). Veras et al. recently subdivided clear cell carcinoma into 3 groups (cystic, adenofibromatous, and indeterminate clear cell carcinoma) to further reveal the association between endometriosis and cystic clear cell carcinoma subtypes (Veras, 2009). Endometrioid adenocarcinomas arising in endometriotic lesions are often Grade 1 at presentation (Horiuchi, 2003), mostly showing typical morphology with various degrees of squamous differentiation (Heaps, 1990; Staats, 2007), similar to endometrioid adenocarcinoma without endometriosis. Sarcomas are the second and third most frequent endometriosis-associated

extraovarian and ovarian tumors, respectively. Adenosarcoma and endometrial stromal sarcoma are the major histological types of sarcomas (Baiocchi, 1990; Heaps, 1990; Slavin, 2000). At least partially, differences in the incidences of tumor types (carcinoma versus sarcoma) depend on the tumor site, and further studies are needed to elucidate this mechanism. Other rare malignant tumors, such as squamous cell carcinoma, malignant mesodermal mixed tumor, and yolk sac tumor, are also reported to develop from endometriosis (Irving, 2011). Although its incidence is very low compared with endometrioid adenocarcinoma or clear cell carcinoma, serous adenocarcinoma has also been associated with endometriosis (Fukunaga, 1997; Modesitt, 2002; Yoshikawa, 2000). Much more rarely, mucinous carcinomas with unusual morphology resembling Mullerian mucinous borderline tumors have also been reported in association with endometriosis (Lee&Nucci, 2003).

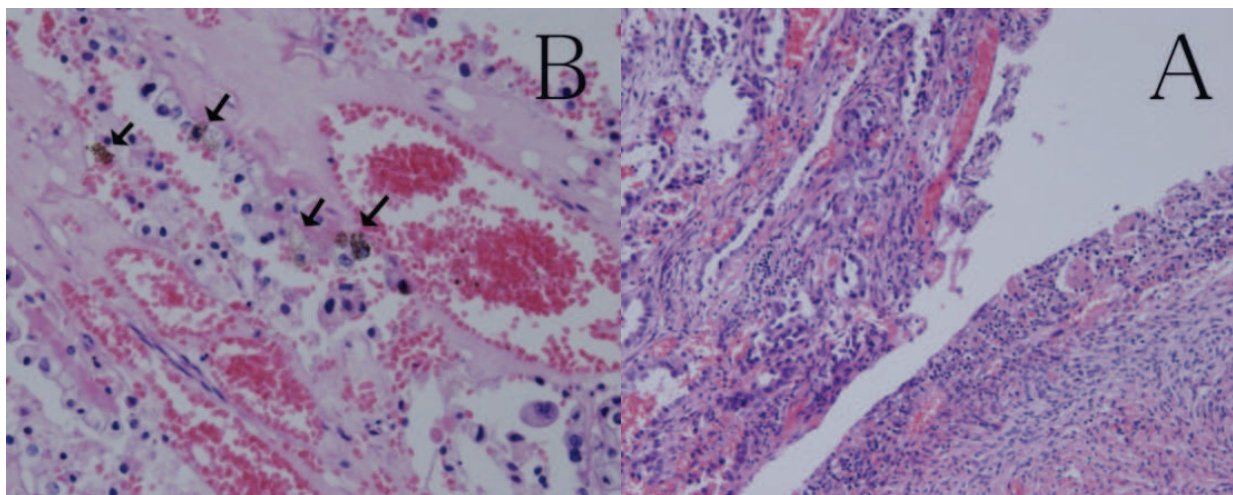


Fig. 2. A. Clear cell carcinoma (left) arising in a endometriotic cyst. B. Hemosiderin deposition (arrows) is observed in the stroma of clear cell carcinoma.

6. Genetic abnormalities and phenotypes of endometriosis-associated ovarian cancer

Genetic mutations specifically associated with ovarian cancer subtypes have been reported (reviewed by (Kurman&Shih, 2011)). Focusing on endometrioid adenocarcinomas, genetic mutations of K-ras, p53, PTEN, beta-catenin, and ATR have been reported (Mizuuchi, 1992; Milner, 1993; Palacios&Gamallo, 1998; Tashiro, 1997; Zigelboim, 2009). Mouse models of endometrioid adenocarcinoma have been reported, either with oncogenic K-ras and conditional PTEN deletion (Dinulescu, 2005) or dysfunction of both the Wnt/beta-catenin and PI3CA/PTEN pathways (Wu, 2007). However, specific genetic alterations of clear cell carcinoma were mostly unknown. Recently, a frequently activated mutation of the PI3CA gene was observed in clear cell carcinoma samples (Kuo, 2009). Most recently, several studies based on novel sequencing technology have elucidated that a significant proportion of clear cell carcinomas harbor a mutation of the ARID1A gene, which encodes the chromatin-remodeling complex protein BAF250A (Jones, 2010; Wiegand, 2010). ARID1A mutation and the consequent loss of BAF250A expression were found not only in clear cell carcinoma samples, but also in endometrioid adenocarcinomas, especially high-grade types

(Wiegand 2010; Wiegand, 2011). Whether ARID1A mutation is an early or late event in endometriosis-associated ovarian cancers related to atypical endometriosis remains to be elucidated. Alterations of other genes, such as p53, p16, and PTEN, have been detected in a low percentage of endometriotic lesions (Martini, 2002; Nezhat, 2008). hMLH, a DNA mismatch repair gene, is another candidate for the malignant transformation of endometriosis (Nyiraneza, 2010 ; Ren F, 2011). hMLH is the causal gene of Lynch syndrome, in which the risk of developing endometrial and ovarian cancers is significantly increased (Schmeler&Lu, 2008). K-ras may also be important because mutated K-ras promotes endometriosis in a mouse model, suggesting that K-ras mutation may be an early event in the carcinogenesis of endometriosis-associated cancers (Cheng, 2011). Finally, a single-nucleotide polymorphism in the intron of ANRIL, a non-coding RNA that regulates p16 expression, has been recently reported to have a strong association with endometriosis (Uno, 2010). The molecular steps from endometriosis development to carcinogenesis remain to be further clarified.

Recent studies have proposed classifying ovarian cancers into two categories: Type I tumors, which rarely harbor the p53 mutation and have an indolent clinical course, and Type II tumors, which feature the p53 mutation and are aggressive (Kurman&Shih, 2010). Within endometriosis-associated ovarian cancers, low-grade endometrioid adenocarcinoma and clear cell carcinomas are considered Type I, while high-grade endometrioid adenocarcinoma is included in the Type II category. However, p53 mutations are detected in both low- and high-grade endometriosis-associated ovarian endometrioid adenocarcinomas (Okuda, 2003), and PI3CA, PPP2R1A, and K-ras mutations are commonly detected in both endometrioid adenocarcinoma and clear cell carcinoma (Campbell, 2004; Jones, 2010 ; Kuo, 2009; McConechy, 2011 ; Mizuuchi, 1992). Recent evidence indicates that ovarian cancers arise from different cell lineages, such as preexisting cystadenomas, ectopic endometrium in endometriotic lesions, and epithelial cells of the Fallopian tubes (Bell, 2005; Kurman&Shih, 2011). Thus, it may be an oversimplification to divide all ovarian cancers into two groups. It may more accurate to categorize endometriosis-associated cancers into the same group, regardless of the histological subtype or tumor grade.

Numerous studies of expression microarray analyses have been published. Cytokines and chemokines, such as interleukin-1 and its downstream factor cyclooxygenase (COX)-2, interleukin-8, TNF- α and its downstream VEGF, TGF- α , and interleukin-6 have been reported to be involved in endometriosis and endometriosis-associated carcinoma (reviewed by (Nezhat, 2008)). An interesting study by Banz et al. revealed that SICA2, CCL14, and TDGF1 were specifically upregulated in both endometriosis samples and endometriosis-associated endometrioid adenocarcinomas, in contrast with serous adenocarcinomas or normal ovarian tissues (Banz, 2010). Another microarray study focusing on endometriosis-associated clear cell carcinoma showed upregulation of hepatocyte nuclear factor (HNF)-1 β , versican, and other markers related to oxidative stress (Yamaguchi, 2010). HNF-1 β is a transcription factor, involved in the regulation of glucose homeostasis and glycogen accumulation, normally expressed in the liver and other organs, which is assumed to have some role in the pathogenesis of clear cell carcinoma of the ovary (Kobayashi, 2009). Recently, a novel attempt to classify

histological subtypes using a small number of biomarkers has been applied to ovarian cancers. A tissue microarray-based analysis selected 21 markers, including CA125, estrogen receptor (ER), insulin-like growth factor 2 (IGF2), Ki-67, p21, p53, progesterone receptor (PGR), and Wilms tumor 1 (WT1), to distinguish histological subtypes; however, only three of the 21 markers could predict outcomes in only high-grade serous carcinoma patients (Koebel, 2008). More recently, however, Kalloger et al. succeeded in reproductively diagnosing five major subtypes of ovarian cancers (high-grade serous, clear cell, endometrioid, mucinous, and low-grade serous) using only nine markers: p16, DKK1 (a Wnt antagonist), HNF-1 β , MDM2, PGR, trefoil factor 3 (TFF3), p53, vimentin, and WT1 (Kalloger, 2011). Immunohistochemical analysis of 155 cases by De Lair et al demonstrated that 89% of clear cell carcinoma had HNF-1 β positive, ER, PGR, and WT1 negative phenotype (DeLair, 2011).

7. Prognosis of endometriosis-associated ovarian cancer

Clear cell adenocarcinoma is known to be associated with chemoresistance and a poor prognosis (Itamochi, 2008). However, most reports analyzing the prognosis of endometriosis-associated ovarian carcinomas (including mostly endometrioid adenocarcinoma and few clear cell carcinoma samples) have shown that endometriosis-associated ovarian carcinomas presented at younger ages, in lower grades and stages, and had significantly better overall survival compared with age-matched controls without endometriosis (Erzen, 2001; Kumar, 2011; Melin, 2011 ; Orezza, 2008). However, recent studies from various countries indicate that clear cell carcinomas consist of heterogeneous tumors with gene alterations, such as HER2 or Met gene amplification (Tan, 2011 ; Yamamoto, 2011; Yamashita, 2011). Therefore, clear cell carcinomas as a subtype are considered to have a worse prognosis than endometrioid adenocarcinomas, especially in Asian cases (Lee, 2011). Recently, the first international symposium of ovarian clear cell carcinoma concluded that although patients with low-stage clear cell carcinoma had a better prognosis than matched controls with high-grade serous carcinoma, high-stage clear cell carcinoma cases had the worst prognosis (Anglesio, 2010). Thus, alternative therapy, such as molecular targeted therapy, should be applied to these aggressive tumors, and a further understanding of the basic biology of the endometriosis-cancer progression, especially the role of oxidative stress, is necessary to prevent carcinogenesis in endometriosis patients (Aris, 2010).

8. Conclusion

We have reviewed the literature on endometriosis-associated ovarian cancer. Further studies are awaited to clarify the exact role of oxidative stress in carcinogenesis.

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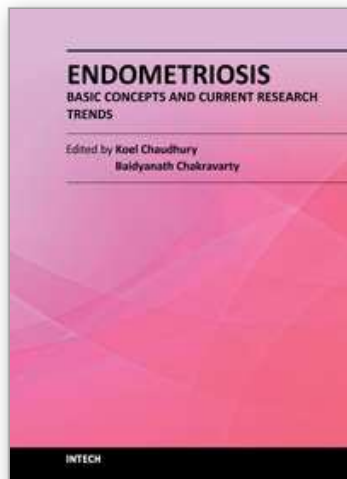
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This book provides an insight into the emerging trends in pathogenesis, diagnosis and management of endometriosis. Key features of the book include overviews of endometriosis; endometrial angiogenesis, stem cells involvement, immunological and hormonal aspects related to the disease pathogenesis; recent research reports on infertility, endometrial receptivity, ovarian cancer and altered gene expression associated with endometriosis; various predictive markers, and imaging modalities including MRI and ultrasound for efficient diagnosis; as well as current non-hormonal and hormonal treatment strategies. This book is expected to be a valuable resource for clinicians, scientists and students who would like to have an improved understanding of endometriosis and also appreciate recent research trends associated with this disease.

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