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Fatigue – a symptom in endometriosis

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STUDY QUESTION: Is fatigue a frequent symptom of endometriosis?

SUMMARY ANSWER: Fatigue is an underestimated symptom of endometriosis as it affects the majority of women with endometriosis, but it is not widely discussed in literature.

WHAT IS KNOWN ALREADY: Fatigue can be a symptom of endometriosis causing major distress impacting the daily activities and quality of life of women with endometriosis. However, few studies with large sample sizes have investigated fatigue as a symptom of endometriosis.

STUDY DESIGN, SIZE, DURATION: The study was designed as a multi-center matched case–control study. Recruitment took place at hospitals and private practices in Switzerland, Germany and Austria between 2010 and 2016. Data was collected from 1120 women, 560 of them with endometriosis. The women with endometriosis were matched to 560 control women in regard to age ±3 years and ethnic background.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Diagnosis of women with endometriosis had to be surgically and histologically confirmed. Surgical exclusion or absence of any endometriosis-identifying symptoms was required for control subjects. Materials included surgical and histological reports as well as data retrieved from a self-administered questionnaire. This study focused on the symptom fatigue in endometriosis. Relationships of variables were established by regression analysis and associations were quantified as odds ratios.

MAIN RESULTS AND THE ROLE OF CHANCE: Frequent fatigue was experienced by a majority of women diagnosed with endometriosis (50.7% versus 22.4% in control women, $P < 0.001$). Fatigue in endometriosis was associated with insomnia (OR: 7.31, CI: 4.62–11.56, $P < 0.001$), depression (OR: 4.45, CI: 2.76–7.19, $P < 0.001$), pain (OR: 2.22, CI: 1.52–3.23, $P < 0.001$), and occupational stress (OR: 1.45, CI: 1.02–2.07, $P = 0.037$), but was independent of age, time since first diagnosis and stage of the disease.

LIMITATIONS, REASONS FOR CAUTION: Women with asymptomatic endometriosis cannot be excluded in the control group which would lead to underestimation of our results. The study's design allows no evaluation of causal effects.

WIDER IMPLICATIONS OF THE FINDINGS: As fatigue is experienced by numerous women with endometriosis, it needs to be addressed in the discussion of management and treatment of the disease. In addition to treating endometriosis, it would be beneficial to reduce insomnia, depression, pain and occupational stress in order to better manage fatigue.

STUDY FUNDING/COMPETING INTEREST(S): There was no additional funding received for this study and no conflict of interest.

TRIAL REGISTRATION NUMBER: ClinicalTrials.gov, NCT 02511626

Key words: endometriosis / fatigue / insomnia / depression / pain

Introduction

Endometriosis is a common gynecological condition affecting about 8–10% of women of reproductive age (Acién and Velasco, 2013). Endometriosis is considered a chronic and progressive condition (Huntington and Gilmour, 2005). Symptoms of endometriosis are mainly dysmenorrhea, chronic pelvic pain, infertility and deep dyspareunia (Bellelis et al., 2010). Furthermore, endometriosis is a risk factor for miscarriages (Kohl Schwartz et al., 2017). These symptoms negatively impact the quality of life, as well as the physical and mental health status, and productivity at work (Fourquet et al., 2011; Hämmerli et al., 2018). Depression is a frequent comorbidity (Chen et al., 2016) and the prevalence of depression is especially high in women with endometriosis experiencing pain (Pope et al., 2015).

However, it has been shown that fatigue is one of the most intense and frequent symptoms (Hansen et al., 2013; Touboul et al., 2013) as well as the symptom with highest associated distress (Lemaire, 2004). The prevalence of fatigue is significantly higher in patients with endometriosis compared to the general female population (Sinaii et al., 2002). Conversely, women with chronic fatigue syndrome often report endometriosis in their gynecological history (Boneva et al., 2011). In addition, patients with endometriosis suffer more often from stress (Hansen et al., 2013; van Aken et al., 2018). The impact of fatigue is vast as women's educational performance is affected as well as playing sports and social activities (Gilmour et al., 2008; Moradi et al., 2014).

Although chronic fatigue is mentioned as one of the most debilitating symptoms of endometriosis, it is not widely known and discussed as such (Riazi et al., 2015). Large studies addressing endometriosis-related symptoms do not systematically evaluate fatigue (Ballard et al., 2008; Bellelis et al., 2010; Abbas et al., 2011) and only few studies with a large sample size of more than 1000 study participants reference fatigue as a symptom of endometriosis (Sinaii et al., 2002; Ballweg, 2004; Hansen et al., 2013).

The aim of this study was to (i) investigate the prevalence of fatigue in women diagnosed with endometriosis compared to an unaffected control group and to (ii) evaluate the confounding effects of endometriosis, pain, BMI, insomnia, depression, motherhood and stress on fatigue.

Materials and Methods

Study design

The study was designed as a multi-center a cross-sectional study investigating the quality of life in women with endometriosis. This analysis compared fatigue in a cohort of endometriosis patients to a cohort of non-endometriosis patients with a focus on prevalences and confounders of fatigue. Outcome was the prevalence of fatigue.

Data collection

Study participants were recruited from different university hospitals, district hospitals and associated private practices in Switzerland, Germany and Austria, as well as from endometriosis self-help groups in Germany. Most of the data was collected from the University Hospital Zurich, the Triemli Hospital Zurich, the district hospitals in Winterthur, Schaffhausen, St. Gallen, Baden, Solothurn, and Walenstadt, the Charité Berlin, the University Hospital Aachen, the Albertinen-Hospital Hamburg, the Vivantes Humboldt-Klinikum Berlin and the University Hospital Graz. Women were approached by medical staff and received information about study participation. After verbal consent, the patients were given additional written information, a questionnaire, a consent form for study participation, and a consent form for confirmation of diagnosis along with a return envelope. In the endometriotic group, the context for consultation was either a post-operative follow-up or a regular check-up monitoring the disease progression. Women of the control group were recruited during their annual check-up or during hospital stays for temporary mild, benign gynecological procedures (for example laparoscopic removal of a benign ovarian cyst) if they met inclusion criteria.

Sample size

A sample size of 387 participants in each group is needed to detect a 10% difference between cases and controls with an alpha of 0.05 and a power of 0.8. As the present study is part of a larger study also including outcome measures where we expected smaller differences, we decided on a sample size of a minimum of 550 study participants in both groups.

Inclusion criteria

Women with surgically and histologically confirmed endometriosis were included in the study regardless of their disease symptoms. Eligible for the control group were only women that showed no pelvic pain or where endometrioses had been surgically excluded by laparoscopy or laparotomy. However, women with other pain than pelvic pain could still be included in the control group. The diagnosis of endometriosis was confirmed and classified using the revised American Society for Reproductive Medicine (rASRM) classification. To be included, women had to be in sufficient command of the language and demonstrate the psychological ability to understand and respond to the given questionnaire. Pregnancy at the time of inclusion was an exclusion criterion for both groups. Data was included when at least 80% of questions relevant for the present evaluation had been answered. Following these criteria, data from 1120 women was available for fatigue evaluation, 560 women with endometriosis and 560 pair-matched women without endometriosis. The women's age ranges from 18 to 59. Age ±3 years and ethnic background were used as matching criteria.

Questionnaire and definitions

The self-administered questionnaire contains questions pertaining to a variety of factors related to quality of life, including factors associated with endometriosis. Along with questions regarding age, nationality and socioeconomic background, the questionnaire addresses questions about the gynecological history, pre-existing health conditions, chronic pain, family history, pregnancy, partnership, sex life, life style and psychological disorders. The questionnaire was developed by endometriosis and psychosomatic specialists from the universities of Zurich and Berlin as well as leading board members of endometriosis self-help groups. The study was registered at ClinicalTrials.gov (NCT 02511626) where further details on the complete questionnaire are available. All data was encrypted and entered into an Access database.

The extent of fatigue and insomnia was categorized into five different levels (1 = never to 5 = very often). Study participants had to answer based on their experiences in the previous 6 months. Furthermore, women were asked to rate their current occupational stress (0 = no stress to 10 = major stress). Moreover, pain was investigated in both groups using questions from the Brief Pain Inventory and the Pain Disability Index. Depression was measured using the Patient Health Questionnaire (PHQ-9) and classified as a score ≥10 (Kroenke and Spitzer, 2002).

The body-mass-index categorizes underweight, overweight and obesity (World Health Organization, 2006). The formula is: BMI = kg/m^2. A body mass index equal or greater to 25 is classified as overweight. Therefore, a high BMI in our analysis corresponds to a BMI greater than 24.9.

Data analysis

Statistical analysis was carried out using the statistical software JMP, Version *13*. SAS Institute Inc., Cary, NC, USA. Results are shown as absolute numbers (*n*), percentages and 95% confidence intervals. Descriptive statistics quantitatively summarize observations made during analysis. Significance of differences in categorical data was tested for using the chi-squared test. Simple and multiple logistic regressions were performed to analyze the relationship between dependent and independent variables. Associations were quantified as odds ratios and adjusted for confounding factors. Confounders were chosen *a priori* based on our prior knowledge from existing literature which exposed a relation between endometriosis, chronic pain, and fatigue (Dunselman *et al.*, 2014), an association between a high BMI and fatigue (Jarosz *et al.*, 2014), and a relation between child and parent sleep patterns (Meltzer and Montgomery-Downs, 2011). Further, prior literature presented a higher prevalence of insomnia in endometriosis patients (Maggiore *et al.*, 2017), a greater risk for developing a major depression (Chen *et al.*, 2016), and a high prevalence of stress in women with endometriosis (Hansen *et al.*, 2013). After confounders were chosen, they were assessed using univariate models. All variables significant at the 0.1 alpha level in the univariate analysis were included in the multivariate analysis.

Ethical approval

All women voluntarily participated in the study and signed an informed consent. The cantonal ethics committees as well as the ethics committees of the participating hospitals approved the study. The guidelines of the World Medical Association Declaration of Helsinki 1964, updated in October 2013, apply to the study. The STROBE criteria were used to draft the manuscript (Von Elm *et al.*, 2007).

Results

In total, 560 women with endometriosis and 560 women without endometriosis were evaluated. An overview of symptoms and conditions experienced by women diagnosed with endometriosis and control women is shown in Table I. Demographic data is presented in Table II. Endometriosis characteristics and related fatigue are shown in Table III. Increasing age was not significantly associated with frequent fatigue ($P = 0.26$).

Table IV presents the multivariate analysis of factors associated with fatigue. Associations between endometriosis stage and fatigue are shown in Table V. The median time since first diagnosis was 2.6 years (first quartile: 0.8 years, third quartile: 6.1 years). Time since first diagnosis in women experiencing frequent fatigue did not significantly differ from women experiencing only occasional or rare fatigue ($P = 0.13$).

An analysis of the association between pain and fatigue can be found in the supplementary information.

Discussion

In our study, the prevalence of frequent fatigue is more than doubled in women diagnosed with endometriosis compared to unaffected control women. Fatigue was associated with endometriosis, pain, insomnia, depression, and occupational stress. The association between endometriosis and frequent fatigue remained significant after controlling for the confounding effects of pain, insomnia, occupational stress, depression, BMI and motherhood. This finding supports an independent effect of endometriosis which cannot be attributed to disease symptoms. Our results show that endometriosis-related fatigue is a frequent symptom which should be addressed in medical care. While the current treatment and management of the disease focuses more on classic symptoms such as pain and infertility (Bernardi and Pavone, 2013; Dunselman *et al.*, 2014; Vercellini *et al.*, 2014), it is important to also address fatigue when treating patients with endometriosis. Physical activity reduces pain (Leeners and Imthurn, 2007) and therefore might be beneficial in endometriosis treatment. As psychological or pharmacological treatments are used to alleviate fatigue when suffering from other conditions (Acciarresi *et al.*, 2014), they could be suitable for treating fatigue in endometriosis. Additionally, these treatments might also improve depression and sleep disturbances.

We considered multiple factors with an influence on fatigue independent of endometriosis. Our regression analysis showed that fatigue is independent of age. A high BMI is associated with frequent fatigue. However, other factors such as pain and depression have a greater influence on fatigue. Our analysis demonstrates that women experiencing pain were more affected by fatigue and that pain is highly associated with endometriosis. Further, it is important to note that pain and mood conditions such as depression often occur together in endometriosis (Smorgick *et al.*, 2013; Pope *et al.*, 2015) which is also reflected in our results. Additionally, depression was associated with frequent fatigue.

Our study shows that frequent fatigue is strongly associated with frequent insomnia which is experienced more often by endometriosis patients than controls and supported by other literature (Maggiore *et al.*, 2017). As child sleep problems have an impact on parent sleep and daytime functioning (Meltzer and Montgomery-Downs, 2011), we suspected being a mother to have an impact on the level of fatigue. In our study, many women with endometriosis are childless, probably due to infertility being one of the major disease symptoms. After adjusting for confounders, the association of low fatigue levels and children became insignificant, indicating that other factors are more important in influencing fatigue.

Long-term endometriosis influences the perceived stress level (Lazzeri *et al.*, 2015) and stress exposure is associated with depression (Kendler *et al.*, 1999; Vinkers *et al.*, 2014). Both, occupational stress and depression were experienced more by women with endometriosis than controls. Patients with endometriosis using positive coping strategies suffer less from depression (Donatti *et al.*, 2017) while avoidance coping styles and passive coping styles are related to poor mental status and higher pain (Zarbo *et al.*, 2018). Negative coping strategies have been found to be significant predictors of fatigue (Nikolaus *et al.*, 2013), therefore, fatigue in endometriosis could be a result of poor disease coping. Furthermore, inflammation caused by endometriosis lesions and the activation of the immune system might be involved in fatigue. Fatigue is a frequent symptom of inflammatory diseases and a positive correlation between inflammatory cytokines and fatigue has been shown, suggesting that the immune system with elevated cytokines could play a role in fatigue symptomology (Bower, 2007; Louati and Berenbaum, 2015). Our analysis shows that high

Table I Symptoms and conditions in women diagnosed with endometriosis and control women.

Fatigue/[1]exhaustion	**Endometriosis (*N* = 554)**	**Controls (*N* = 548)**	***P*-values[2]**
Frequent	*N* = 281 (50.7%)	*N* = 123 (22.4%)	*P* < 0.001
Occasional	*N* = 150 (27.1%)	*N* = 190 (34.7%)	
Rare	*N* = 123 (22.2%)	*N* = 235 (42.9%)	
Pain	**Endometriosis (*N* = 554)**	**Controls (*N* = 546)**	
Yes	*N* = 315 (56.9%)	*N* = 70 (12.8%)	*P* < 0.001
No	*N* = 239 (43.1%)	*N* = 476 (87.2%)	
Insomnia[1]	**Endometriosis (*N* = 555)**	**Controls (*N* = 546)**	
Frequent	*N* = 162 (29.2%)	*N* = 68 (12.5%)	*P* < 0.001
Occasional	*N* = 155 (27.9%)	*N* = 113 (20.7%)	
Rare	*N* = 238 (42.9%)	*N* = 365 (66.9%)	
Depression[3]	**Endometriosis (*N* = 514)**	**Controls (*N* = 491)**	
Yes	*N* = 141 (27.4%)	*N* = 53 (10.8%)	*P* < 0.001
No	*N* = 373 (72.6%)	*N* = 438 (89.2%)	
Occupational stress[4]	**Endometriosis (*N* = 509)**	**Controls (*N* = 513)**	
High	*N* = 322 (63.3%)	*N* = 280 (54.6%)	*P* < 0.001
Low	*N* = 187 (36.7%)	*N* = 233 (45.4%)	

[1]Frequent = often/very often, occasional = sometimes, rare = seldom/never.
[2]Pearson χ^2-test.
[3]Yes = Patient Health Questionnaire (PHQ-9) Score ≥10.
[4]High = scale 6–10, low = scale 1–5.

Table II Demographic data.

Nationality	**Endometriosis (*N* = 558)**	**Controls (*N* = 559)**
Swiss	*N* = 234 (41.9%)	*N* = 301 (53.8%)
German	*N* = 257 (46.1%)	*N* = 164 (29.3%)
Austrian	*N* = 8 (1.4%)	*N* = 12 (2.1%)
Other	*N* = 59 (10.6%)	*N* = 82 (14.7%)
Age	**Endometriosis (*N* = 560)**	**Controls (*N* = 560)**
Mean in years	37.9 ± 7.2	37.6 ± 8.9
Education	**Endometriosis (*N* = 550)**	**Controls (*N* = 557)**
Primary	*N* = 27 (4.9%)	*N* = 18 (3.2%)
Secondary	*N* = 106 (19.3%)	*N* = 130 (23.3%)
Vocational[1]	*N* = 211 (38.4%)	*N* = 192 (34.5%)
Tertiary	*N* = 192 (34.9%)	*N* = 195 (35.0%)
Other	*N* = 14 (2.5%)	*N* = 22 (3.9%)
Motherhood	**Endometriosis (*N* = 560)**	Controls (*N* = 560)
Yes	*N* = 161 (28.8%)	*N* = 265 (47.3%)
No	*N* = 399 (71.3%)	*N* = 295 (52.7%)
High BMI[2]	**Endometriosis (*N* = 555)**	**Controls (*N* = 553)**
Yes	*N* = 152 (27.4%)	*N* = 134 (24.3%)
No	*N* = 403 (72.6%)	*N* = 419 (75.8%)

[1]Apprenticeship, vocational baccalaureate.
[2]High = >24.9.

occupational stress, as well as depression, is associated with frequent fatigue. Due to higher stress levels, the hypothalamic pituitary adrenal (HPA) axis is altered in patients with endometriosis (Van Uum *et al.*, 2008; van Aken *et al.*, 2018). Being chronically exposed to high stress can result in adrenal fatigue which could be another possible explanation for a relation between endometriosis and fatigue.

Furthermore, our results indicate that fatigue is independent of the disease stage which differs from previous literature (Ashrafi *et al.*, 2016). Likewise, the time since first diagnosis does not differ with the level of fatigue.

Limitations

The data was retrieved from a self-administered questionnaire and answers on fatigue were based on experiences in the past 6 months. Therefore, answers, including perception of sleepiness, are subjective and at risk for recall biases. Whenever possible, questions were based on prior validated questionnaires. Additional aspects, where no validated questionnaire was available, were based on clinical experience and revised by the governing body of the German endometriosis self-help groups. Furthermore, the study design does not allow to evaluate causal effects. Additional confounding factors may not have been included in the statistical analysis as the evaluation focused on endometriosis and did not include every other possible disease which could potentially influence fatigue. However, such diseases will be present in both groups. Some of the evaluated answers only reflect a short period of time and do not necessarily represent a constant condition.

Medication such as GnRH analogs, progestins, and especially pain killers likely confound fatigue and related symptoms. Unfortunately, we have no information on the exact medication taken during the full period relevant for the present investigation of fatigue. Therefore, the association between endometriosis and fatigue will partly have to be attributed to side effects of medication. However, this situation represents clinical reality where medication always aims for the best possible compromise between disease symptoms on the one hand and side effects on the other hand. As a consequence, we assume that our findings represent experiences of women living with the combined symptoms of endometriosis and related medication. Stress is limited to occupational stress since the questionnaire did not ask for general stress. As some women in the control group might have undiagnosed endometriosis, differences in fatigue might have been underestimated. In contrast, exclusion of women with pelvic pain in the control group might have resulted in overestimation.

Table III Endometriosis characteristics.

rASRM stage	Endometriosis (*N* = 558)	No./% of those with frequent fatigue
1	*N* = 100 (17.8%)	*N* = 50 (50%)
2	*N* = 113 (20.3%)	*N* = 58 (51.3%)
3	*N* = 166 (29.9%)	*N* = 77 (46.4%)
4	*N* = 178 (32.0%)	*N* = 94 (52.8%)
Location/type[1]	**Endometriosis (*N* = 556)**	**No./% of those with frequent fatigue**
Pelvic wall/sacrouterine ligament/adhesions	*N* = 528 (95.0%)	*N* = 264 (50.0%)
Douglas pouch/ rectovaginal septum	*N* = 401 (72.2%)	*N* = 207 (51.6%)
Endometrioma	*N* = 276 (49.6%)	*N* = 132 (47.8%)

[1]Multiple locations/types possible.

Conclusion

To improve the quality of life in women with endometriosis, addressing fatigue should, in addition to chronic pain and infertility, become a routine part of medical care. Together with the standard treatment of endometriosis, it would be beneficial to reduce insomnia, pain, depression and occupational stress in order to better manage fatigue.

Table IV Factors associated with fatigue/exhaustion (multivariate analysis).

Predictor	Crude OR (95% CI)	Crude *P*-values	Adjusted OR[1] (95% CI)	Adjusted[1] *P*-values
Frequent fatigue[2]				
Endometriosis	3.56 (2.74; 4.62)	<0.001	2.02 (1.39; 2.95)	<0.001
High BMI[3]	1.58 (1.20; 2.09)	0.001	1.30 (0.89; 1.93)	0.18
Pain	5.09 (3.88; 6.67)	<0.001	2.22 (1.52; 3.23)	<0.001
Frequent insomnia[2]	14.39 (9.89; 20.92)	<0.001	7.31 (4.62; 11.56)	<0.001
Depression[4]	10.43 (7.08; 15.37)	<0.001	4.45 (2.76; 7.19)	<0.001
Motherhood	0.71 (0.55; 0.92)	0.009	1.07 (0.74; 1.56)	0.72
High occupational stress[5]	1.86 (1.42; 2.44)	<0.001	1.45 (1.02; 2.07)	0.037

[1]Adjusted for endometriosis, BMI, pain, insomnia, depression, motherhood and occupational stress.
[2]Frequent = very often/often.
[3]High = BMI > 24.9.
[4]Depression = Patient Health Questionnaire (PHQ-9) Score ≥10.
[5]High = scale 6–10.

Table V Endometriosis stage in association with fatigue/exhaustion.

Predictor		Crude OR (95% CI)	Crude *P*-values	Adjusted OR[1] (95% CI)	Adjusted[2] *P*-values
Frequent fatigue[2]					
rASRM stage	Reference				
I or II	No endometriosis	3.55 (2.54;4.98)	<0.001	1.94 (1.21; 3.12)	0.006
III or IV	No endometriosis	3.52 (2.62; 4.71)	<0.001	1.97 (1.30; 2.98)	0.001
III or IV	rASRM I or II	1.02 (0.64; 1.60)	0.95		

[1]Adjusted for BMI, pain, insomnia, depression, motherhood and occupational stress.
[2]Frequent = often/very often.

Supplementary data

Supplementary data are available at *Human Reproduction online*.

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Authors' roles

A.R.-W., A.S.K.S., M.M.W. and B.L. are responsible for the analysis of data. A.R.-W. and B.L. prepared the manuscript. Finalization of the manuscript was conducted by all authors. B.L. was the principal investigator and conducted the study. Other investigators were A.S.K.S., M.R., M.M.W., F.H., S.VO., M.E., B.I., P.I. and D.F. Collection of data was carried out by A.S.K.S. (site Winterthur), K.G. (site Zurich), M.R. (site Berlin), M.M.W. (site Aachen and Graz), F.H. (site St. Gallen), S.V.O. (site Zurich), M.E. (site Schaffhausen), B.I. (site Zurich), P.I. (site Zurich) and B.L. (site Zurich). K.G. was responsible for the management of the database. K.G., P.I., D.F. and B.L. were involved in the concept of the study.

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Conflict of interest

There is no conflict of interest declared.

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