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자궁내막증에서 aromatase의 발현과 임상적 중등도와의 연관성

미래아이산부인과[1], 중앙대학교병원 산부인과[2],
인제대학교 서울백병원 산부인과[3]

이일한[1] · 김동호[2] · 노지현[3] · 고재환[3] · 김용봉[3]

Expression of aromatase in endometiosis and its relation to clinical laboratory and surgical parameters

Il-Han Lee, M.D.[1], Dong-Ho Kim, M.D.[2], Ji Hyun Noh, M.D.[3],
Jae Whoan Koh, M.D.[3], Yong Bong Kim, M.D.[3]

[1]Mire-I OB & GY Women's Clinic; [2]Department of Obstetrics and Gynecology, Chung-Ang University Hospital; [3]Department of Obstetrics and Gynecology, Paik Hospital, Inje University College of Medicine, Seoul, Korea

Objective: Aromatase is the key enzyme for the conversion of C19 steroids into estrogen in certain human tissues. We studied to evaluate the aromatase expression in eutopic endometirum and endometriotic lesion and its relationship to clinical and laboratory parameters.

Methods: The study included 78 cases of endometriotic lesion and 14 cases of eutopic endometrium and 30 cases of normal uterine endometrium obtained through laparoscopic surgery and curettage. The frozen tissue specimens were examined by immunohistochemistry using aromatase. Clinical symptoms, laboratory findings, and operative findings were analyzed and compared in according to aromatase expression.

Results: We observed positive immunohistochemical expression for aromatase in endometriotic lesion from 46/78 patients (59.0%). Aromatase expression was elevated in comparison to eutopic endometrium (5/14 patients, P=0.032) and the difference was more pronounced when eutopic endometriums from patients with endometriosis were compared with those of healthy controls (2/30 patients, P<0.001). Aromatase-positive patients had more moderate-to-severe chronic pelvic pain, higher CA-125 level significantly. Also in operative findings, severe grade endometriosis, bilateral endometriomas, and associated leiomyoma and adenomyosis were more frequent in aromatase positive patients. High values of white blood cell count, erythrocyte sedimentation rate, CA 19-9 were more frequent in aromatase positive patients notwithstanding insignificant differences.

Conclusion: Unopposed local biosynthesis of estrogens by increased expression of aromatase in eutopic endometrium and endometrial tissue could be involved in the development or maintenance of endometriosis and other uterine estrogen-triggered diseases. Our findings suggest increased expression of aromatase may be related with severity, activity, and chronic pelvic pain in patients with endometriosis.

Key Words: Aromatase, Endometrioma, Tumor markers, Endometriosis

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교신저자 : 김용봉
E-mail : kimyb2@unitel.co.kr
* 이 연구는 인제대학교 학술 연구비에 의하여 지원되었음.

Endometriosis is an estrogen (E)-dependent disease characterized by the presence of endometrial glands and stroma within the pelvic peritoneum and other extrauterine sites and is linked to pelvic pain and

infertility. Although the etiology is not well-established, several local immunological and biochemical alterations may be present.[1,2] Abnormal levels of different cytokines and markers of inflammation were described in the serum and peritoneal fluid of women with endometriosis. These alterations are probably related to the progression of the disease, the embryotoxic activity observed *in vitro*, and the possible associated infertility.[3,4] In addition, molecular anomalies such as the aberrant expression of the aromatase were described in the eutopic[5,6] and ectopic[7] endometrium of some women with endometriosis. In general, however, aromatase expression is absent in the eutopic endometrium, and aromatase is not expressed in the endometrium of disease-free women. Aromatase is the key enzyme for the conversion of C19 steroids into estrogen in certain human tissues, such as the placenta, gonads, adipose tissue.[8] On the other hand, prostaglandin E2 (PGE2) appears to be the most potent known inducer of aromatase in endometriosis.[9,10] This aromatase activity could give rise to a local biosynthesis of estrogen which in turn could increase PGE2 formation by up-regulation of cyclooxygenase type 2.[7,10] Consequently, positive feedback loop for continuous local productions of estrogen and PGs is established, favoring the proliferative and inflammatory characteristics of endometriosis because of the hormone-dependent character of the disease. But, aromatase expression rate in endometriosis and its relation to clinical symptoms are reported insufficiently.

Materials and Methods

We recruited 78 women with endometriosis who had undergone laparoscopic surgery with conservative surgery, or a hysterectomy and salpingooophorectomy because of severe endometriosis. The controls group included 30 women who had undergone endometrial curettage or hysterectomy for non-endometriosis related gynecologic disease like dysfunctional uterine bleeding or nonfunctional ovarian tumors. The average age of the 78 women who had a endometriosis was 34.3±8.5 (SD) years and that of the control group was 37.4±6.6 (SD) years. 17 patients from the experimental group and none from the control group were infertile, whereas 30 patients from experimental group and 23 patients from normal group had children respectively. Patients had not received any previous medical or surgical treatment for endometriosis at least 3 months before surgery. Transvaginal ultrasound was performed in all outpatients, and evaluation of symptomatology was performed with the application of a visual analogue scale for endometriosis that included the symptoms of dysmenorrhea, dyspareunia, and chronic pelvic pain, graded on a 10-point scale.[11] Laboratory tests included white blood cell count (WBC), erythrocyte sedimentation rate (ESR), tumor markers (CA-125 and CA 19-9). Blood samples were collected in the second half of the menstrual cycle.

During surgery, endometriosis was evaluated and catalogued according to the revised classification criteria of the American Society for Reproductive Medicine.[12,13] Samples of endometriomas, peritoneal endometriotic implants, and deep-infiltrating lesions if any, were taken to study aromatase expression and then sent for pathological analysis. Furthermore, eutopic endometrium was obtained by the pathologist immediately after removal of the organ in patients undergoing hysterectomy. Informed consent was obtained from each woman, and the study was approved by two persons of the Institutional Review Board on the use of human subjects at the Chung-Ang University Hospital (No: C2008081-184).

1. Immunohistochemistry for aromatase

Immunohistochemistry for aromatase was described

Table 1. Expression of aromatase in normal, eutopic endometrium and endometriotic lesion of patients with endometriosis

	Endometriotic lesion, No. (%) (n=78)	Eutopic endometrium, No. (%) (n=14)	Normal endometrium, No. (%) (n=30)
Gland	39 (50.0)	5 (35.7)	2 (6.7)
Stroma	37 (47.4)	0	0
Gland+Stroma	30 (38.5)	0	0
Total	46 (59.0)†	5 (35.7)*,†	2 (6.7)*

*$P<0.05$ in eutopic vs normal endometrium.

†$P<0.05$ in endometriotic tissue vs eutopic endometrium.

by Velasco et al.[14] Briefly, tissue samples were fixed with 10% paraformaldehyde solution, paraffin-embedded, Sections that measured 4 μm thick were deparaffinized with xylene and rehydrated in graded ethanols, washed briefly in phosphate-buffered saline (PBS, 0.01 M, pH 7.2), and incubated in hydrogen peroxide (0.3%) in methanol for 30 minutes to block endogenous peroxidase. After washing in PBS, sections were blocked in normal goat serum (Vector Laboratories, Burlingame, CA, USA) diluted 2% in PBS for 20 minutes at room temperature. Tissues were then incubated with a mouse anti human cytochrome P450 aromatase monoclonal antibody (Serotec Ltd, Oxford, UK) diluted 1:10 in PBS overnight at 4℃. For each case, a corresponding section was incubated with nonimmune rabbit serum as a negative control. After they were washed with PBS, staining for specimens was performed by using the conventional avidin-biotin-peroxidase complex method using a vesctastain ABC kit (Vector Laboratories). 3-amino-9-ethyl carbazole was used as a chromogen. Then, the slides were counterstained with Mayer's hematoxylin. Human placental sections were used as a positive control for aromatase.[15]

2. Tumor markers assays

The serum tumor markers CA19-9 and CA-125 were quantified by a microparticle enzyme immunoassay with the use of the AXSYM system (Abbott Diagnostics, Abbott Park, IL, USA).

3. Statistical analysis

All analyses were performed with the SPSS Windows Release 12.0 software package (SPSS Inc., Chicago, IL, USA). Comparisons of two groups were performed with the unpaired *t*-test. Differences were considered statistically significant at $P<0.05$.

Results

We observed positive immunohistochemical expression for aromatase in endometriotic tissues from 46 of 78 women (59.0%) (Table 1).

1. Aromatase staining in uterine endometrium and endometriotic tissue from women with endometriosis

Table 1 and Figure 1 to 3 depict the results of aromatase staining in endometrial tissue and in endometriotic lesions of patients with endometriosis. In eutopic endometrium, glandular aromatase staining was found in 5 of 14 women (35.7%) and there was no staining in the stroma. In endometriotic gland, immunostaining of aromatase was observed in 39 of 78 women (50.0%) and there were 37 of 78 cases (47.4%) aromatase staining in the stromal compounds of endometriotic implants although staining was weaker in the stroma than in the glandular epithelium. There

were significantly higher levels of aromatase in the endometriotic lesions than in the eutopic endometrium ($P<0.05$) (Table 1).

2. Aromatase staining in normal endometrium

We observed stained negative for aromatase in 28 of 30 cases (93.3%) and there was weak staining in 2 of 30 cases (6.7%) in normal glandular epithelium. We were unable to detect aromatase expression in any of the stromal tissue components in the normal endometrium. There were significantly higher levels of aromatase in the eutopic endometriums than in the normal endometriums ($P<0.05$) (Table 1).

3. Correlation of aromatase expression with clinical, laboratory and surgical parameters

Table 2 showed the clinical findings of endometriosis according to the expression of aromatase, and the clinical data observed in nonendometriotic patients. There were no infertile cases in the control group. Infertility was observed more frequently in patients with positive expression for aromatase, but there was no significant difference between negative

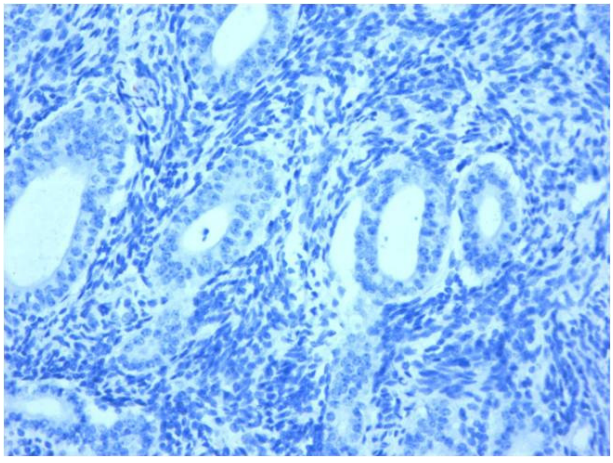

Fig. 1. Endometrial specimen from healthy control lacking aromatase expression (H&E stain, ×400).

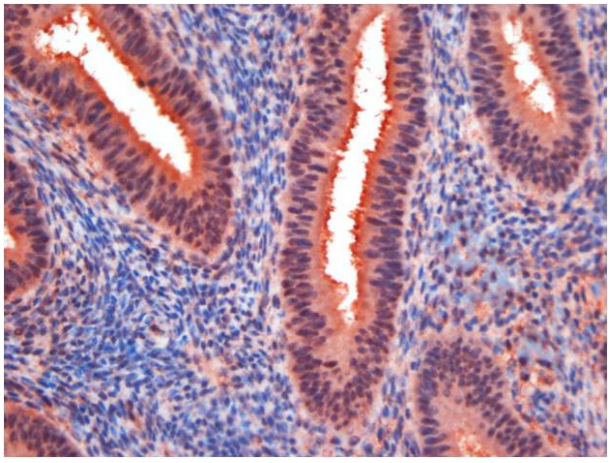

Fig. 2. Eutopic uterine endometrium from an endometriotic patient exhibiting moderate glandular expression of aromatase in the cytoplasm of respective cells (H&E stain, ×400).

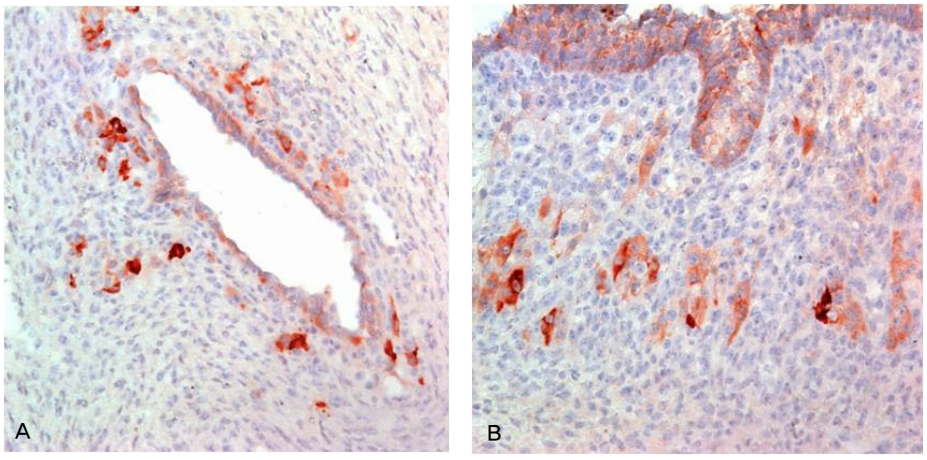

Fig. 3. Representative tissue biopsy from a peritoneal endometriotic lesion with strong aromatase expression in glandular and stromal components (A, H&E stain, ×200; B, H&E stain, ×400).

and positive cases for aromatase (11/46 vs 6/32, $P>0.05$). Patients positive for aromatase had more severe disease-related symptoms such as severe chronic pelvic pain in comparison with those negative for aromatase (28/46 vs 14/32, $P<0.05$). Table 3 provided data about laboratory finding, clinical stage, presence and size of endometriomas. Serum CA-125 level is higher in patients positive for aromatase than those negative for aromatase (80.1 vs 56.5 U/mL, $P<0.001$), but there was no significant difference in the levels of serum CA 19-9 and other inflammatory markers (WBC, ESR). In operative findings, aromatase positive patients had high grade clinical findings of endometriosis in comparison with aromatase negative cases (41/46 vs 10/32, $P<0.001$). The presence of endometrioma was seen frequently in aromatase positive patients, which was not significant (39/46 vs 26/32, $P>0.05$). But bilaterality of endometrioma (24/46 vs 5/32, $P<0.05$) and presence of leiomyoma or adenomyosis (18/46 vs 9/32, $P<0.05$) were higher in patients positive for aromatase than those negative for aromatase.

Discussion

It was pointed out that aberrant expression of ar-

Table 2. Clinical findings in patients with endometriosis according to immunohistochemical expression for aromatase

Clinical findings		Aromatase expression with endometriosis (n=78)		No endometriosis (n=30)	*P*-value
		Positive (n=46)	Negative (n=32)		
Age (yr)		34.2±9.6	35.1±7.9	37.4±6.6	NS
BMI (kg/m^2)		22.3±2.16	21.4±3.18	22.5±3.63	NS
Infertility (%)		11 (23.9)	6 (18.8)	0	>0.05
Patient with previous pregnancy (%)		17 (37.0)	13 (40.6)	23 (76.7)	NS
Severe symptoms (%)	Dysmenorrhea	17 (40.5)	13 (40.6)		NS
	Chronic pelvic pain	28 (60.9)	14 (43.8)		<0.05
	Dyspareunea	5 (10.9)	3 (9.4)		NS
	VAS >4	27 (58.7)	24 (75.0)		NS

BMI: body mass index, VAS: visual analogical scale.

Table 3. Laboratory and operative findings in patients with endometriosis according to aromatase expression

	Aromatase expression with endometriosis (n=78)		No endometriosis (n=30)	*P*-value
	Positive (n=46)	Negative (n=32)		
WBC (10^6/L)	6.483±3.008	6.271±2.901	5.896±2.749	NS
ESR (mm/hr)	25.3±19.3	22.6±17	21.7±17.5	NS
CA 19-9 (U/mL)	37.5±52.4	30.2±33.1	31.1±24.3	NS
CA-125 (U/mL)	80.1±78.5	56.5±52.1	21.3±14.6	<0.001
Grade 3,4 endometriosis (%)	41 (89.1)	10 (31.2)		<0.001
Presence of endometrioma (%)	39 (84.8)	26 (81.3)		>0.05
Bilateral endometrioma (%)	24 (54.2)	5 (15.6)		<0.05
Combined leiomyoma or adenomyosis (%)	18 (39.1)	9 (28.1)		<0.05

WBC: white blood cell, ESR: erythrocyte sedimentation rate.

omatase in the glandular epithelium and stromal cells of endometriosis gives rise to the conversion of circulating androstenedione into estrone in this tissue, and this local estrogen production may promote the growth of endometriotic implants.[16,17]

In this study, aromatase expression was found to be significantly elevated in endometriotic glands compared with eutopic endometrium. In addition, this difference was even more pronounced when comparing uterine endometrium from endometriotic patients with that of healthy controls, supporting the hypothesis of basic differences between healthy endometrium and eutopic endometrium on a molecular level.[17] This may be suggestive of a genetic defect in women with endometriosis. When defective endometrium with increased aromatase expression reaches the pelvic peritoneum by retrograde menstruation, it causes an inflammatory reaction that exponentially increases local aromatase activity, i.e., estrogen formation, induced directly or indirectly by PGs and cytokines. Increased uterine aromatase expression and increased local estrogen production might therefore be at a higher risk of developing endometriosis or other uterine estrogen-triggered diseases. Support for this hypothesis is given by studies reporting elevated endometrial aromatase expression in patients with benign proliferative disorders of the myometrium (i.e., submucous myomas) compared with healthy controls.[18] In addition altered endometrial aromatase expression has indeed been linked with the development of endometrial cancer.[19] It has been well-known that normal glandular endometrium lacks aromatase expression, but , in present study, weakly noticeable staining was seen in 2 out of 30 cases, probably due to false positive back ground staining or interobserver discrepancy among pathologists.

However, not all patients show positive aromatase expression in endometriotic tissues. In our study, aromatase was detected in 59% of cases, which could present more severe endometriosis, with higher values of CA-125 or a stronger inflammatory reaction. But in this study, we did not observe marked differences between patients with or without aromatase expression in endometriotic tissue, probably because of the low number of cases. Aromatase-positive patients had more endometriomas, frequently bilateral, and more moderate-to-severe chronic pelvic pain. These cases seemed to be related to the presence of infertility or associated leiomyomas. These findings suggest that women with aromatase in the endometriotic tissues could show major severity and aggressiveness of the disease. This is probably caused by the local biosynthesis of E and the stimulation of PGE2, which are associated with proliferation, migration, angiogenesis, apoptosis resistance, and even invasiveness in several human cell lines. Several reports[14] revealed that the addition of peritoneal fluid, TNF, and especially interleukin (IL)-6 stimulated the basal enzymatic activity observed in endometriotic stromal cells, which suggests that the local production of estrogen in endometriosis may be stimulated by factors such as cytokines or prostanoids present in the peritoneal fluid of patients with endometriosis. Thus, the presence of aromatase and the consequent synthesis of estrogen may promote the growth of endometriotic implants, and probably favor the formation of leiomyomas, which are more frequent in women with endometriosis.[20,21] It has been well-known that pain in endometriosis is correlated with the extent of the disease and the presence of deep-infiltrating endometriosis. However, in this study, we found a low number of cases to relate the presence of these positive implants to the severity of symptoms. In accordance with Heilier et al.,[22] previous treatments did not affect aromatase expressions in these patients. As for tumor markers, the increase of serum CA-125 levels in relation to the severity of endometriosis has been also well-known,[23] although CA-125 value for diagnosis of

the disease is limited because normal values can frequently be observed in patients with severe endometriosis.[24] The diagnostic sensibility is greater if the level of CA-125 is high. In our study, the value of CA-125 was elevated significantly in the aromatase positive endometriosis group. Other markers, such as CA 19-9, increase slightly in severe cases, but do not show a good diagnostic value for endometriosis. According to Somigliana et al.,[25] CA 19-9 and IL-6 did not add significant information with respect to the CA-125 test alone for diagnosis in either early or advanced stages of endometriosis. Elevated values of the blood sedimentation rate are associated with inflammation, chronicity, and dysglobulinemia. In our study, this increase was more frequently observed in aromatase positive endometriosis patients. In accordance with Zhang et al.,[26] although the causes of endometriosis remain unclear, a composite theory of retrograde menstruation with implantation of endometrial fragments, in conjunction with peritoneal factors to stimulate cell growth, has been widely accepted. Molecular alterations, such as the presence of aromatase in endometriotic tissues, could also be involved in the development or maintenance of the disease, and are possibly related to these immunological disorders.

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= 국문초록 =

목적: 본 연구는 자궁내막증 조직, eutopic endometrium 및 정상 자궁내막조직에서의 aromatase 발현율 차이를 알아보고 aromatase 발현군과 비발현군 간의 임상적 중증도의 차이를 알아보고자 시행되었다.

연구 방법: 자궁내막증으로 진단되어 수술을 시행 받은 78명의 환자와 그 중에서 eutopic endometrium의 채취가 가능했던 14명의 환자를 실험군으로 하였고 난소 낭종이나 기능성 자궁 출혈로 소파술 및 자궁 절제술을 시행받은 30명의 환자를 대조군으로 하였다. 각각의 동결 절편한 조직들에서 aromatase를 이용한 면역조직화학염색을 시행하여 aromatase의 발현 정도를 비교하였고 발현 여부에 따라 환자군의 임상 증상, 검사실 소견, 수술 소견을 나누어 비교 분석하였다.

결과: Aromatase는 총 78명의 자궁내막증 조직에서 46명 (59.0%)이 발현 되었다. 이는 eutopic endometrium의 발현율보다 유의하게 높았으며 (P<0.05), eutopic endometrium의 발현율 역시 정상 조직군에 비해 유의하게 높았다 (P<0.05). Aromatase 양성인 환자는 음성인 환자에 비해서 중등도의 만성 골반통 비율, CA-125 수치가 유의하게 높았고 (P<0.05), 수술 소견에서도 중증병기 (P<0.001), 양측성 자궁내막종의 존재 (P<0.05), 근종이나 선근증의 동반 정도가 유의하게 높았다 (P<0.05). 혈중 백혈구 수치와 적혈구 침강속도, CA 19-9는 양성군에서 다소 높게 관찰되었으나 통계적 유의성은 보이지 않았다.

결론: 자궁내막증환자에 있어서 eutopic endometrium과 자궁내막증 조직 내의 aromatase 발현은 국소적인 에스트로겐을 형성함으로써 자궁내막증의 발생과 유지에 연관이 있는 것으로 나타났고, aromatase의 발현의 증가는 자궁내막증의 중등도 및 활성도에 중요한 영향을 미치는 것으로 나타났다.

중심단어: Aromatase, 자궁내막종, 종양표지물질, 자궁내막증