

The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey

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STUDY QUESTION: To what extent do the management of endometriosis and the symptoms that remain after treatment affect the quality of life in women with the disease?

SUMMARY ANSWER: Many women with endometriosis had impaired quality of life and continued to suffer from endometriosis-associated symptoms even though their endometriosis has been managed in tertiary care centres.

WHAT IS KNOWN ALREADY: The existing literature indicates that quality of life and work productivity is reduced in women with endometriosis. However, most studies have small sample sizes, are treatment related or examine newly diagnosed patients only.

STUDY DESIGN, SIZE, DURATION: A cross-sectional questionnaire-based survey among 931 women with endometriosis treated in 12 tertiary care centres in 10 countries.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women diagnosed with endometriosis who had at least one contact related to endometriosis-associated symptoms during 2008 with a participating centre were enrolled into the study. The study investigated the effect of endometriosis on education, work and social wellbeing, endometriosis-associated symptoms and health-related quality of life, by using questions obtained from the World Endometriosis Research Foundation (WERF) GSWH instrument (designed and validated for the WERF Global Study on Women's Health) and the Short Form 36 version 2 (SF-36v2).

MAIN RESULTS AND THE ROLE OF CHANCE: Of 3216 women invited to participate in the study, 1450 (45%) provided informed consent and out of these, 931 (931/3216 = 29%) returned the questionnaires. Endometriosis had affected work in 51% of the women and affected relationships in 50% of the women at some time during their life. Dysmenorrhoea was reported by 59%, dyspareunia by 56% and chronic pelvic pain by 60% of women. Quality of life was decreased in all eight dimensions of the SF-36v2 compared with norm-based scores from a general US population (all $P < 0.01$). Multivariate regression analysis showed that number of co-morbidities, chronic pain and dyspareunia had an independent negative effect on both the physical and mental component of the SF-36v2.

LIMITATIONS, REASONS FOR CAUTION: The fact that women were enrolled in tertiary care centres could lead to a possible over-representation of women with moderate-to-severe endometriosis, because the participating centres typically treat more complex and referred cases of endometriosis. The response rate was relatively low. Since there was no Institute Review Board approval to do a non-responder investigation on basic characteristics, some uncertainty remains regarding the representativeness of the investigated population.

WIDER IMPLICATIONS OF THE FINDINGS: This international multicentre survey represents a large group of women with endometriosis, in all phases of the disease, which increases the generalizability of the data. Women still suffer from frequent symptoms, despite tertiary care management, in particular chronic pain and dyspareunia. As a result their quality of life is significantly decreased. A patient-centred approach with

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extensive collaboration across disciplines, such as pain specialists, psychologists, sexologists and social workers, may be a valuable strategy to improve the long-term care of women with endometriosis.

STUDY FUNDING/COMPETING INTEREST(S): The WERF EndoCost study is funded by the World Endometriosis Research Foundation (WERF) through grants received from Bayer Schering Pharma AG, Takeda Italia Farmaceutici SpA, Pfizer Ltd and the European Society of Human Reproduction and Embryology. The sponsors did not have a role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript. L.H. is the chief executive and T.D. was a board member of WERF at the time of funding. T.D. holds the Merck-Serono Chair in Reproductive Medicine and Surgery, and the Ferring Chair in Reproductive Medicine at the Katholieke Universiteit Leuven in Belgium and has served as consultant/research collaborator for Merck-Serono, Schering-Plough, Astellas and Arresto.

Key words: endometriosis / quality of life / patient questionnaire / international multicentre survey

Introduction

Endometriosis is one of the most common gynaecological diseases. The estimates of the prevalence of endometriosis among the general population of women of reproductive age vary between 2 and 10% (Eskenza and Warner, 1997). The prevalence rises to 30–45% in women with infertility and/or pain (Gruppo italiano per lo studio dell'endometriosi, 1994; Meuleman et al., 2009). The most pronounced complaint of women with endometriosis is pain, which can be expressed in a variety of symptoms including dysmenorrhoea, dyspareunia, chronic pelvic pain, dysuria and dyschesia, as well as fatigue and infertility (Kennedy et al., 2005).

The treatment options for women with endometriosis are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, assisted reproduction or a combination of these (Kennedy et al., 2005). Clinicians tend to measure the results of their interventions through the decrease in symptoms and the reduction of endometriotic lesions. Women mainly evaluate the results of treatment, apart from the decrease in symptoms, based on an increased feeling of wellbeing and/or the ability to resume daily activities satisfactorily, i.e. through their quality of life (Berlim and Fleck, 2003; Jones et al., 2006).

In recent years, there has been an increasing interest in the effect of endometriosis on health-related quality of life (HRQoL) (Gao et al., 2006). Qualitative interview-based studies on quality of life with small patient numbers ($n < 24$) revealed that the experience of severe and chronic pain was the most pronounced complaint, having an impact on all aspects of everyday life (Denny, 2004; Jones et al., 2004; Huntington and Gilmour, 2005). In some larger questionnaire-based studies, it was reported that quality of life was significantly reduced in women with endometriosis (Mathias et al., 1996; Sepulcri Rde and do Amaral, 2009; Fourquet et al., 2010). In addition, mental wellbeing was discovered to be decreased in a majority of women with endometriosis (Sepulcri Rde and do Amaral, 2009). However, these studies all have relatively small sample sizes ($n < 107$). Nnoaham et al. investigated the impact of endometriosis on HRQoL and work productivity in 1418 women across five continents scheduled for laparoscopic surgery, of which 745 women were consequently diagnosed with endometriosis (Nnoaham et al., 2011). They confirmed reduced quality of life and work impairment in women diagnosed with endometriosis compared with those—with similar symptoms—who did not have endometriosis. However, the study included only newly diagnosed women (incident cases), and thus

was not able to investigate the longer term effects of the disease following actual treatment (Nnoaham et al., 2011).

In conclusion, there is a need for a large comprehensive study addressing the quality of life in a prevalent group of women with endometriosis, because existing studies have small sample sizes, are treatment related or examine only newly diagnosed patients. A more detailed view on the impact of endometriosis on HRQoL can be achieved by a large-scale study including both women with recently diagnosed endometriosis as well as treated women who have lived with the disease for many years. The World Endometriosis Research Foundation (WERF) EndoCost study is an international multicentre survey, which calculated costs of endometriosis from a societal perspective (Simoens et al., 2012). A secondary aim of the study was to investigate the extent to which the management of endometriosis and the symptoms that persist after treatment affect the HRQoL in women with the disease.

Materials and Methods

Perspective

The WERF EndoCost study was conducted to measure costs of illness and HRQoL in women with endometriosis. This paper will focus particularly on the quality of life aspects of endometriosis-associated symptoms. The methods of the WERF EndoCost study are reported in detail elsewhere (Simoens et al., 2011, 2012).

Setting

A research network, the WERF EndoCost Consortium, was established in 2007 comprising 12 representative tertiary care centres from 10 countries. The definition of a representative centre was based on the recognition of this centre as a referral centre for women with endometriosis-associated symptoms within and outside a country. For each country, one or more gynaecologists and one health economist with a major interest in endometriosis participated in the network.

Study population and recruitment

The study population included women with a laparoscopic and/or histological diagnosis of endometriosis, who had at least one contact related to endometriosis-associated symptoms during 2008 with a participating centre. The diagnosis of endometriosis was not necessarily made in this time period, but could have been made earlier. The study excluded women with suspected endometriosis and women with a history of endometriosis who came to the hospital for a clinical problem unrelated to the disease.

Ethical approval

Ethical approval was obtained from the ethical committee/Institute Review Board (IRB) of each participating centre. Women were required to sign an informed consent form in order to participate in the study. All eligible patients received an information letter and consent form in August 2009. If they gave their consent they were asked to complete questionnaires addressing HRQoL in the beginning of October 2009.

Questionnaires

Country- and language-specific questionnaires were used to determine current socio-demographic characteristics such as marital status, education, work situation and medical history such as surgery, fertility treatments and any co-morbidities from a lifetime perspective.

Questions obtained from the WERF GSWH instrument (designed and validated for the WERF Global Study on Women's Health) (Nnoaham *et al.*, 2011) were used to determine the impact of endometriosis on education, work and social wellbeing from a lifetime perspective, i.e. any impact experienced in the period from first symptoms until completing the questionnaire. Furthermore, questions from the WERF GSWH instrument were used to measure current symptoms, such as dysmenorrhoea, dyspareunia and chronic pelvic pain (recall period 3 months).

Validated language versions of the Short Form 36 version 2 (SF-36v2) questionnaire were used to measure HRQoL (Ware *et al.*, 1993). The SF-36v2 is designed to measure the current health status (recall period 4 weeks) and allows the comparison of the examined population to a general standard population (Ware *et al.*, 1993, 2000).

Disease criteria

Endometriosis was staged at the time of diagnosis based on hospital records using the revised American Fertility Society (r-AFS) classification: I (minimal), II (mild), III (moderate) or IV (severe) (American Fertility Society, 1985). Stages I/II and III/IV were analysed together.

Data collection

Data collection and input into the central database were carried out by each participating centre. Each centre had the opportunity to contact women to supplement answers for missing values. An analysis checked whether women with missing data were comparable to women with a complete data set in terms of women characteristics. Overall quality assurance of data entry and data analysis was carried out by the coordinating health economist (S.S.).

Sample size

This study was designed to measure symptoms and quality of life rather than test a specific hypothesis. Therefore, no sample size calculation was conducted. The inclusion of women was performed during a complete year in order to obtain a representative sample of women with frequent visits to the hospital and women with only an annual check-up. Each referral centre identified eligible women and invited them on 31 August 2009 to participate in the study. A total of 3216 women received an invitation letter and 1450 provided informed consent in time to be mailed the questionnaires on 24 September 2009.

Analysis

Statistical analyses were primarily of a descriptive nature. For categorical data, characteristics are reported as relative frequencies data and, for continuous data, as mean, SD and 95% confidence interval of the mean. Missing data were not imputed for the descriptive analysis. In order not to overestimate the symptoms and effect of endometriosis on education, work and social

wellbeing, a conservative approach was chosen. If data were missing, they were analysed as if the questioned symptom was not present.

The SF-36v2 is a generic instrument containing eight dimensions of HRQoL: physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional problems and mental health. There are two summary components: physical health (PCS) and mental health (MCS). For each SF-36v2 dimension, item scores were coded, summed and transformed to T-score-based scores (norm-based scores), with higher scores meaning better quality of life. The scorings are standardized across the Short Form family of adult tools using the means and SDs from the 1998 US general population (Ware *et al.*, 1993, 2000). Norm-based scores in the US general population have a mean of 50 and an SD of 10. Norm-based scores are available for women in different age categories. Calculations were performed using the official QualityMetric Health Outcomes Scoring Software. Missing data were substituted using the QualityMetric's Missing Data Estimator in case at least half of the data in that scale were present (referred to as the 'half-scale rule' of missing data estimation).

To determine the effect of endometriosis on quality of life, the eight domains of the SF-36 and summary measures of women with endometriosis were compared with the normative data of the general population in the respective age groups, using single-sided *t*-tests. Effect sizes were calculated as the standardized mean difference between patient and population norm-based score (Cohen's *d*). Effect sizes around 0.2 are considered as small effects, around 0.5 as moderate and around 0.8 or more as large effects (Cohen, 1988).

A linear regression analysis was used to assess the effect of demographic, clinical and socio-economic characteristics as well as current symptoms (dysmenorrhoea, dyspareunia, chronic pelvic pain) on the SF-36 summary measures: PCS and MCS. First univariate analyses were performed to explore the separate effect of a variable on the summary measures. All data shown in Tables I–VII that had a significant effect (at 5% level) were included in the multivariate regression analysis. A backward method to select independent variables was applied, with the final model restricted to variables significant at the 5% level. The multivariate linear regression analysis was run including age and some dummy variables representing the countries and races (confounding factors).

Results

Out of 3216 women invited to participate in the study, 1450 women (1450/3216 = 45%) provided informed consent and had questionnaires posted to them, 931 women (931/3216 = 29%) returned the questionnaires.

Table I shows the demographic and clinical characteristics of the participating women. Furthermore, this table shows that the mean delay for the diagnosis of endometriosis was 5.5 years, based on both patient delay (time interval between onset of symptoms to first doctor visit; mean 2.1 years) and physician delay (time interval between first doctor visit and diagnosis of endometriosis; 3.4 years). Furthermore, the table shows the number of doctors and complementary therapists consulted by the patient before the diagnosis of endometriosis was made.

Tables II and III demonstrate that women with endometriosis frequently underwent more than one surgery (mean 2.2 surgeries). Table IV shows that the majority of women (79%) received at least one or more hormonal treatments during their life and presents the type of hormonal treatment they received. Table V shows that 42% of women received fertility treatment and presents the type of treatment they received.

Table I Characteristics of women ($n = 931$), delay, number of physicians and complementary therapists consulted before diagnosis.

	Mean/number	SD/percentage	Minimum–maximum	95% CI of the mean
Age (years)	36.1	6.8 SD	14–67	35.7–36.6
Height ^{a,b} (cm)	167.3	6.3 SD	136–195	166–167
Weight ^{a,b} (kg)	71.7	26.3 SD	41–230	70.0–73.4
Current marital status				
Single and living with partner ^b	210	23		
Married ^b	523	56		
Single and not living with partner	127	14		
Divorced/separated	69	7		
Widowed	1	0		
Unknown	1	0		
r-AFS stage				
Minimal–mild (stage I–II)	223	24.0		
Moderate–severe (Stage III–IV)	573	61.5		
Unknown	135	14.5		
Number of co-morbidities	1.9	1.6 SD	0–11	1.8–2.0
Age at first symptoms ^{a,b} (years)	24.8	8.2 SD	10–65	24.2–25.4
Age at diagnosis ^a (years)	30.3	6.6 SD	12–65	29.8–30.8
Years since diagnosis ^a	5.5	4.9 SD	1–33	5.2–5.9
Patient delay (years)	2.1	4.0 SD	0–32	1.8–2.4
Doctor delay ^{a,b} (years)	3.4	5.3 SD	0–38	3.0–3.8
Total delay ^{a,b} (years)	5.5	6.6 SD	0–38	5.0–5.9
Number of physicians consulted ^{a,b,c}	3.0	2.5 SD	0–30	2.8–3.2
Number of complementary therapists consulted ^{a,b,c}	0.5	1.7 SD	0–25	0.4–0.6

r-AFS, revised American Fertility Society; CI, confidence interval.

^aFactors included in the backward regression analysis for the physical component.

^bFactors included in the backward regression analysis for the mental component.

^cBefore diagnosis of endometriosis.

Table II Number of surgeries in women's medical history.

	Mean	SD	Minimum–maximum	95% CI of the mean
Number of laparoscopies ^{a,b}	1.7	1.3	0–10	1.6–1.8
Number of laparotomies ^a	0.5	0.9	0–6	0.5–0.6
Total number of surgeries	2.2	1.5	0–13	2.1–2.3

^aFactors included in the backward regression analysis for the physical component.

^bFactors included in the backward regression analysis for the mental component.

Table VI shows that a significant proportion of women experienced that endometriosis had a negative effect on work (51%), relationships (50%) and education (16%) at some time during their life, i.e. time between the first symptoms and the day of completing the questionnaire

Table III Patient with at least one surgery.

	n	Percentage
Laparoscopy	555	60
Laparotomy	68	7
Both laparoscopy and laparotomy	270	29
Of which patients with major surgeries		
Ovariectomy	211	23
Hysterectomy	108	12
Bowel procedure ^a	202	22
Bladder procedure ^a	81	9
Ureter procedure	62	7
No surgery	38	4

Women could have had one or more laparoscopies or laparotomies. The same applies for ovariectomies, bowel procedures, etc. Furthermore, women could have more than one procedure in one surgery, for example both hysterectomy and ovariectomy.

^aFactors included in the backward regression analysis for the physical component.

Table IV Hormonal treatments (lifetime perspective).

	n	Percentage
Oral contraceptives	497	53
Progestagen	211	23
GnRH analogues	387	42
Levonorgestrel-releasing intrauterine system	108	12
Other (danazol, letrozol)	44	5
No hormonal treatment	194	21
Two or more hormonal treatments	387	42

Women could have used more than one treatment.

Table V Subfertility and subfertility treatments (lifetime perspective).

	n	Percentage
Subfertility	407	44
Treatment subfertility	391	42
Of which ^a , hormone treatment	171	18
IUI	182	20
IVF	266	29

^aWomen could have more than one treatment IUI: intrauterine insemination.

Table VI Effect of endometriosis on education, work and social wellbeing (lifetime perspective).

	n	Percentage
Time lost to education ^{a,b}	150	16
Affected job ^{a,b}	472	51
Affected relationship ^{a,b}	468	50

^aFactors included in the backward regression analysis for the physical component.

^bFactors included in the backward regression analysis for the mental component.

Table VII Current symptoms.

	Number of patients	Percentage
Dysmenorrhoea ^{a,b}	533	57
Dyspareunia ^{a,b}	441	47
Pain at other times (chronic pain) ^{a,b}	554	60

^aFactors included in the backward regression analysis for the physical component.

^bFactors included in the backward regression analysis for the mental component.

(lifetime perspective). A substantial percentage of these women (48%) had to reduce working hours; however, only a few women lost or changed a job due to endometriosis (Supplementary data, Table SI). Of the women with affected relationships, 67% experienced significant

problems with their partner due to endometriosis (34% of the total of 931 investigated women) and 19% of women considered endometriosis as a cause of their divorce (10% of the 931 investigated women) (Supplementary data, Table SI).

Table VII shows the three main endometriosis pain symptoms that were present at the time of completing the questionnaire (current symptoms). Dysmenorrhoea was reported by 57%, dyspareunia was reported by 47% and chronic pain was reported by 60% of women. In total 71% of the women reported at least one of these three painful symptoms. Of the women with dyspareunia, 80% had to alter their sexual behaviour in terms of interrupting or avoiding intercourse due to pain (Supplementary data, Table SII).

Table VIII shows the results of the eight dimensions and summary components of the SF-36v2 HRQoL questionnaires (current situation). For age categories 25–34 years and 35–44 years, scores were compared with the norm-based scores of women in the same age category of the US general population and the calculated effect sizes (Cohen, 1988; Ware et al., 1993, 2000). There was a significant reduction of quality of life for all domains of the SF-36v2 and within both age categories. The largest reduction of quality of life was measured for the domains general health (25–34 years: 0.70 SD; 35–44 years: 0.66 SD), social functioning (25–34 years: 0.69 SD; 35–44 years: 0.66 SD) and mental role limitation (25–34 years: 0.62 SD; 35–34 years: 0.76 SD). The reduction of quality of life on the physical summary component was comparable with the reduction on the mental component.

According to the multivariate regression analysis, conducted to explore which factors had an independent effect on the PCS and MCS, the final model retained 7 out of 19 factors included in the analysis with the physical component scale as a dependent variable. Quality of life was positively affected by income and negatively affected by the number of comorbidities, presence of chronic pain, number of physicians consulted, presence of dyspareunia, effect on job and number of laparotomies (Supplementary data, Table SIIIa). Out of 15 factors included in the multivariate regression analysis with the mental component scale as a dependent variable, 5 were retained in the final model. Quality of life was positively affected by 'having a partner present' and negatively affected by BMI, presence of chronic pain, number of co-morbidities and presence of dyspareunia (Supplementary data, Table SIIIb). Number of co-morbidities, chronic pain and dyspareunia were the common factors with a negative effect on quality of life in both regression models.

Discussion

In this multicentre international questionnaire-based cross-sectional survey, the HRQoL of 931 women visiting tertiary care centres because of endometriosis-associated symptoms was assessed. This large number of participants provided the opportunity to present a well-founded estimation of the impact of endometriosis on several aspects of life as well as which factors contribute to the decreased quality of life in these women.

Women suffering from endometriosis reported negative effects on education, work and social wellbeing

Results from the WERF GSWH questionnaire revealed a profound impact of endometriosis on education, work and social wellbeing experienced in

Table VIII Results of the SF-36v2 HRQoL questionnaires, according to age (years).

	Endometriosis norm-based score	Population norm-based score	P-value	Effect size (Cohen's <i>d</i>)
Physical functioning	49.7			
Age group 25–34 (<i>n</i> = 349)	50.3	53.0	<0.01	0.27 SD
Age group 35–44 (<i>n</i> = 429)	49.8	51.5	<0.01	0.17 SD
Physical role limitation	45.3			
Age group 25–34 (<i>n</i> = 347)	45.3	51.8	<0.01	0.65 SD
Age group 35–44 (<i>n</i> = 428)	45.6	51.5	<0.01	0.58 SD
Pain	45.6			
Age group 25–34 (<i>n</i> = 349)	45.7	51.5	<0.01	0.57 SD
Age group 35–44 (<i>n</i> = 429)	45.7	49.9	<0.01	0.42 SD
General health	43.5			
Age group 25–34 (<i>n</i> = 351)	43.9	50.8	<0.01	0.70 SD
Age group 35–44 (<i>n</i> = 431)	43.6	50.3	<0.01	0.66 SD
Vitality	45.7			
Age group 25–34 (<i>n</i> = 348)	45.8	48.1	<0.01	0.23 SD
Age group 35–44 (<i>n</i> = 429)	46.1	48.4	<0.01	0.23 SD
Social functioning	42.5			
Age group 25–34 (<i>n</i> = 350)	42.6	49.5	<0.01	0.69 SD
Age group 35–44 (<i>n</i> = 431)	42.7	49.4	<0.01	0.66 SD
Mental role limitation	42.4			
Age group 25–34 (<i>n</i> = 346)	43.6	49.8	<0.01	0.62 SD
Age group 35–44 (<i>n</i> = 428)	42.5	50.1	<0.01	0.76 SD
Mental health	43.9			
Age group 25–34 (<i>n</i> = 348)	44.2	47.8	<0.01	0.36 SD
Age group 35–44 (<i>n</i> = 428)	44.1	47.9	<0.01	0.38 SD
Summary components				
Physical component	47.9			
Age group 25–34 (<i>n</i> = 345)	47.9	53.0	<0.01	0.51 SD
Age group 35–44 (<i>n</i> = 425)	48.1	51.6	<0.01	0.35 SD
Mental component	42.0			
Age group 25–34 (<i>n</i> = 346)	42.5	47.1	<0.01	0.46 SD
Age group 35–44 (<i>n</i> = 426)	42.2	47.9	<0.01	0.57 SD

the period between women's first symptoms and completing the questionnaire. The impact on education appeared to be less pronounced, since only 16% of the responding women indicated that they lost significant time of their education due to endometriosis-associated symptoms. This might be caused by the fact that the mean reported age at first symptoms is 24 years at which time most women have finished their formal education. In contrast, the effect of endometriosis on work was clearly noteworthy with 51% of women stating that endometriosis significantly affected their job at some time during their life. Very importantly, endometriosis had a profound impact on relationships in half of the participating women. Many of them experienced significant problems with their partner due to endometriosis and some of them considered endometriosis as a cause of their divorce. Our data confirm the negative influence of endometriosis on education, work and social wellbeing as has been addressed in earlier studies. In one previous study on 78 women diagnosed with endometriosis 15 years prior to the study, women reported that in this 15-year period, 8.5% suffered from an affected education, 49.3% had impaired work

ability, 15% had serious problems in their relationships and 7.7% suffered from a broken relationship due to the symptoms of endometriosis (Fager-vold et al., 2009). In another study of 107 women with previous surgery for endometriosis, work was affected in 66% (Fourquet et al., 2010).

Women continued to suffer from dysmenorrhoea, chronic pelvic pain and dyspareunia, despite treatment

In the interpretation of symptoms that were present at the time the questionnaire was completed (current symptoms), it should be taken into account that women included in the study had received multiple treatments including several hormonal treatments, fertility treatments and, for most, at least one surgical intervention. Despite these treatments, the majority of the women were still not symptom free. More than half of the women still reported dysmenorrhoea, with a substantial group having such severe pain that it prevented them from going to work or

they had to lay down frequently. More than half of the women reported chronic pelvic pain and almost half of the women suffered from dyspareunia with, as a result, an interruption or avoidance of intercourse because of pain. The high prevalence of symptoms in our study is consistent with the results from three earlier studies in considerably smaller cohorts of women with chronic endometriosis patients who frequently reported both dysmenorrhoea (71–94%) and dyspareunia (32–70%) (Fagervold *et al.*, 2009; Fourquet *et al.*, 2010; Tripoli *et al.*, 2011). It can be concluded that despite multiple treatments in tertiary care centres, it may not be possible to reduce the prevalence of symptoms with that of an otherwise healthy population of women as described, for example, in the study by Jamieson, where dysmenorrhoea was present in 26%, dyspareunia in 20% and chronic pain in 16% of the women (Jamieson and Steege, 1996). Nevertheless, the literature indicates that, overall, these patients still have improved quality of life when compared with the situation before treatment, even though specific symptoms persisted after treatment or recurred after a certain symptom-free period (Vercellini *et al.*, 2009; Berlanda *et al.*, 2010).

Women with endometriosis had impaired quality of life

The SF-36v2 norm-based scores of the eight domains and summary component were significantly lower than the norm-based scores of the control population, indicating that women with endometriosis had impaired quality of life associated with their condition. Based on the calculated effect sizes (Cohen's *d*) the effect of endometriosis on HRQoL was considered as large (around 0.8) for general health, social functioning and mental role limitation; moderate (around 0.5) for physical role limitation and pain; small (around 0.2) for physical functioning, vitality and mental health. The effect sizes found in women with endometriosis were comparable with effect sizes found for Crohn's disease. In 635 patients with Crohn's disease from 39 Spanish hospitals, the effect size was large for general health, social functioning, physical role limitation and vitality; moderate for role mental role limitation, pain and mental health and low for physical function (Juan *et al.*, 2003).

Dyspareunia, chronic pain and number of co-morbidities had a negative effect on quality of life

The multivariate regression analysis, executed to designate which factors had an independent effect on quality of life, revealed that the number of co-morbidities had a significant negative effect on both the physical and mental components of the SF-36v2. The number of co-morbidities can be considered an important health status indicator which is indeed expected to affect generic quality of life. Besides number of co-morbidities, only dyspareunia and chronic pain were common factors in both regression models. The importance of these two symptoms affecting the quality of life is strengthened by the fact that 50% of the women suffered from dyspareunia and almost 60% of the women suffered from chronic pelvic pain. Consistent with our study, a comparable association between affected sexual life and lower quality of life score was revealed in a population of women experiencing infertility (Chachamovich *et al.*, 2007).

Dysmenorrhoea was not found to be a significant factor in the multivariate analysis, showing no independent effect on either the physical or the mental component. However, this conclusion should be drawn with caution. Women with amenorrhoea due to ovariectomy or medication

were classified as 'no dysmenorrhoea' in the used WERF GSWH questionnaire (Nnoaham *et al.*, 2011) because, by the nature of the condition, they can no longer have dysmenorrhoea. Affected work due to endometriosis had a negative effect on the physical component of the quality of life measurement. Nevertheless, the causality of this relationship remains uncertain. It can be assumed that work affected by endometriosis-associated symptoms results in a lower quality of life. On the contrary, a lower quality of life might affect work. Having a partner appeared to be a factor with a strong positive effect on the mental component of quality of life. It is understandable that having partner support might be instrumental in increasing the mental aspects of women's quality of life. However, this effect may not be exclusively reserved for women with endometriosis.

From this study questions arise on directions for new investigations. For instance, this study revealed that half of the women still suffer from dyspareunia, and dyspareunia had a significant effect on quality of life. Furthermore, a large number of the women had significant problems with their partner, while having a partner improved their quality of life. These results suggest interactions between dyspareunia, sexual (dys)function and the quality of the relationship. To clarify these interactions and develop ways to cope with dyspareunia, to limit sexual dysfunction and to strengthen relationships, more in-depth research should be carried out.

Limitations and strengths of the study

Some limitations of the present study should be taken into account. A cross-sectional design was used, which does not permit analysis of any causal inference. Longitudinal studies would allow the confirmation of some causal assumptions derived by the described associations. In order to compare the quality of life of women with endometriosis with a general population, the official norm-based scores derived from the 1998 US general population by Qualitymetric Incorporated were used (Ware *et al.*, 2000). It has to be recognized that these scores were collected 10 years before the current study and only included women from the USA, while the current study included women from Europe as well as from the USA. However, the official 1998 US general population scores were not updated and there are no norm-based scores available derived from both European and US women. In 2004–2005 Maglante *et al.* made an attempt to update the norm-based scores (Maglante *et al.*, 2012). This resulted in higher norm-based scores than the original ones and there were no scores available for women below the age of 35 years. Therefore, in this study the US 1998 scores were used, which led to a more conservative estimation of the decreased quality of life in women with endometriosis.

The method of inclusion implies that women with moderate-to-severe endometriosis are possibly over-represented in the current patient sample, because women were enrolled in tertiary care centres, which typically treat more complex and referred cases of endometriosis. Preferably, apart from women treated in tertiary care centres, this type of investigation should include women treated in general hospitals and by general practitioners. Finally, the response rate was low (29%) (Cummings *et al.*, 2001), possibly due the fact that women were approached by mail rather than during an outpatient contact. The subsample of women who participated in the study may have been highly motivated to answer the questions, possibly because they were more symptomatic than the non-responders. Conversely, non-responders

may not have participated because they did not want a daily or weekly reminder of the impact of their disease. A non-responder investigation of basic characteristics, such as r-AFS stage and number of surgeries, would have been informative to answer the question of whether patients with more serious endometriosis were over represented in our study. However, this was not feasible because no IRB approval was given to conduct chart review on women who have not given their consent for the study in some of the participating countries. Nevertheless, the patient population appears to be representative of the overall population with endometriosis in a given country (Gylfason et al., 2010; Nnoaham et al., 2011; Simoens et al., 2012). Altogether, because of the inclusion of tertiary care centres and the low response rate, we admit that some uncertainty exists regarding possible over-representation of women with more serious endometriosis in our study population.

The strength of this study is the large number of participants and the international multi-centre approach. Moreover, these findings represent a large group of women with endometriosis, in all phases of the disease, from 10 different countries, which increase the generalizability of the data. In addition, this study gathered important patient-reported outcomes on symptoms and quality of life after treatment and the relation between these symptoms and quality of life.

Future directions

This study has taught us that medical and surgical treatment of the disease at present has not been completely satisfactory, i.e. despite multiple treatments, many women still suffer from frequent symptoms, including chronic pain, dysmenorrhoea and dyspareunia. Endometriosis is a true chronic disease that, in most women, cannot be cured but only brought 'under control' (Vercellini et al., 2009). A treatment that solely aims to eradicate the underlying disease is not sufficient. To improve the quality of life of these women the medical care should also address the emotional, sexual and social problems that come with the disease. Therefore, besides continuation of improving surgical techniques and medical therapy, future directions in treatment should also include teaching patients how to cope with chronic pelvic pain, to explore ways to have sexual intercourse without pain and to teach patients how to strengthen relationships with their partner and friends so they will be supportive in coping with the disease instead of drifting apart due to potential misunderstandings. Furthermore, strategies should be developed which provide guidance for women and employers in finding ways to manage the impact of symptoms of endometriosis during work. A patient-centred approach towards endometriosis care, with extensive co-operation across disciplines, such as psychologists, sexologists and social workers, might be a valuable strategy to meet these challenges.

Conclusion

Many women with endometriosis have impaired quality of life and continue to suffer from endometriosis-associated symptoms even when their disease was managed in tertiary care centres. Dyspareunia and chronic pain were two factors with a significant impact on both the physical and mental components of quality of life.

Supplementary data

Supplementary data are available at <http://humrep.oxfordjournals.org/>.

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Authors' roles

A.A.G., T.M.D., G.A.J.D., C.D.D., L.H. and S.S. conceived and designed the EndoCost study, analysed and interpreted the data, wrote the first draft of the manuscript and supervised the study. All other authors were involved in the data collection and critical revision of the manuscript, and provided technical support.

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Conflict of interest

L.H. is the chief executive and T.M.D. was a board member of WERF at the time of funding. T.M.D. holds the Merck-Serono Chair in Reproductive Medicine and Surgery, and the Ferring Chair in Reproductive Medicine at the Katholieke Universiteit Leuven in Belgium and has served as consultant/research collaborator for Merck-Serono, Schering-Plough, Astellas and Arresto.

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Appendix

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