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Research Article

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Clinical Presentation of Endometrioid Epithelial Ovarian Cancer with Concurrent Endometriosis: A Multicenter Retrospective Study

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Abstract

Background: Endometrioid epithelial ovarian cancer (EEOC) is frequently diagnosed in conjunction with endometriosis and is suggested to arise during the process of endometriosis. This study evaluates the clinical manifestations, including endometriosis-related symptoms and their relationships according to the coexistence of endometriosis.

Methods: Using medical records, a retrospective analysis was conducted on 221 patients treated for EEOC at four tertiary educational hospitals between 2000 and 2008. The initial presenting symptoms, particularly those related to endometriosis, were examined in relation to the coexistence of endometriosis or other clinical variables.

Results: Endometriosis was identified in 82 (37.1%) of the 221 patients with EEOC. The most common symptoms were pelvic pain followed by gastrointestinal symptoms, palpable mass, abdominal distension, vaginal bleeding, and newly developed or exacerbated dysmenorrhea (18.1%) and dyspareunia (13.6%). Notably, dysmenorrhea and dyspareunia were frequently observed in patients with endometriosis. Among 210 patients identified with pretreatment serum CA-125, 54 (25.7%) displayed normal CA-125 levels (<35 units/mL) and 23.3% and 29.9% of patients without and with endometriosis had normal CA-125 levels, respectively ($P = 0.381$). Additionally, 32.6% of the patients with early-stage EEOC displayed normal CA-125 levels.

Conclusions: In this large series of patients with EEOC, the main presenting symptoms were pelvic pain followed by gastrointestinal symptoms, palpable mass, abdominal distension, vaginal bleeding, and newly developed or exacerbated dysmenorrhea and dyspareunia. Dyspareunia and dysmenorrhea were more frequently detected in patients with endometriosis. Normal CA-125 levels cannot be applied as a marker to exclude EEOC, particularly at the early stages. *Cancer Epidemiol Biomarkers Prev; 19(2); 398–404. ©2010 AACR.*

Introduction

Ovarian carcinoma is the leading cause of death from gynecologic malignancies. Annually, new diagnoses and mortalities from ovarian cancer are estimated at 21,650 and 15,520, respectively, in the United States alone (1). Although considerable research efforts have been directed toward improving treatment outcomes and survival in patients with ovarian cancer, effective screening tools with satisfactory sensitivity and false-positive rates have not been developed (2). The identification of acceptable screening tools to achieve a minimum positive predictive value of 10% and a sensitivity of 99.6% for screening the general population of postmenopausal women is a significant challenge (2, 3).

Ovarian cancer has diverse clinical and surgical manifestations based on the corresponding histology (4-8). Endometrioid epithelial ovarian cancer (EEOC) and ovarian clear cell carcinoma (OCCC) have some shared as well as some distinct risk factors related to endometriosis, and therefore, separate consideration of these ovarian cancers is suggested (9). The symptoms of ovarian cancer, such as abdominal swelling or pain, are generally vague (10). Logically, we can assume that endometriosis-related symptoms are more frequent in ovarian cancer–related endometriosis such as EEOC or OCCC. In an earlier study, we reported a high incidence of endometriosis-related symptoms in patients with OCCC (11).

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Although several reports support the theory that EEOC and OCCC arise in endometriosis (12-15), several differences in carcinogenesis and clinical manifestations between EEOC and OCCC have been suggested (7, 9). Endometrial cancer/hyperplasia is more frequently diagnosed with EEOC (9.1–38.6%) as a synchronous tumor compared with other epithelial ovarian cancers, including OCCC (16-18). The purpose of this study was to investigate the prevalence of the coexistence of endometriosis in patients with EEOC and their related clinical manifestations.

Materials and Methods

The study subjects consisted of 221 patients treated for EEOC between 2000 and 2008 at four tertiary educational hospitals in Korea. Data were obtained retrospectively from individual medical records. Histologic classification of ovarian cancer was based on the WHO system (19). Each case was staged according to the current International Federation of Gynecology and Obstetrics staging system (20). The presence of endometriosis was determined from H&E-stained sections of resected specimens. The coexistence of endometriosis was diagnosed by confirming the presence of ectopic endometrial glands or stroma. Age, parity, body mass index, previous diagnosis of endometriosis or infertility, age at menarche, menopausal status, presenting symptoms, International Federation of Gynecology and Obstetrics stage, serum CA-125 level, treatments for endometriosis (such as gonadotropin-releasing hormone agonist, danazol, and oral contraceptives), and the coexistence of other gynecologic diseases were retrospectively reviewed.

The distribution of patient characteristics was presented as median (range) for continuous variables and frequency (%) for categorical variables. The *t* test and one-way ANOVA were used for analysis of continuous variables, and Pearson's χ^2 test was applied for categorical variables. All reported *P* values are two-sided, and the results were considered significant at $P < 0.05$. Statistical analyses were done using Stata 10 for Windows package (Stata Corp.).

Results

Clinical characteristics and presenting symptoms were statistically comparable among the individual hospitals. The clinical features of the 221 patients with EEOC are summarized in Table 1. The median age was 47 years. Overall, age was significantly higher in patients without endometriosis (50.0 versus 43.8 years; $P < 0.001$). Body mass index was also elevated in patients without endometriosis (23.8 versus 22.0 kg/m^2; $P = 0.007$). Patients with endometriosis were more commonly diagnosed at the early stages (57.6% versus 76.8%; $P = 0.004$). Thirteen of the 82 patients (15.9%) with endometriosis had been previously diagnosed with endometriosis. On the other hand, only 1 of the 142 patients without endometriosis had a previous diagnosis. Among these 14 patients, 8 underwent laparoscopic operations and had a pathologic diagnosis. As expected, the rate of infertility was higher (5.0% versus 14.6%; $P = 0.014$) and the frequency of pregnancy and delivery was lower in patients with endometriosis. Moreover, endocrinological treatments, such as gonadotropin-releasing hormone agonists (0% versus 6.1%; $P = 0.003$) and oral contraceptives (6.5% versus 15.9%; $P = 0.024$), were more frequently used in patients with endometriosis. Only one patient without endometriosis used danazol. Age at menarche was not statistically different between the two groups. Climacteric women were more commonly classified into patient groups without endometriosis (50.4% versus 28.0%; $P = 0.001$). Approximately 10.9% (24 of 221) of the patients displayed synchronous endometrial cancer/hyperplasia. Distribution of endometrial cancer among the two groups was not statistically different ($P = 0.348$).

Preoperative CA-125 levels were measured in 210 patients (133 without endometriosis and 77 with endometriosis). The serum CA-125 level was not statistically different between the two groups ($P = 0.381$). A higher number of patients with early-stage EEOC contained CA-125 within the reference range compared with those with advanced-stage EEOC [32.6% (44 of 135) versus 13.3% (10 of 75); $P = 0.002$; data not shown]. The serum CA-125 level was normal in 31 of 133 (23.3%) patients without endometriosis and in 23 of 77 (29.9%) patients with endometriosis (Table 1). Serum CA-125 was statistically different ($P = 0.001$) in patient groups according to the stage and coexistence of endometriosis (Table 2). In post hoc analyses, patients displaying advanced-stage EEOC without endometriosis had higher CA-125 levels compared with those diagnosed with early-stage EEOC without endometriosis ($P = 0.002$) and those with early-stage EEOC with endometriosis ($P = 0.003$). There was no difference in CA-125 levels among patients with and without endometriosis and advanced-stage EEOC ($P = 0.570$).

The main symptoms at initial presentation of the 221 patients with EEOC are shown in Table 3. The most common symptoms were pelvic pain (52.9%) followed by gastrointestinal symptoms (41.6%), palpable mass (40.3%), abdominal distension (39.4%), vaginal bleeding (19.9%), and newly developed or exacerbated endometriosis-related symptoms [dysmenorrhea (18.1%) and dyspareunia (13.6%)]. Incidental diagnosis was made in 13.1% of patients, and less than 10% displayed upper abdominal pain.

The presenting symptoms appeared 1 to 4 months before patients were diagnosed with EEOC. The most long-standing symptoms were newly developed or exacerbated dyspareunia or dysmenorrhea (4 months). Vague symptoms, such as pelvic pain, gastrointestinal symptoms, and upper abdominal pain, appeared an average of 3 months before EEOC diagnosis. Vaginal bleeding was evident at a median of 2.5 months before EEOC

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Table 1. Clinical characteristics of patients with EEOC based on the coexistence of endometriosis

Characteristics	EEOC (*n* = 221)	EEOC without endometriosis (*n* = 139)	EEOC with endometriosis (*n* = 82)	*P*
Age (y), median (range)	47.0 (22-78)	50.0 (22-78)	43.8 (22-78)	<0.001
BMI, median (kg/m^2)	23.1 (16.1-37.1)	23.8 (17.2-37.1)	22.0 (16.1-32.9)	0.007
FIGO stage, *n* (%)				
I + II	143 (64.7)	80 (57.6)	63 (76.8)	0.004
III + IV	78 (35.3)	59 (42.4)	19 (23.2)	
Previous diagnosis of endometriosis, *n* (%)	14 (6.3)	1 (0.7)	13 (15.9)	<0.001
Age at menarche, median (y)	13.0 (9.0-18.0)	13.0 (9.0-18.0)	13.0 (10.0-16.0)	0.470
No. of deliveries, median (range)	2 (0-7)	2 (0-7)	2 (0-5)	0.001
No. of pregnancies, median (range)	3 (0-12)	3 (0-12)	2 (0-7)	0.001
Infertility, *n* (%)	19 (8.6)	7 (5.0)	12 (14.6)	0.014
Menopausal state, *n* (%)	93 (42.1)	70 (50.4)	23 (28.0)	0.001
Use of GnRH agonist, *n* (%)	5 (2.3)	0	5 (6.1)	0.003
Use of danazol, *n* (%)	1 (0.5)	1 (0.7)	0	0.441
Use of OCs >3 mo, *n* (%)	22 (10.0)	9 (6.5)	13 (15.9)	0.024
Coexistences of endometrial cancer/hyperplasia, *n* (%)	24 (10.9)	13 (9.4)	11 (13.4)	0.348
CA-125* (units/mL), median	102.5 (5.0-17,553)	128.0 (5.0-17,553)	69.0 (5.5-15,600)	0.263
CA-125* <35 units/mL, *n* (%)	54 (25.7)	31 (23.3)	23 (29.9)	0.381

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; GnRH, gonadotropin-releasing hormone; OCs, oral contraceptives.
*CA-125 levels were measured in 210 patients, specifically in 133 patients without endometriosis and in 77 patients with endometriosis.

diagnosis. The interval from manifestation to EEOC diagnosis was the shortest in the case of unusual symptoms such as palpable mass and abdominal distension.

Symptoms did not differ statistically between the two patient groups based on the coexistence of endometriosis, except those related to endometriosis, such as newly developed or exacerbated dysmenorrhea and dyspareunia. Newly developed or exacerbated dysmenorrhea (12.2% versus 28.0%; $P = 0.003$) and dyspareunia (9.4% versus 20.7%; $P = 0.017$) were more frequent in patients with endometriosis. Upon evaluation of symptoms according to stage, pelvic pain (47.6% versus 62.8%; $P = 0.030$), gastrointestinal symptoms (31.5% versus 60.3%; $P < 0.001$), abdominal distension (27.3% versus 61.5%; $P < 0.001$), and upper abdominal pain (3.5% versus 15.4%; $P = 0.002$) were more common in patients with advanced-stage EEOC. Other symptoms, including newly developed or exacerbated dysmenorrhea and dyspareunia, were not significantly different between the two patient groups.

Discussion

In the present study, 37.1% (82 of 221) of patients presented with coexisting endometriosis and EEOC. This result is similar to previous reports (Table 4), including all stages of EEOC (28.4%; range, 13.6-42.9%; refs. 17, 18, 21-25). Endometriosis is frequently identified at all stages of EEOC (5.3%; range, 2.01-26.8%) compared with other epithelial ovarian cancers (21, 23, 24, 26). As depicted in Table 1, endometriosis was more commonly detected in early-stage EEOC (44.1%, 63 of 143), consistent with earlier

Table 2. Serum CA-125 level based on the coexistence of endometriosis and stages in patients with EEOC

Stage	Serum CA-125			*P*
	EEOC (*n* = 210)	EEOC without endometriosis (*n* = 133)	EEOC with endometriosis (*n* = 77)	
I + II	60.1 (5.5-3,610.0)	60.1 (5.8-3,610.0)	62.0 (5.5-3,080.0)	0.001
III + IV	342.0 (5.0-17,553.0)	379.0 (5.0-17,553.0)	206.4 (6.6-15,600.0)	

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Table 3. Presenting symptoms of patients with EEOC based on the coexistence of endometriosis and stage

Symptoms	EEOC (n = 221)	Interval from symptoms to diagnosis of EEOC (mo), median (range)	Coexistence of endometriosis			Stage		
			No (n = 139)	Yes (n = 82)	P	Early (n = 143)	Advanced (n = 78)	P
Pelvic pain	117 (52.9%)	3.0 (0.1-60.0)	73 (52.5%)	44 (53.7%)	0.870	68 (47.6%)	49 (62.8%)	0.030
Gastrointestinal symptoms	92 (41.6%)	3.0 (0.3-60.0)	58 (41.7%)	34 (41.5%)	0.969	45 (31.5%)	47 (60.3%)	<0.001
Palpable mass	89 (40.3%)	1.0 (0.3-12.0)	54 (38.8%)	35 (42.7%)	0.398	56 (39.2%)	33 (42.3%)	0.669
Abdominal distension	87 (39.4%)	1.0 (0.3-5.0)	57 (41.0%)	30 (36.6%)	0.516	39 (27.3%)	48 (61.5%)	<0.001
Vaginal bleeding	44 (19.9%)	2.5 (0.3-20.0)	30 (21.6%)	14 (17.1%)	0.417	27 (18.9%)	17 (21.8%)	0.604
Dysmenorrhea*	40 (18.1%)	4.0 (1.0-60.0)	17 (12.2%)	23 (28.0%)	0.003	26 (18.2%)	14 (17.9%)	0.966
Dyspareunia*	30 (13.6%)	4.0 (1.0-24.0)	13 (9.4%)	17 (20.7%)	0.017	16 (11.2%)	14 (17.9%)	0.161
Incidental diagnosis	29 (13.1%)	—	15 (10.8%)	14 (17.1%)	0.182	23 (16.1%)	6 (7.7%)	0.067
Upper abdominal pain	17 (7.7%)	3.0 (0.3-36.0)	11 (7.9%)	6 (7.3%)	0.872	5 (3.5%)	12 (15.4%)	0.002

NOTE: Fisher's exact test.
*Newly developed or exacerbated.

studies (16, 27). Our findings support the hypothesis that EEOC arises from endometriosis of the ovary (7, 12, 13, 25).

In 2004, Goff et al. (28) reported that ovarian cancer is not a silent disease, and severe and frequent symptoms of more recent onset warrant further diagnostic investigation in a prospective case-control study. More than two thirds of patients with ovarian cancer had recurring symptoms (median number of two symptoms), including back pain (45%), fatigue (34%), bloating (27%), constipation (24%), abdominal pain (22%), and urinary symptoms (16%; ref. 28). In 2005, Smith and colleagues investigated the target symptoms for ovarian cancer using records from the Surveillance, Epidemiology and End Results database linked to the Medicare claims record in California. The group reported that patients with ovarian cancer display target symptoms, such as abdominal swelling and pain, more than 6 months before diagnosis (10). The authors concluded that the evaluation of women with unexplained "target symptoms" should include pelvic imaging and/or measurement of CA-125 levels to facilitate earlier diagnosis of ovarian cancer (10). Therefore, investigation of symptoms in conjunction with other screening tools may yield more cost-effective screening tools for ovarian cancer. However, it must be considered that the target symptoms in the study are relatively vague, such as abdominal pain (30.6%), abdominal swelling (16.5%), gastrointestinal symptoms (8.4%), and pelvic pain (5.4%; ref. 10).

Endometriosis is frequently diagnosed along with EEOC and OCCC. However, the symptoms specific for endometriosis-associated epithelial ovarian cancer remain to be established (9). Recently, we reported unique symptoms including hard palpable mass (32.6%) and newly developed or exacerbated dysmenorrhea (32.6%) and dyspareunia (25.6%) in patients with OCCC (11). In the present study, pelvic pain (52.9%) was the most common indication in patients with EEOC followed by gastrointestinal symptoms (41.6%), palpable mass (40.3%), abdominal distension (39.4%), vaginal bleeding (19.9%), and upper abdominal pain (7.7%). The incidence of vaginal bleeding was relatively high (19.9%), considering that 10.9% of patients with EEOC have coexisting endometrial hyperplasia or cancer. Newly developed or exacerbated endometriosis-related symptoms [dysmenorrhea (18.1%) and dyspareunia (13.6%)] were not the main symptoms in patients with EEOC, particularly those without endometriosis. The presenting symptoms are distinct between not only EEOC and ovarian cancer but also EEOC and OCCC in terms of pattern and frequency (10, 11). Although endometriosis is suggested as the common origin of EEOC and OCCC, the differences between the two ovarian carcinoma types may be attributed to distinct molecular pathologies and clinical manifestations (7, 9, 29-31). The symptoms of ovarian cancer have thus far been described as silent or vague. However, these authors propose "different symptoms by different histologies of cancers in the same ovary." These findings should be helpful in establishing programs for the early detection and screening of ovarian cancers.

Serum CA-125 is commonly used in routine clinical practice and is elevated in the preclinical asymptomatic phase of the disease, with raised levels detected in 25% of serum samples collected 5 years before ovarian cancer diagnosis (32). Preoperative CA-125 can be used to predict severe endometriosis and malignant disease of the ovary (33, 34). In general, the sensitivity of CA-125 in predicting ovarian cancer is 81% to 91% (35-38). We assumed a higher incidence of elevated serum CA-125 in patients with EEOC because a significant number of patients displayed

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comorbidity with endometriosis. Contrary to our predictions, approximately a quarter of patients displayed CA-125 levels within the reference range in the present study. Similarly, the CA-125 level was normal in about a third of patients with OCCC (11). The higher incidence of normal serum CA-125 seems to be associated with the higher proportion of early-stage disease in patients with EEOC or OCCC. Therefore, we should bear in mind that normal levels of CA-125 cannot be effectively used as a marker to exclude ovarian cancer in these patients.

Endometriosis is a common disease (7-15%) in all women of reproductive age (39). The incidence of ovarian cancer (0.72-3.92%) and EEOC (0.25-0.77%) in patients with endometriosis is higher than that in the general population (Table 4). Endometriosis is a risk factor for cancer overall [relative risk (RR), 1.04-1.2], breast cancer (RR, 1.3), ovarian cancer (RR, 1.43-1.9), endocrine tumor (RR, 1.36), hematologic malignancies (RR, 1.4), non–Hodgkin lymphoma (RR, 1.24), and brain tumor (RR, 1.22; refs. 15, 40). In ovarian cancer, EEOC (RR, 2.2-2.53) and OCCC (RR, 3.0-3.37) are more high-risk histologies compared with other epithelial ovarian cancers (9, 26). This might be explained by the shared pathophysiology between endometriosis and cancer, such as immune alterations and hormonal imbalance (14).

There are two reasons for the higher incidence of EEOC and OCCC in patients with endometriosis. First, direct transformation, a transition from benign to malignant epithelium, is often evident (17, 22, 25). Second, iron released by hemorrhage in the endometrial cyst induces

Table 4. Literature review

(A) Prevalence of ovarian cancer or EEOC in patients with endometriosis

Author	Year	Country	Incidence of OC from endometriosis	Incidence of EEOC from endometriosis (%)	Others
Brinton	2005	Denmark	1.82% (31/1,699)	0.77% (13/1,699)	Medical Conditions Linked Registry Study, Denmark (mean FU, 11.4 y)
Kobayashi	2008	Japan	0.72% (46/6,398)	0.25% (16/6,398)	Japanese SCSEOC trial (median FU, 12.8 y)
Brinton	1997	Sweden	3.92% (29/738)	—	Hospital discharged patients diagnosis of endometriosis (mean FU, 11.4 y)
Melin	2006	Sweden	0.48% (122/25,430)	—	National Swedish Inpatient Register (mean FU, 12.7 y)

(B) Prevalence of coexisting endometriosis in patients with EEOC

Author	Year	Country	Coexistences of endometriosis with OC	Coexistences of endometriosis with EEOC	Others
Valenzuela	2006	Spain	—	13.6% (3/22)	TFBTME, 1/3 (33.3%)
Jimbo	1997	Italy	14.5% (25/172)	23.1% (3/13)	—
DePriest	1992	USA	—	26.1% (11/42)	TFBTME, 4/11 (36.4%)
Vercellini	1993	Italy	11.2% (52/466)	26.3% (30/114)	—
McMeekin	1995	USA	—	30.8% (28/91)	—
Lim	2009	Korea	—	37.1% (82/221)	This study
Fukunaga	1997	Japan	26.8% (48/179)	41.9% (13/31)	—
Ogawa	2000	Japan	29.1% (37/127)	42.9% (3/7)	Significant proportion of EEOC and OCCC: 50/127 (39.4%) TFBTME, 23/37 (62.2%)
Sainz de la Cuesta	1996	USA	27.8% (22/79)	39.1% (9/23)	Included only stage I EEOC
Deligdisch	2007	France/ Italy	—	72.5% (29/40), endometriotic cyst 35.0% (14/40), pelvic endometriosis	Included only stage I EEOC, 17/40 (42.5%) Symptomatic pelvic mass, 19/40 (47.5%) Vaginal bleeding, 19/40 (47.5%)
Brinton	2005	Denmark	2.01% (50/2,491)	—	Medical Conditions Linked Registry Study, Denmark (mean FU, 11.4 y)

Abbreviations: EC, endometrial cancer; FU, follow-up; OC, ovarian cancer; SCSEOC, Shizuoka Cohort Study on Endometriosis and Ovarian Cancer; TFBTME, transition from benign to malignant epithelium.

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persistent oxidative stress and frequent DNA mutations (41). In the current study, 37.1% of patients with EEOC displayed coexisting endometriosis in a routine pathologic examination. We believe that endometriosis will be more frequently identified in EEOC cases in a prospective setting (11).

Fourteen patients in our study had a previous history of endometriosis, most displaying coexisting endometriosis. However, the majority of patients diagnosed with endometriosis before EEOC detection had moderate to severe endometriosis requiring surgical management. Eight of the 14 patients previously diagnosed with endometriosis were subjected to laparoscopic procedures. Only six patients were diagnosed based on clinical manifestations. The symptoms of endometriosis seem different from subclinical to those requiring surgical management (42). Therefore, a significant proportion of patients with mild symptoms might not be diagnosed before the diagnosis of EEOC.

Selection bias and other confounders found in retrospective studies were other possibilities, and we made an effort to minimize these as much as possible. Symptoms were collected based on a retrospective review of medical charts. Possible missing data may suggest an underestimation of some of the parameters of interest. However, our data revealed consistent and characteristic symptoms in patients with EEOC from large databases from four training hospitals. A prospective study might reveal a higher incidence of symptoms suggestive of EEOC. This issue will be addressed by the Korean Outcome Research and Analysis of Gynecologic malignancy, which has collected prospective data similar to the Surveillance, Epidemiology, and End Results program in the United States.

In conclusion, the presenting symptoms in patients with EEOC are pelvic pain followed by gastrointestinal symptoms, palpable mass, abdominal distension, vaginal bleeding, endometriosis-related symptoms, and upper abdominal pain. Newly developed or exacerbated endometriosis-related symptoms, such as dysmenorrhea and dyspareunia, were frequently identified in patients with endometriosis. Approximately one quarter of patients with EEOC and one third of patients with early-stage EEOC had normal CA-125 levels. Therefore, normal levels of CA-125 do not seem effective as a marker to exclude EEOC, particularly at the early stages.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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