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High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis

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BACKGROUND: Women with endometriosis may also have associated disorders related to autoimmune dysregulation or pain. This study examined whether the prevalence of autoimmune, chronic pain and fatigue and atopic disorders is higher in women with endometriosis than in the general female population. METHODS AND RESULTS: A cross-sectional survey was conducted in 1998 by the Endometriosis Association of 3680 USA members with surgically diagnosed endometriosis. Almost all responders had pain (99%), and many reported infertility (41%). Compared with published rates in the general USA female population, women with endometriosis had higher rates of hypothyroidism (9.6 versus 1.5%, $P < 0.0001$), fibromyalgia (5.9 versus 3.4%, $P < 0.0001$), chronic fatigue syndrome (4.6 versus 0.03%, $P < 0.0001$), rheumatoid arthritis (1.8 versus 1.2%, $P = 0.001$), systemic lupus erythematosus (0.8 versus 0.04%, $P < 0.0001$), Sjögren's syndrome (0.6 versus 0.03%, $P < 0.0001$) and multiple sclerosis (0.5 versus 0.07%, $P < 0.0001$), but not hyperthyroidism or diabetes. Allergies and asthma were more common among women with endometriosis alone (61%, $P < 0.001$ and 12%, $P < 0.001$ respectively) and highest in those with fibromyalgia or chronic fatigue syndrome (88%, $P < 0.001$ and 25%, $P < 0.001$ respectively) than in the USA female population (18%, $P < 0.001$ and 5%, $P < 0.001$ respectively). CONCLUSIONS: Hypothyroidism, fibromyalgia, chronic fatigue syndrome, autoimmune diseases, allergies and asthma are all significantly more common in women with endometriosis than in women in the general USA population.

Key words: autoimmune/chronic fatigue syndrome/endocrine/endometriosis/fibromyalgia

Introduction

Endometriosis, a disease in which endometrial tissue grows outside the uterus, affects an estimated 8–10% of reproductive age women, and may cause pelvic pain or infertility, although in many it is asymptomatic (Ha *et al*., 1994; Duleba, 1997; Taylor *et al*., 1997; Beckmann *et al*., 1998; Lebovic *et al*., 2001). The pathogenesis of endometriosis is not well understood. It is likely that endometrial cells from retrograde menstruation adhere to the peritoneal surfaces and proliferate, causing peritoneal inflammation (Halme *et al*., 1984; Duleba, 1997; Lebovic *et al*., 2001). Since retrograde menstruation is more common than endometriosis, other factors must enable the attachment and growth of ectopic endometrial tissue. One theory is that a defect in immunosurveillance, such as impaired apoptosis of menstrual effluent, may occur in some with endometriosis. Features of women with endometriosis that are consistent with an autoimmune aetiology include increased polyclonal B-cell activity, abnormalities in T- and B-cell function, familial inheritance (Bancroft *et al*., 1989; Lebovic *et al*., 2001; Nothnick, 2001), high T- and B-lymphocyte counts (Badawy *et al*., 1987), reduced natural killer cell activity (Oosterlynck *et al*., 1991; Nothnick, 2001), high serum levels of IgG, IgA and IgM autoantibodies (Gleicher *et al*., 1987; Nothnick, 2001) and antiendometrial antibodies (Wild and Shivers, 1985; Meek *et al*., 1988; Grosskinsky and Halme, 1993).

If immune surveillance is altered in women with endometriosis, then these women might have autoimmune diseases, such as Hashimoto's thyroiditis, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), rheumatoid arthritis (RA) and multiple sclerosis (MS). Since degranulating eosinophils and eotaxin have been reported in those with endometriosis (Blumenthal *et al*., 2000; Hornung *et al*., 2000), atopic diseases, such as allergies, asthma and eczema may also be more common with endometriosis. Additionally, others have reported the occurrence of fibromyalgia in women with endometriosis (Clauw and Chrousos, 1997), although population-based studies have not been done. Thus, women with endometriosis

who have pelvic pain may have chronic generalized pain and fatigue, i.e. fibromyalgia and chronic fatigue syndrome.

The goal of this study was to examine whether the prevalence of autoimmune and endocrine diseases, fibromyalgia, chronic fatigue syndrome and atopic disorders were more common in women with endometriosis than in the general female population. There are no such previous population-based studies. In 1998, the Endometriosis Association surveyed members in the USA and Canada to characterize the symptoms associated with endometriosis. Based on anecdotal reports to the Endometriosis Association and observations by some endometriosis clinicians, this survey also sought to describe the frequency of autoimmune and related diseases among women with endometriosis. We report on the symptoms of pain and infertility described by these women, the prevalence of common autoimmune and endocrine diseases, chronic pain and fatigue states, and familial history of endometriosis and other diseases. We compare these reports of diagnosed diseases with published rates in women in the USA.

Materials and methods

Data Source

In 1998, the Endometriosis Association (Headquarters, Milwaukee, WI, USA) mailed a survey to ~10 000 female members living in the USA and Canada, with ~5% of members being in Canada. This questionnaire gathered self-reported information about symptoms of endometriosis and general medical history. Of 5500 women respondents, 4000 surveys were available for analysis in the present study. The other 1500 were not processed due to time and budgetary constraints. The Endometriosis Association stripped personal identifying information to ensure confidentiality, and under their direction, The Dieringer Research Group, Inc. (Milwaukee, WI, USA) coded the surveys. The Office of Human Subjects Research at the National Institutes of Health, Bethesda, Maryland, and the Committee on Human Research, The George Washington University, Washington, DC, granted exemptions from Investigational Review Board reviews for the evaluation of this anonymous survey.

Measures

Ethnicity/race, education level, family's total annual income and date of birth were tabulated. Because endometriosis is most accurately diagnosed by surgery, only those women with endometriosis diagnosed by laparoscopy (n = 3199) or laparotomy (n = 481) were included in analyses (n = 3680). The age at diagnosis was calculated by subtracting the year of diagnosis from each respondent's birth year. The age of first pelvic symptoms included categories for ages <15 and 15–45 years divided into 5 year age groups, and age >45 years.

The existence, location and severity of endometriosis-related pain were described. Pain severity was graded as mild, mild to moderate, mild to severe, moderate, moderate to severe, and severe. The duration of incapacitation was categorized by time intervals varying from <24 h to weeks (<24 h, 1–2 days, 2–3 days, 3–6 days, 1–2 weeks, 2–3 weeks, 4 weeks, and not specified).

Reproductive history, including infertility and the number of miscarriages and ectopic pregnancies, was summarized. Women who did not describe their pregnancy history (n = 2023) and those who were pregnant (n = 53) were excluded from reproductive history analyses.

Diseases diagnosed by a physician were categorized as (i) autoimmune inflammatory diseases, including systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), rheumatoid arthritis (RA) and multiple sclerosis (MS), (ii) endocrine diseases, including diabetes mellitus (DM), hypothyroidism and hyperthyroidism, and (iii) fibromyalgia and chronic fatigue syndrome. MS was included as an autoimmune inflammatory disease although there is some question whether it has an autoimmune origin (Chabas *et al*., 2001). Also, the survey did not distinguish between insulin-dependent and insulin-resistant diabetes, although most women probably had insulin resistance rather than insulin dependence due to the mean age at diagnosis of diabetes (35.5 years). In addition, women may not have recognized the name 'Hashimoto' or 'Graves', or may not have been told they had these conditions when they were diagnosed with hypothyroidism or hyperthyroidism. Hashimoto's thyroiditis was combined with hypothyroidism and Graves' disease with hyperthyroidism. Thus, the category of endocrine diseases was a mixture of autoimmune endocrine, such as Graves' disease, Hashimoto's thyroiditis and insulin-dependent diabetes, and general endocrine diseases, such as insulin-resistant diabetes.

Subjects reported asthma, eczema and allergies, although the method of diagnosis was not ascertained. Those reporting at least one allergy to pollens, dust, trees, paint, grasses, cigarette smoke, perfumes/fragrances, cleaning products, foods and environmental chemicals were considered to have allergies.

Family history of endometriosis indicated which family member was affected, and included mother, sister(s), daughter(s), maternal and paternal grandmothers, nieces, aunts and cousins. Only relatives reported to have diagnosed endometriosis were used in analyses (n = 1610). Family history of autoimmune inflammatory, endocrine, or fibromyalgia or chronic fatigue syndrome included the relative for each disease. While each woman had one mother and two grandmothers, the total number of affected and unaffected relatives was not known.

Ascertainment of prevalence estimates in the general population

PubMed and Medline were searched from 1969 to 2001 to obtain prevalence estimates in the general female population for the selected diseases. Reports identified by key words such as epidemiology, prevalence, incidence or disease susceptibility were reviewed. Disease prevalence (rate per 100 000 women) was compared with prevalence estimates in the general female population calculated from review articles (Jacobson *et al*., 1997; Reyes *et al*., 1997; Lawrence *et al*., 1998) or from the USA Census Bureau data (United States Census Bureau, 2001). Rates of diabetes among reproductive-aged women were obtained from the CDC Diabetes Surveillance Report (Geiss, 1997). The infertility rate was obtained from the National Survey of Family Growth (Abma *et al*., 1997), and rates for allergies and asthma were obtained from the NHANES I Epidemiologic Follow-up Study of 1992 (Idler *et al*., 2000).

Data analysis

Age, education level, income and ethnicity/race were compared with the general USA female population in 1998 using Z-tests. Prevalence estimates of diagnosed diseases among women with endometriosis were calculated and compared with rates in the general population using a series of Z-tests. We used t-tests to compare the severity of pain, median age of first pelvic symptoms, age at endometriosis diagnosis, and age at diagnosis of autoimmune inflammatory or endocrine disorder, or fibromyalgia and chronic fatigue syndrome in women with endometriosis alone and those with the co-morbid conditions. Z-tests and χ^2-tests evaluated differences in rates for allergies, asthma and eczema. The association of endometriosis with co-morbid diseases among relatives was assessed by χ^2-tests. Those respondents with family members with diagnosed endometriosis and

Table I. Demographic characteristics of respondents with surgically diagnosed endometriosis compared with the general USA female population

Characteristic	Study population		General USA female population (%)
	n	%	
Sex: female	3680	100	51.1
Age (years)[a]	(*n* = 3570)		(*n* = 138 218 000)
<15	1	0.0	20.5
15–19	35	1.0	6.7
20–24	198	5.5	6.3
25–29	561	15.7	6.8
30–34	811	22.7	7.4
35–39	878	24.6	8.2
40–44	684	19.2	8.0
45–49	309	8.7	7.0
⩾50	93	2.6	29.4
Education level[a]	(*n* = 3610)		
Did not complete high school	20	0.6	21.7
High school graduate	258	7.2	32.9
Some college	709	19.6	18.6
College graduate	1514	41.9	14.1
Postgraduate degree	968	26.8	5.5
Other	141	3.9	7.2
Combined family annual income[a]	(*n* = 3462)		
$0–24 999	321	9.3	24.0
$25 000–49 999	924	26.7	29.4
$50 000–74 999	981	28.3	21.6
⩾$75 000	1236	35.7	25.0
Race/ethnicity[a]	(*n* = 3340)		
White	3167	94.8	72.2
Black	64	1.9	12.5
Hispanic	62	1.9	10.9
Native American	8	0.2	0.7
Asian	27	0.8	3.7
Other	12	0.4	–[b]

Women with surgically diagnosed endometriosis completing the Endometriosis Association survey in 1998. General USA female population data (1998) from the USA Census Bureau (2001).
[a]$P < 0.001$ compared with the general USA female population.
[b]Not available.

co-morbid diseases were compared with respondents with family members with diagnosed endometriosis and no other conditions.

To limit confounding of analyses, only those women indicating a disease in only one category—autoimmune inflammatory diseases, endocrine diseases, or fibromyalgia or chronic fatigue syndrome—were compared for associations with other conditions. Also, for all analyses, those who did not indicate a 'yes' or 'no' answer were excluded for that particular question. However, if a woman was only asked to 'check' the applicable item, 'no' included all who answered 'no' and those who skipped the question.

In order to determine the effect of misclassification of either the study sample or the general population, a sensitivity analysis was done. Models were developed to determine a threshold for an overestimation of disease rates for the study sample and an underestimation of true prevalence in the general population such that the difference between the two groups would disappear.

Results

Study population

Most respondents were white, with only 5% blacks, Hispanics, Native Americans, Asians, and others (Table I). The mean age was 35.6 years (median 36.0, range 14–89). Ninety-one per cent were of reproductive age (15–45 years). Almost 90% had at least some college education; 42% were college graduates and 27% had earned a postgraduate degree. Sixty-four per cent reported a combined family income >$50 000 and 36% had an income >$75 000. Compared with the general population, women completing the questionnaire had a higher income and were more likely to be white ($P < 0.001$), of reproductive age ($P < 0.001$) and college-educated ($P < 0.001$).

Symptoms and diagnosis of endometriosis

Endometriosis was diagnosed surgically in all included women (Table II). Almost all women (99%) reported pain ascribed to endometriosis, and 96% had pain during menses (Table III), which is higher than the 13–15% rate for dysmenorrhoea in the general population (Mathias *et al*., 1996; Campbell *et al*., 1997). Almost 70% had pelvic symptoms before the age of 20, with 38% symptomatic before age 15 years. By contrast, only 7% were diagnosed with endometriosis by age 20 years, with 74% diagnosed between the ages of 20 and 35 years. Most women had a 10 year delay between the onset of symptoms and the diagnosis of endometriosis.

Over 70% of respondents described their menstrual pain as moderate or severe (Table III). Perimenstrual pain during urination was noted by 31% and rectal pain by 58%. Bloating

Table II. Diagnosis and important characteristics of endometriosis

Characteristic	*n*	%
Diagnosed endometriosis		
Surgical diagnosis	3680	100.0
Laparoscopy	3199	86.9
Abdominal surgery or laparotomy	481	13.1
Pain (n = 3597)	3543	98.5
Infertility (n = 3680)	1516	41.2
Age when experienced first pelvic symptoms (years) (n = 3655)		
<15	1404	38.4
15–19	1042	28.5
20–24	453	12.4
25–29	362	9.9
30–34	229	6.3
35–39	94	2.6
40–44	35	0.9
⩾45	10	0.3
Never had symptoms	26	0.7
Age when endometriosis diagnosed (years) (n = 3495)		
<15	25	0.7
15–19	218	6.2
20–24	668	19.1
25–29	1024	29.3
30–34	883	25.3
35–39	442	12.7
40–44	183	5.2
⩾45	52	1.5

Women with surgically diagnosed endometriosis completing the Endometriosis Association survey in 1998.

was reported by 84% compared with 12–16% of the general female population reporting water retention or bloating (Ramcharan *et al*., 1992; Campbell *et al*., 1997). Menstrual headaches were more common in women with endometriosis (64%) than in healthy women without endometriosis reported in other studies (45%) (Dawood, 1985).

Among the general USA population, 22% of women report an inability to carry on normal work during menses (Campbell *et al*., 1997). By comparison, 81% of survey respondents were unable to work, including doing household chores, because of pelvic pain. Although 73% usually recovered within 3 days, almost 10% reported at least a few weeks of debilitation and 87% complained of fatigue or low energy.

All women with fibromyalgia or chronic fatigue syndrome reported pain (n = 320). Pain was more severe in those with fibromyalgia ($P < 0.01$) compared with those with endometriosis alone. Forty-two women (1%) reported having been diagnosed with both fibromyalgia and chronic fatigue syndrome. Another 21 women reported having both fibromyalgia and chronic fatigue syndrome in addition to an endocrine (n = 11) or autoimmune inflammatory disease (n = 10).

Infertility and reproductive history

Overall, 41% reported infertility (Table II), a 4-fold greater risk than the USA reproductive-aged population (Abma *et al*., 1997; Stephen and Chandra, 1998). Of the 1604 women who described their pregnancy history, 21% (n = 329) had at least one miscarriage and 2% (n = 37) reported at least one ectopic pregnancy. The USA population rates for miscarriage and ectopic pregnancy are 14 and 1% respectively (Saraiya *et al*., 1999).

Figure 1 shows infertility rates for those with endometriosis alone, autoimmune inflammatory diseases, endocrine disorders, or fibromyalgia or chronic fatigue syndrome. The infertility rates for women with endometriosis alone were similar to those with endometriosis and at least one co-morbid disease in all age groups, except for significantly lower rates in 25–34 year olds with endocrine diseases and fibromyalgia or chronic fatigue syndrome ($P < 0.01$), and higher rates in 35–44 year olds with endocrine disorders ($P < 0.05$). All infertility rates among women in the sample were significantly higher than the USA population ($P < 0.001$). When those with diseases from more than one category were included, the infertility rates were not significantly altered (data not shown).

Autoimmune inflammatory diseases, endocrine disorders and fibromyalgia or chronic fatigue syndrome in women with endometriosis

Approximately 20% of respondents had one or more co-existing diseases, of whom, up to 31% were diagnosed with fibromyalgia and/or chronic fatigue syndrome, including some who also had other autoimmune inflammatory and endocrine diseases (Figure 2). Of the co-morbid diseases, hypothyroidism, fibromyalgia and chronic fatigue syndrome were the most common and were diagnosed in 10, 6 and 5% of the study population respectively. Chronic fatigue syndrome was much more common in women with endometriosis than the general population (Table IV, $P < 0.0001$) and hypothyroidism and fibromyalgia were about seven times and twice as common in women with endometriosis respectively (Table IV, $P < 0.0001$). The autoimmune inflammatory diseases SLE, SS, RA and MS each occurred more frequently in women with endometriosis (Table IV, $P < 0.001$) than in the general population. The prevalence of hyperthyroidism and diabetes in the study population was similar to that of the general population.

The sensitivity analysis revealed that the levels of misclassification both in the study sample and the general population would have to be very high for the observed differences to disappear. For SLE and chronic fatigue syndrome, there would have to be a minimum of 75% overestimation of disease prevalence in the study sample in addition to a 90% underestimation in the general population for the rates between the groups to be similar. Also, there would have to be at least a 50% overestimation among survey respondents and a 75% underestimation in the general population for the difference for MS to be negligible. For hypothyroidism, the sensitivity analysis indicated a 75% overestimation among study participants and a 50% underestimation in the population for the comparison to be insignificant. A 25% overestimation in the sample and 25% underestimation in the population would explain away the observed difference for fibromyalgia.

Chronology (age of first pelvic symptoms, age at endometriosis diagnosis and age at diagnosis of co-morbid diseases)

Table V presents the age of first pelvic symptoms, age at endometriosis diagnosis and age at diagnosis of co-morbid diseases, excluding those reporting more than one co-morbid

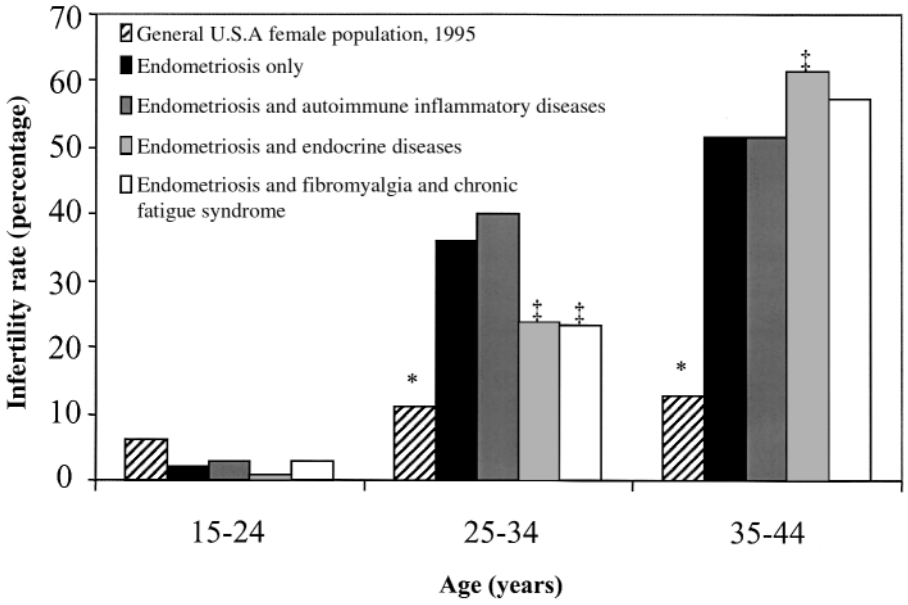

Figure 1. Infertility rates in women with surgically diagnosed endometriosis and other diseases compared with the USA female population.*$P < 0.001$ for infertility in each group compared with the general population. ‡$P < 0.05$ for infertility in each group compared with women with endometriosis alone.

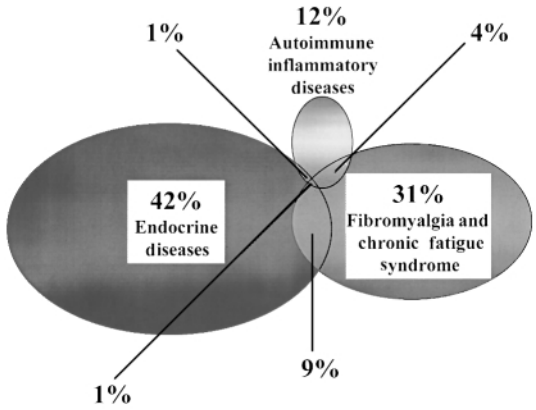

Figure 2. Distribution of co-morbid diseases among 20% of women with surgically diagnosed endometriosis and at least one other disease. Autoimmune inflammatory diseases include systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis and multiple sclerosis, and endocrine diseases include diabetes, hypothyroidism and hyperthyroidism. Intersections of the diagram are not drawn to scale.

disease. Women who had pelvic symptoms at a younger age were more likely to develop SLE, RA, SS or chronic fatigue syndrome ($P < 0.05$). All women, those with endometriosis alone or those with endometriosis and another disease, had about a 10 year delay in the diagnosis of endometriosis after the onset of pelvic symptoms. Endometriosis diagnosis aged >30 years was more common for those with SS ($P < 0.01$), any thyroid disease ($P < 0.01$) and fibromyalgia ($P < 0.01$). Other diseases were usually diagnosed ⩾4 years after the diagnosis of endometriosis, except for RA ($P < 0.001$), hypothyroidism ($P < 0.05$) and hyperthyroidism ($P < 0.05$), which were all diagnosed before age 30 years.

Allergies, asthma and eczema

The rates of allergies and other atopic conditions were higher among women with endometriosis than among women in the USA population, and higher still if they had other diseases. Allergies occur in 18% of women in the general population (Idler *et al*., 2000) compared with 61% among women with endometriosis only, and 69, 72 and 88% among women with autoimmune inflammatory diseases, endocrine diseases and fibromyalgia and/or chronic fatigue syndrome respectively ($P < 0.001$). The asthma rate among women in the general population is 5% (Idler *et al*., 2000), compared with 12% for those with endometriosis alone ($P < 0.001$), 13% with autoimmune inflammatory diseases ($P < 0.001$), 11% with endocrine diseases ($P < 0.001$) and 25% with fibromyalgia and/or chronic fatigue syndrome ($P < 0.001$) (Figure 3).

Allergies were more common among women with endometriosis and either an endocrine disease (72%), or fibromyalgia or chronic fatigue syndrome (88%) compared with those with endometriosis alone (61%; $P < 0.001$) (Figure 3). Asthma and eczema rates were significantly higher for women with fibromyalgia and/or chronic fatigue syndrome (25 and 26% respectively) compared with women with endometriosis alone (12%; $P < 0.0001$ and 15%; $P < 0.0001$ respectively). Those respondents reporting fibromyalgia and/or chronic fatigue syndrome, and one other autoimmune inflammatory or endocrine disorder had rates of allergies (79%), asthma (29%) and eczema (19%; $P < 0.05$), similar to those observed in women with only fibromyalgia or chronic fatigue syndrome.

Familial endometriosis and familial co-morbid diseases

Two-thirds of subjects stated that relatives had diagnosed ($n = 1610$) or suspected ($n = 2404$) endometriosis,

Table III. Description of pain, other symptoms and incapacitation

Characteristic	*n*	%
Location of pain (n = 3543)		
Uterus (mid pelvis)	2975	84.0
Lower back	2818	79.5
Abdomen	2631	74.3
Both ovaries	2273	64.2
Rectum	2056	58.0
Sides	1824	51.5
Legs	1422	40.1
One ovary only	1291	36.4
Chest	471	13.3
All other locations	597	16.9
Severity of pain (n = 3506)		
Mild	72	2.0
Mild to moderate	214	6.1
Mild to severe	735	21.0
Moderate	304	8.7
Moderate to severe	1593	45.4
Severe	588	16.8
Pain timing (n = 3543)		
Pain during menses	3382	95.5
Pain during ovulation	2934	82.8
Pain at other times in the menstrual cycle	2680	75.6
Symptoms (n = 3680)		
Pain symptoms		
Painful bowel movements, diarrhoea, intestinal upset	3131	85.1
Pain with/after intercourse	2388	64.9
Headaches, dizziness	2338	63.5
Pain related to urination	1134	30.8
Fatigue symptoms		
Fatigue, exhaustion, low energy	3214	87.3
Bleeding symptoms		
Heavy bleeding	2377	64.6
Irregular bleeding	1613	43.8
Premenstrual spotting	1334	36.2
Mid-cycle bleeding	958	26.0
Other symptoms related to menses		
Abdominal bloating	3086	83.9
Nausea, stomach upset	2345	63.7
Unable to carry on normal work, as a result of endometriosis (n = 3662)	2953	80.6
Duration of incapacitation (n = 2902)		
<24 h	645	22.2
1–2 days	1029	35.5
2–3 days	432	14.9
3–6 days	308	10.6
1–2 weeks	136	4.7
2–3 weeks	85	2.9
4 weeks	56	1.9
Not specified	211	7.3

suggesting a familial tendency for endometriosis (Table VI). One-fourth knew (n = 298) or suspected (n = 819) that their mother had endometriosis, and twice the number of maternal relatives were affected compared with paternal relatives.

Among those having family members with diagnosed endometriosis, 40% had a relative with at least one autoimmune inflammatory disease, 34% had at least one endocrine disease, and 48% had fibromyalgia or chronic fatigue syndrome. SLE, MS, hypothyroidism, hyperthyroidism, DM, fibromyalgia and chronic fatigue syndrome (all $P < 0.0001$) were more common among relatives if the respondent also had the disease compared with those who had endometriosis alone.

Discussion

We report an increased prevalence of hypothyroidism, fibromyalgia and chronic fatigue syndrome, and autoimmune inflammatory diseases in women with endometriosis compared with the general USA female population. Women with endometriosis also were more likely to have allergies, asthma and eczema, particularly if they also had fibromyalgia or chronic fatigue syndrome. We additionally report significant pain and debility in a large cohort of women with endometriosis and a 10 year delay in the diagnosis of endometriosis after the onset of pelvic pain. Moreover, family members of women with endometriosis more commonly had endometriosis as reported by others (Kennedy *et al*., 2001; Treloar and Kennedy,

Table IV. Prevalence estimates for co-morbid diseases compared with the USA general female population

	% (no.) of study sample (n = 3680)	Prevalence among women with endometriosis (per 100 000)	Estimated prevalence among the general USA female population from the literature (per 100 000)	Prevalence odds ratio	95% CI	P
Autoimmune inflammatory diseases						
Systemic lupus erythematosus	0.8 (31)	842.4	41.0[a]	20.7	14.3–29.9	< 0.0001
Multiple sclerosis	0.5 (19)	516.3	73.0[a]	7.1	4.4–11.3	< 0.0001
Rheumatoid arthritis	1.8 (68)	1847.8	1247.6[a]	1.5	1.2–1.9	0.001
Sjögren's syndrome	0.6 (23)	625.0	26.3[a]	23.9	15.5–36.5	< 0.0001
Endocrine diseases						
Diabetes mellitus	1.5 (56)	1521.7	1350.0[b]	1.1	0.9–1.5	NS
Hypothyroidism	9.6 (354)	9620.0	1459.3[a]	7.2	6.4–8.0	< 0.0001
Hyperthyroidism	1.7 (63)	1712.0	1973.5[a]	0.9	0.7–1.1	NS
Chronic pain and fatigue states						
Fibromyalgia	5.9 (217)	5896.7	3400.0[c]	1.8	1.6–2.1	< 0.0001
Chronic fatigue syndrome	4.6 (170)	4619.6	25.6[d]	180.5	147.2–242.0	< 0.0001

[a]Jacobson *et al*. (1997).
[b]Geiss (1997).
[c]Lawrence *et al*. (1998).
[d]Reyes *et al*. (1997).

Table V. Age of first pelvic symptoms, and age at diagnosis of endometriosis and co-morbid diseases

	First pelvic symptoms	Endometriosis diagnosis	Diagnosis of co-morbid disease
Endometriosis only	18.9 ± 0.2 (2227)	28.7 ± 0.1 (2227)	N/A
Autoimmune inflammatory diseases			
Systemic lupus erythematosus	15.2 ± 0.9 (17)[a]	26.9 ± 1.1 (17)	31.5 ± 4.6 (17)[b]
Multiple sclerosis	18.8 ± 2.2 (17)	27.8 ± 2.2 (17)	36.2 ± 4.8 (17)[b]
Rheumatoid arthritis	17.0 ± 0.9 (51)[a]	28.0 ± 0.8 (51)	25.6 ± 1.5 (51)[b]
Sjögren's syndrome	14.0 ± 0.8 (10)[a]	32.6 ± 1.6 (10)	39.9 ± 6.7 (10)[b]
Endocrine diseases			
Diabetes mellitus	18.1 ± 1.0 (47)	30.7 ± 1.1 (47)	35.5 ± 3.3 (47)[b]
Hypothyroidism	18.0 ± 0.5 (217)	30.6 ± 0.4 (217)[a]	29.6 ± 0.7 (206)[c]
Hyperthyroidism	19.7 ± 1.1 (50)	31.2 ± 0.8 (50)[a]	29.9 ± 1.2 (50)[c]
Chronic pain and fatigue states			
Fibromyalgia	18.0 ± 0.6 (147)	30.2 ± 0.5 (147)[a]	35.6 ± 1.1 (147)[b]
Chronic fatigue syndrome	17.2 ± 0.7 (106)[a]	29.2 ± 0.7 (106)	35.0 ± 1.8 (106)[b]

Values are mean ± SE (n).
Age categories for pelvic symptoms: 12 for <15 years, 17 for 15–19 years, 22 for 20–24 years, 27 for 25–29 years, 32 for 30–34 years, 37 for 35–39 years, 42 for 40–44 years, 47 for >45 years.
[a]$P < 0.05$ compared with women with endometriosis only.
[b]$P < 0.001$ age at diagnosis of co-morbid disease compared with subjects' age at endometriosis diagnosis.
[c]$P < 0.05$.
N/A = not applicable.

2002). In the current study, family members also had autoimmune inflammatory diseases, endocrine diseases and chronic fatigue states, especially if the survey respondent also had the same autoimmune inflammatory disease, endocrine disorder, fibromyalgia or chronic fatigue syndrome.

The delay in endometriosis diagnosis is significant and has been previously reported (Laufer *et al*., 1997). Since women appear to develop symptoms shortly after menarche and are not diagnosed with endometriosis for years, it is unknown whether endometriosis actually develops at menarche as others have reported (Hadfield *et al*., 1996; Reese *et al*., 1996), or if endometriosis develops over time. It also is unclear whether treating pain early could prevent chronic pelvic pain from developing in these women. Thus, attempts should be made to diagnose and treat endometriosis in adolescent women. In this sample, endometriosis was generally diagnosed after rheumatoid arthritis and thyroid diseases, which were diagnosed in the 20s, a younger age than usually seen in the USA population. By contrast, the diagnosis of endometriosis preceded the other autoimmune inflammatory diseases.

The early onset of thyroid disease and rheumatoid arthritis, as well as the higher rate of autoimmune inflammatory diseases, supports our hypothesis of an immunological aspect to endometriosis. Moreover, the high rate of physician-diagnosed

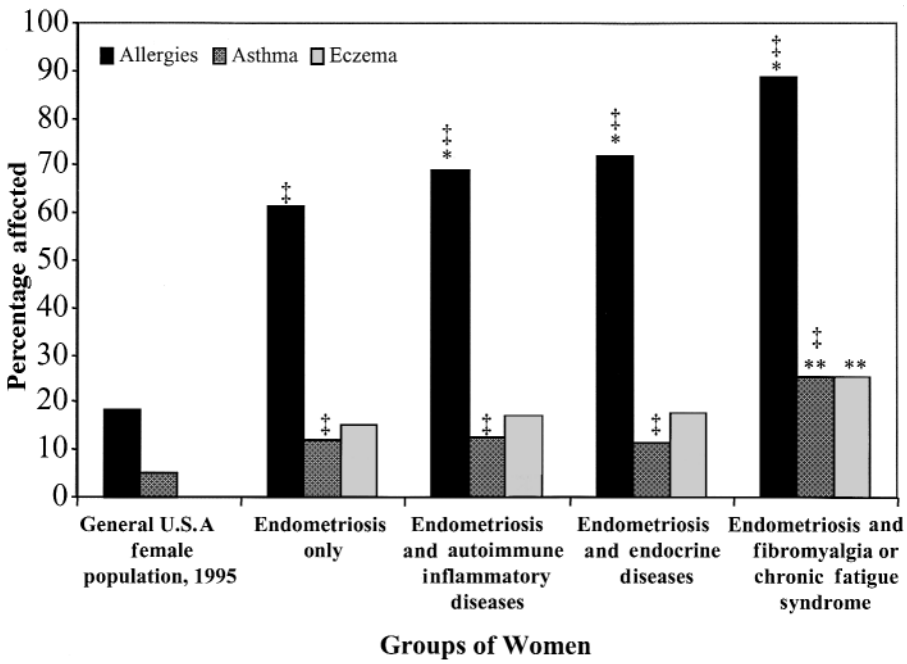

Figure 3. Allergies, asthma, and eczema among women with surgically diagnosed endometriosis. *$P < 0.001$ for allergies among women with endocrine disease, or fibromyalgia or chronic fatigue syndrome (comparison to women with endometriosis alone). **$P < 0.0001$ for asthma and eczema among women with fibromyalgia or chronic fatigue syndrome (comparison to women with endometriosis alone). ‡$P < 0.001$ for all comparisons to the general USA female population.

Table VI. Familial endometriosis among women with surgically diagnosed endometriosis

Family member	Diagnosed endometriosis		Suspected endometriosis	
	No.	%	No.	%
Mother ($n = 1117$)[a]	298	8.1	819	22.3
Maternal grandmother ($n = 378$)[a]	55	1.5	323	8.8
Paternal grandmother ($n = 133$)[a]	29	0.8	104	2.8
Immediate				
Sister ($n = 848$)	383	–[b]	465	–[b]
Daughter ($n = 60$)	11	–[b]	49	–[b]
Maternal relatives				
Niece ($n = 144$)	57	–[b]	87	–[b]
Aunt ($n = 426$)	202	–[b]	224	–[b]
Cousin ($n = 391$)	277	–[b]	114	–[b]
Paternal relatives				
Niece ($n = 44$)	23	–[b]	21	–[b]
Aunt ($n = 264$)	126	–[b]	138	–[b]
Cousin ($n = 209$)	149	–[b]	60	–[b]
Total no.	1610		2404	

[a]Percentage based on study population ($n = 3680$) as the denominator.
[b]Percentage of total affected not available.

fibromyalgia in women with chronic pain from endometriosis suggests an association among different aspects of chronic pain. The co-existence of allergies, asthma, eczema and autoimmune disease in women with fibromyalgia or chronic fatigue syndrome may also suggest an underlying role for the immune system in fibromyalgia and chronic fatigue syndrome. Whereas fibromyalgia has been associated with endometriosis, the association of chronic fatigue syndrome with endometriosis has not been reported (Clauw and Chrousos, 1997).

The strength of this study is its statistical power due to the large sample size. About 50% of those surveyed responded to the questionnaire, an above-average response rate. By only analysing responses from those with surgically diagnosed endometriosis and physician-diagnosed diseases, the likelihood of each diagnosis is more certain. By restricting the analysis of co-morbid diseases to women having only one other disease, the likelihood of confounding is limited.

One limitation of this type of study is selection bias. Almost all the members of the Endometriosis Association completing this survey reported pain, with two-thirds experiencing moderate to severe pain and significant debility. Since the Endometriosis Association provides education and support

services, as well as research, perhaps most joined the Association to seek support for pain. Thus, these respondents may over-represent endometriosis-related pain and under-represent women with other symptoms, such as infertility, though the prevalence of infertility in the sample is nonetheless high. Women with infertility may seek support for their infertility first, perhaps through other patient support groups. Thus, the findings of this study may not apply to women with endometriosis and no pain. Also, members of the Endometriosis Association pay annual fees and may be more likely to join if they have more knowledge and resources. This may explain why white and educated women from a higher socioeconomic level are over-represented compared with the general population, especially since other studies have shown that endometriosis does not occur only in white, educated women of higher socioeconomic status (Chatman, 1976; Miyazawa, 1976; Houston *et al*., 1988). The demographic observations in this sample may also reflect a diagnostic bias, since educated women with a higher income may be more likely to be diagnosed with endometriosis.

The fact that these data derive from a self-reported survey has several limitations (Hook and Regal, 1992; Warnecke *et al*., 1997; Bergmann *et al*., 1998; Lawrence *et al*., 1998). Women may misinterpret questions, may not recognize the name of specific diseases or may not accurately report conditions experienced by family members (Warnecke *et al*., 1997; Bergmann *et al*., 1998; Lawrence *et al*., 1998). Recall and reporting errors may also occur (Warnecke *et al*., 1997), especially when trying to remember the age of medical events or medical diseases for relatives. Also, it is possible that some diseases were not recognized by physicians and were never diagnosed (Jacobson *et al*., 1997). Other limitations include incomplete or missing data from respondents who skipped questions (Hook and Regal, 1992).

In addition, because of the younger age of women in the study sample, prevalence estimates obtained from other reports, which may have included a broader age range, may not be appropriate for comparison. For example, hypothyroidism is common in older, often postmenopausal, women (Canaris *et al*., 2000). By contrast, most women responding to this survey were of reproductive age.

Study limitations also may result from misclassification for diseases in the general population depending on whether they were diagnosed by a clinician or self-reported. Prevalence rates for many of the diseases were calculated from pooled disease rates from dozens of published articles using standardized medical definitions, and included clinical and laboratory evaluation (Jacobson *et al*., 1997). Due to insufficient data from the USA, the prevalence estimates for Sjögren's syndrome and Hashimoto's thyroiditis/hypothyroidism also included data from international studies. Chronic fatigue syndrome (Reyes *et al*., 1997) was rigorously defined using a combination of patient interviews, laboratory testing and a physician diagnosis. Fibromyalgia prevalence was derived from a population-based study in which a large proportion were examined by a clinician (Lawrence *et al*., 1998). Diabetes diagnoses were based on a self-reported survey conducted by the Centers for Disease Control and Prevention (Geiss, 1997) surveillance system.

We presented the prevalence odds ratio with 95% confidence intervals and the sensitivity analysis to address the misclassification of diseases in both populations. The sensitivity analysis confirms that even if the disease prevalence is underestimated in the general population and overestimated in the study sample, the rates reported in women with endometriosis are significantly higher and the differences appear real.

In conclusion, the present study is the first to provide data on the characteristics and co-morbid states of women with pain from endometriosis. Women with endometriosis frequently suffer from autoimmune inflammatory diseases, hypothyroidism, fibromyalgia, chronic fatigue syndrome, allergies and asthma. It is evident that women with pelvic pain are not diagnosed as having endometriosis for many years, suggesting that physicians, especially those taking care of adolescents, should consider the diagnosis. These data suggest a strong association between endometriosis and autoimmune disorders and indicate the need to consider the coexistence of other co-morbid conditions in women with endometriosis.

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