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Visceral syndrome in endometriosis patients

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ABSTRACT

Objective: Pain related to bowel and bladder function is seen more often in endometriosis. This study explored whether employed endometriosis patients experience multiple visceral symptoms more often than reference women without the disease.
Study design: In a cohort study, 610 patients with diagnosed endometriosis and 751 reference women completed an electronic survey based on the EHP-30 questionnaire. Percentages were reported for all data. Principal component analysis was used to find underlying structures of correlations among variables, and Cronbach's alpha reliability analysis was used to demonstrate internal consistency of each scale. The level of statistical significance was set at $p < 0.025$ in all the analyses.
Results: Principal component analysis pointed at a specific visceral symptom-complex relating to the abdominal organs. This correlation was called "visceral syndrome" and consisted of the seven symptoms; "abdominal pain with no relation to menstruation", "pain during urination", "pain during defecation", "constipation or diarrhea", "irregular bleeding", "nausea or vomiting" and "feeling tired/lack of energy", with a Cronbach's alpha value $\alpha = 0.85$. More women with endometriosis than reference women suffered between five and seven symptoms from the visceral syndrome (22.7% vs. 2.7%) and more women with endometriosis compared to women with pain from other conditions suffered between five and seven symptoms from the visceral syndrome (22.7% vs. 3.2%).
Conclusion: These data indicate that a significant number of endometriosis patients suffer from a specific symptom correlation, which is uncommon in women without the disease. These findings and previous data may suggest the occurrence of a visceral syndrome in endometriosis.

Introduction

Endometriosis is a frequent cause of pelvic pain. The disease is associated with endometrium-like tissue outside the uterus in the abdominal cavity, which causes inflammation and adherence formation, mostly in the pelvis [1]. Patients with endometriosis represent a significant socio-economic burden due to disablement and hospital treatment [2,3], and recent data indicate that employed endometriosis patients have lower work ability compared to reference women without the disease [4].

Apart from pain related to the genital organs, gastrointestinal symptoms are prevalent even without involvement of the bowel [5]. Urinary symptoms compatible with interstitial cystitis are also reported more frequently in women with endometriosis [6]. Simultaneous occurrence of these problems would present a major burden for the patient, but data on the frequency of multiple extragenital visceral symptoms in addition to endometriosis related pain are sparse.

In the present study, we explored whether endometriosis patients in occupation experience multiple visceral symptoms more often than reference women without endometriosis, using a well-described cohort of employed women.

Materials and methods

Respondents were recruited via the Danish Endometriosis Association, the Endometriosis Centre at Aarhus University Hospital, an advert in the specialist journal of a major Danish union and Facebook. A questionnaire was distributed and answered online. Information about the study was given on the front page of the electronic questionnaire. Respondents were

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anonymous and gave their informed consent electronically before answering any questions.

The questions of the questionnaire were developed specifically for the purpose of this study and piloted twice to correct misunderstandings. The questionnaire was used to collect information on pain and other endometriosis related symptoms among diagnosed endometriosis patients in employment and a group of employed reference women. Respondents were in all age categories from less than 19 years to more than 50 years old. Only a diagnosis of endometriosis by laparoscopy and/or MRI was considered valid. In our center, MRI was used for confirmation of the clinical diagnosis in patients who preferred medical or no treatment for deeply infiltrating disease with affection of the bowel wall. The investigation was performed by one subspecialized radiologist. In accordance with the literature [7], we see a positive predictive value of about 95% for this approach to the diagnosis of endometriosis. These cases comprised 27 out of 610 patients in the present material.

Respondents did not know about the specific interest in endometriosis before answering the questions. The questionnaire was based on the patient generated questionnaire Endometriosis Health Profile 30-questionnaire (EHP-30) to secure that endometriosis related symptoms were included. It was not possible to use EHP-30 since the phrasing " . . . How often because of your endometriosis have you . . . ?" made it impossible to compare endometriosis patients with "healthy" reference women.

Regarding questions of "symptoms disturbing at work . . . ", the respondents could choose between five continuous response categories including "always/to a very great extent", "often/to a great extent", "sometimes/to some degree", "rarely/to a less extent" and "never/not at all". Respondents with answers "always/to a very great extent" and "often/to a great extent" were considered having unacceptable pain/symptoms.

The study was approved by the Danish Data Protection Agency (J. no. 2011-41-6504).

Further and detailed information on data sampling, demographic characteristics of the study groups and details about the EHP30-based questionnaire were presented in a recent study [4].

Statistical methods

Percentages were reported for all data, and chi-square tests were used to detect statistical differences in demographics between the groups. Continuous variables were investigated using Mann–Whitney *U* test. Principal component analysis with direct oblimin rotation and Kaiser normalization were used to find underlying structures of correlations among variables and to see if a larger number of variables represent one or more scales. Cronbach's alpha reliability analysis was used to demonstrate internal consistency of each scale. The level of statistical significance was set at $p < 0{,}025$ in all the analyses. Statistical analyses were performed using SPSS version 19.

Results

1850 women opened the survey link and 1452 completed the survey (80%). The study included 610 diagnosed endometriosis patients (E) and 751 reference subjects (R) of whom 487 endometriosis patients and 583 reference subjects were employed at the time of the survey (Table 1).

Demographics

For patients with endometriosis the majority of respondents were between 26 and 35 years, whereas for reference women the majority of respondents were between 20 and 30 years. In both groups the majority of respondents were married or living together with a partner, had no children, had a higher education (3–4 years) and was working full time or more (Table 1).

Table 1
Demographic characteristics of patients with endometriosis (E) and reference women (R). Denmark 2011–2012.

Characteristics	R $N = 751$	E $N = 610$	*P* value
Age group, years	(%)	(%)	<0.001
≤19	1.3	1.2	
20–25	23.1	7.2	
26–30	18.7	20.7	
31–35	14.4	28.7	
36–40	11.1	18.9	
41–45	11.2	13.5	
46–50	6.7	5.9	
>50	13.7	3.8	
Marital status	(%)	(%)	<0.001
Married/living together	67.3	79.9	
In a relationship/living apart	9.9	7.6	
Divorced	4.5	2.3	
Single	18.0	10.0	
Widowed	0.3	0.2	
Children	(%)	(%)	<0.001
No children	41.7	48.1	
1	18.3	25.0	
2	27.8	20.6	
3	9.4	5.6	
>3	2.8	0.7	
Level of education	(%)	(%)	<0.001
No vocational education	23.3	11.3	
Skilled	10.0	11.6	
Higher education			
<3 years	17.2	20.7	
3–4 years	32.1	37.9	
>4 years	11.3	12.4	
Other	6.1	6.1	
Occupation	(%)	(%)	<0.001
Full time or more	36.4	44.3	
Part time	9.4	15.8	
Flexijob or rehabilitation	4.5	6.7	
Off work sick or incapacity benefit	11.6	10.8	
Enrolled in education	25.4	10.2	
Other	12.7	12.2	

Pain

Women suffering from endometriosis reported more frequent and more severe daily pain than reference women (Table 2). Of all women with endometriosis 90.8% suffered some kind of abdominal pain compared to 30.4% of reference women. Regarding pain in chest or stomach 29.2% of women with endometriosis suffered this compared to 13.7% of reference women. Among women in the reference group pain was more frequently located in the shoulders/back (55.4%) compared to women with endometriosis (32.3%).

Principal component analysis of symptoms disturbing during the work day showed a distinctive correlation, where specific symptoms had a tendency to occur simultaneously (Tables 3A and 3B). The first component of symptom correlation included abdominal pain with no relation to menstruation, pain during urination, pain during defecation, constipation or diarrhea, irregular bleeding, nausea or vomiting and feeling tired/lack of energy. This component was called "visceral syndrome" with a Cronbach's alpha value $\alpha = 0.85$. The second component of symptom correlation included pain while standing, sitting and walking, and pain during physical activity. This component was

Table 2
Pain level, illnesses and endometriosis-related symptoms of patients with endometriosis (E) and reference women (R). Denmark 2011–2012.

Characteristics	R *N* = 751	E *N* = 610	*P* value
Endometriosis diagnosis	–	(%)	
Laparoscopy	–	448	
MR	–	27	
Laparoscopy and MR	–	135	
Daily pain	(%)	(%)	<0.001
No pain	40.7	15.8	
Little pain	29.6	29.1	
Some pain	14.4	32.7	
Much pain	13.8	19.5	
So burdened one cannot endure	1.5	3.0	
Pain frequency in the last 4 weeks	(%)	(%)	<0.001
Every day	26.2	28.9	
Every second day	7.6	13.3	
Once or twice a week	14.2	20.3	
A couple of days	17.9	22.6	
One day	15.9	6.2	
No pain	18.2	8.7	
Pain location	(%)	(%)	
Head	46.9	32.6	
Neck/throat	37.7	23.0	
Shoulders/back	55.4	32.3	
Arms/hands	21.7	10.0	
Chest/stomach	13.7	29.2	
Pelvis/abdomen	30.4	90.8	
Legs/feed	28.5	19.0	
No pain	11.2	3.1	
Disease category[a]	(%) (*N* = 583)	(%) (*N* = 487)	
Permanent injury from accident	17.0	15.3	0.045
Diseases in the musculoskeletal system	37.7	27.7	<0.01
Cardiovascular diseases	8.2	5.9	0.348
Respiratory diseases	10.9	11.1	0.473
Psychological diseases	16.1	14.8	0.411
Neurological diseases	16.5	15.3	0.433
Digestion diseases	8.5	15.5	<0.001
Abdomen diseases	9.5	84.6	<0.001
Skin diseases	21.0	21.7	0.935
Tumor/cancer	1.4	1.5	0.297
Gland- and metabolism diseases	6.5	5.3	0.70
Blood diseases	2.6	3.0	0.874
Congenital diseases or malfunctioning	6.5	5.7	0.262
Other diseases	12.4	12.3	0.665
Specific diseases[a]	(%) (*N* = 583)	(%) (*N* = 487)	
Lupus	1.3	0.4	< 0.01
Rheumatoid arthritis	5.5	1.8	< 0.001
Type 1 diabetes	1.1	0.9	0.01
Asthma	11.9	11.8	0.017
Allergy or eczema	32.0	33.6	0.138
Fibromyalgia	2.2	1.5	<0.01
Chronic Fatigue syndrome	0.9	6.0	<0.001
Depression	19.9	17.4	0.02
Stress	17.8	18.3	0.319
Migraine	15.7	17.1	0.095
Symptoms disturbing at work in the last 4 weeks[a]	(%) (*N* = 583)	(%) (*N* = 487)	≤0.001
Menstruation pain	5.2	21.6	
Abdominal pain with no relation to menstruation	4.5	29.1	
Pain during urination	1.8	8.6	
Pain during defecation	2.7	15.8	
Irregular bleeding	2.7	10.2	
Constipation or diarrhea	4.3	19.7	
Nausea or vomiting	4.1	9.5	
Felt tired/lack of energy	23.9	54.8	
Headache	16.4	23.1	
Pain while standing	11.4	11.8	
Pain while sitting	12.0	14.7	
Pain while walking	11.0	12.5	
Pain during physical activity	14.4	19.8	

[a] Women in occupation.

Table 3A
Principal component analysis of endometriosis-related symptoms.

Principal component analysis of symptoms disturbing at work	Component	
	1	2
Menstruation pain	0.562	−0.148
Abdominal pain with no relation to menstruation	0.775	−0.551
Pain during urination	0.701	−0.441
Pain during defecation	0.798	−0.441
Irregular bleeding	0.656	−0.289
Constipation or diarrhea	0.720	−0.425
Nausea or vomiting	0.625	−0.422
Felt tired/lack of energy	0.618	−0.642
Headache	0.443	−0.522
Pain while standing	0.433	−0.900
Pain while sitting	0.476	−0.852
Pain while walking	0.395	−0.910
Pain during physical activity	0.458	−0.894

Note: The 2 components explain 57,65% of the variance.

Table 3B
Cronbach's alpha.

Syndromes	Abdominal-syndrome	Non-specific pain syndrome
	Abdominal pain with no relation to menstruation	Pain while standing
	Pain during urination	Pain while sitting
	Pain during defecation	Pain while walking
	Irregular bleeding constipation or diarrhea	Pain during physical activity
	Nausea or vomiting	
	Felt tired/lack of energy	
Cronbach's alpha	0.85	0.93

Note: Cronbach's alpha could not be heightened by including or excluding one or more variables.

called "musculoskeletal syndrome" with Cronbach's alpha value $\alpha = 0.93$.

When comparing endometriosis patients with reference women regarding the two syndromes, significant differences in the number of symptoms appeared between the groups (Table 4). Endometriosis patients suffered more than reference women from symptoms associated with the visceral syndrome ($p < 0.001$) and symptoms belonging to the musculoskeletal pain syndrome ($p < 0.001$). When defined by the occurrence of at least five of seven symptoms, the visceral syndrome was found in 22.7% of endometriosis patients vs. 2.7% of reference women. When occurrence of the visceral syndrome was hypothetically applied for diagnosis of endometriosis in the total group of employed endometriosis patients and control women, a sensitivity and specificity of 22.8% and 97.3% was found, respectively. The positive predictive value was 87.4% and the negative predictive value was 60.1% (Table 5).

Regarding the musculoskeletal pain syndrome 25.9% of women with endometriosis vs. 15.0% of reference women suffered four out of four symptoms in the musculoskeletal syndrome.

When analysis was restricted to include only women with pain in both groups, 24.3% of endometriosis patients vs. 2.2% of reference women suffered five to seven of seven symptoms in the visceral syndrome. For the musculoskeletal syndrome, 29.8% of endometriosis patients vs. 20.9% of reference women suffered four out of four symptoms.

There was a coincidence of both syndromes present in 58 of all women included in this study. When analysis was restricted to include only women suffering from the visceral syndrome, the musculoskeletal syndrome was present in 52.7% of the women suffering from the visceral syndrome.

Comments

Our results showed significant differences in character and severity of pain symptoms between employed women with and

Table 4
The difference in number of symptoms in the syndromes between endometriosis patients (E) and the reference group (R) and between endometriosis patients in pain and reference women in pain for other reasons than endometriosis (O)

Syndromes	R $N = 583$	E $N = 487$	p value
Abdominal syndrome	(%)	(%)	<0.001
7 symptoms	0.7	1.6	
6 symptoms	0.9	6.3	
5 symptoms	1.1	14.8	
4 symptoms	2.2	15.7	
3 symptoms	4.4	15.9	
2 symptoms	13.1	16.6	
1 symptom	33.1	13.6	
0 symptoms	44.4	15.5	
Non-specific pain syndrome	(%)	(%)	<0.001
4 symptoms	15.0	25.9	
3 symptoms	5.6	11.8	
2 symptoms	7.4	9.2	
1 symptom	8.5	14.8	
0 symptoms	63.5	38.3	
Syndromes	O $N = 352$	E $N = 364$	p value
Abdominal syndrome	(%)	(%)	<0.001
7 symptoms	0.0	1.9	
6 symptoms	1.1	7.4	
5 symptoms	1.1	17.0	
4 symptoms	2.8	18.1	
3 symptoms	6.5	17.0	
2 symptoms	17.9	18.1	
1 symptoms	38.6	11.0	
0 symptoms	31.8	9.3	
Non-specific pain syndrome	(%)	(%)	<0.001
4 symptoms	20.9	29.8	
3 symptoms	8.5	13.5	
2 symptoms	10.7	10.4	
2 symptoms	11.3	16.3	
0 symptoms	48.5	30.0	

Table 5
Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the visceral syndrome.

		Endometriosis		
Visceral syndrome		Positive (487)	Negative (583)	
	Positive (127)	True positive (111)	False positive (17)	PPV 87.4%
	Negative (943)	False negative (376)	True negative (567)	NPV 60.1%
		Sensitivity 22.8%	Specificity 97.3%	

without endometriosis. Women with endometriosis seemed to run a much higher risk of daily pain together with multiple other symptoms. These included abdominal pain with no relation to menstruation, pain during urination, pain during defecation, constipation or diarrhea, irregular bleeding, nausea or vomiting and feeling tired/lack of energy. In fact, more than one in five endometriosis patients with pain experienced five to seven of the seven symptoms, compared to 2.2% of reference women with pain from other causes. In addition, headache was seen more often. Somatic, musculoskeletal pain was also more prevalent in endometriosis patients than reference women, but the difference was considerably smaller compared to the visceral symptoms.

Our findings agree with earlier reports that bowel and bladder problems are more prevalent in endometriosis patients. Thus, irritable bowel syndrome [8] and interstitial cystitis [6,9] are seen more often. Epidemiological studies also support that endometriosis patients are at higher risk of migraine [10,11]. Our findings indicate that the individual patient often suffers from a combination of such symptoms, suggesting the potential occurrence of a "visceral syndrome" in endometriosis. This syndrome might be of diagnostic value in the diagnosis of endometriosis, as suggested by the positive predictive value calculated in the present material, but further prospective studies are needed to assess this aspect.

Studies in women undergoing laparoscopic sterilization have shown that endometriosis is a coincidental finding in around 20% of normal women without pain problems [12,13] and it might be argued that bladder and/or bowel disease represent the real cause of pain when symptoms from these organs occur in combination with endometriosis. However, increasing evidence from animal studies indicate a pathogenetic link between endometriotic lesions and painful dysfunction of abdominal organs. Studies in rats have shown that experimental inflammation in one organ may induce so-called "cross-organ effects" or "viscero-visceral crosstalk" [14] in other sites, via autonomous reflex arches involving afferent and efferent nerves [15]. In accordance, experimental endometriosis in rats induced an inflammatory reaction in the bladder wall with decreased micturition threshold [16].

Altered visceral sensory function involves both peripheral and central sensitization and may represent a significant factor in endometriosis-associated visceral dysfunction and pain [14]. In the rat model, experimental endometriosis induces vaginal hyperalgesia [17], and rectal hypersensitivity has recently been demonstrated in endometriosis patients [18]. This included cases with minimal-mild endometriosis, while abdominal pain patients without irritable bowel syndrome or endometriosis had normal sensitivity [18]. Finally, endometriosis patients display sensory innervation of the functional layer of the endometrium in contrast to normal controls where these nerves seem absent [19,20]. Such changes in autonomous neuronal function may cause visceral pain, including an increased risk of migraine [14].

Our findings also indicated that endometriosis patients more often than reference women suffered from musculoskeletal symptoms, although the difference was less pronounced. This, together with the fact that 52.7% of women suffering from the visceral syndrome also suffered from the musculoskeletal syndrome, could represent viscero-somatic convergence [21] of impulses onto the dorsal horn [22] and central sensitization [14,23]. Of interest, many of these patients show cutaneous allodynia which can be diagnosed clinically [24]. These findings and our data support the clinical experience that physical therapy should be an integral part of the treatment.

In a former study [4] we found that five factors were associated with poor work ability among women with endometriosis. These factors included "tiredness", "frequent pain", "severe daily pain", "feeling depressed at work" and "more sick days" and could indicate development into a chronic pain state. In women with endometriosis 90.8% suffered from abdominal pain and more than one in four of these patients (28.9%) suffered from daily pain. This might reflect that a significant portion of these women had in fact developed a chronic state where pain is autonomous from the pre-existing disease.

The present study is limited by the focus on working women, where only symptoms with an impact on work life were included. Future studies should include all categories of endometriosis patients together with further relevant symptoms, like e.g., dyspareunia. Limitations of the present study and our recent paper on work ability of endometriosis patients [4] also include that patients were recruited from the Danish Patient's Association, and a tertiary referral center, and not from a random sample of patients. Moreover, recruitment was based on presence at the internet and an individual motivation for participating, as opposed to e.g., postal questionnaires. However, this aspect applied to both endometriosis patients and the reference group, and the ease of electronic contact and direct registration of data implied that a large number of women participated, with potential improvements in representativeness [4]. Strengths of our study also included the incorporation of reference women and a questionnaire that could be answered by both groups. This allowed for the demonstration of a correlation of apparently unspecific symptoms occurring more often in women with endometriosis.

These data on visceral dysfunction in women with endometriosis have important clinical aspects. Patients with multiple and diffuse pain are often dismissed as psychosocial cases with so-called "functional" problems, i.e., without any organic background. Our results and previous studies indicate that these women might suffer from visceral dysfunction involving autonomic reflex reactions and altered sensory function, and that these changes could be secondary to endometriosis. More research is required to assess the potential, causal relationship and reversibility of these problems by medical and surgical therapy of endometriosis, together with efforts to define future possibilities for prevention and treatment.

In conclusion, our results and previous studies indicate that a significant number of endometriosis patients suffer from a visceral syndrome characterized by multiple symptoms compared to control women without the disease. The possible etiological role of endometriosis should be born in mind in cases with apparently unspecific visceral problems, especially when symptoms show cyclic variations. Future research should focus on the mechanisms involved and possible new treatment strategies.

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