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## ARTICLE



# What is the societal burden of endometriosis-associated symptoms? A prospective Belgian study


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**Abstract** Endometriosis is a complex disease that affects a large number of women of reproductive age and imposes a significant burden on patients and society. The aim of this study was to evaluate diagnosis, comorbidities, healthcare resource use, treatment patterns, costs and quality of life of women with endometriosis seen in a Belgian tertiary care centre. A total of 134 patients were included in a prospective questionnaire-based cost-of-illness study. Patients were diagnosed after a median delay of 2 years after onset of symptoms. Almost all patients reported having at least one comorbidity. Total annual costs per patient were €9872 (95% confidence interval €7930–11,870), with costs of productivity loss representing 75% of total costs. Hospitalizations, surgeries, infertility treatments, pain and anxiety increased total costs significantly ( $P \leq 0.001$ ). Patients generated an average of 0.82 QaLY over a 1-year time horizon. This study showed that direct and indirect costs attributable to endometriosis-associated symptoms are substantial. Earlier diagnosis and cost-effective treatment of endometriosis may decrease productivity loss, quality of life impairment and healthcare consumption and consequently reduce total costs to patients and society. 

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**KEYWORDS:** comorbidities, costs, endometriosis, quality of life, resource use, treatment

## Introduction

Endometriosis is a gynaecological disorder defined as the presence of endometrial-like tissue outside the uterus, associated with a chronic, inflammatory reaction (Kennedy et al., 2005). Ectopic tissue can be found in the pelvis, affecting the peritoneum and pelvic organs. Endometriosis requires invasive surgery to diagnose, based on laparoscopic visualization of implants. Therefore, the prevalence of endometriosis in the general population is difficult to determine. An estimated 10% of women of reproductive age are affected (Anon, 1994; Eskenazi and Warner, 1997; Meuleman et al., 2009).

Endometriosis is associated with a variety of symptoms, mainly consisting of pelvic pain (e.g. dysmenorrhoea, chronic pelvic pain, deep dyspareunia) and subfertility, but can also remain asymptomatic. Symptoms are often non-specific, as a result of which endometriosis is often misdiagnosed or remains undiagnosed for years (Rogers et al., 2009).

At present, there is no curative treatment available for endometriosis and current treatment strategies aim to reduce symptoms. Medical treatment is based on hormonal suppression of ovarian function by the use of combined oral contraceptives, progestins or gonadorelin analogues, while surgical treatment aims to remove all endometriotic tissue and to restore normal anatomy. Despite adequate treatment, some women remain symptomatic and 5-year recurrence rates up to 50% are reported (Guo, 2009).

Endometriosis-associated symptoms affect the patient's physical, mental and social wellbeing (Kennedy et al., 2005) and also impose a substantial economic burden on patients, their families and society at large (Gao et al., 2006; Simoens et al., 2007, 2011b). The international multicentre World Endometriosis Research Foundation (WERF) EndoCost study measured quality of life and costs from a societal perspective revealing annual total costs of €9500 (95% CI €8559–10,599) per woman (Simoens et al., 2012). The estimated national societal burden ranged from €0.8 million in Denmark to €49.6 billion in the USA. Factors contributing to the cost of endometriosis included costs related to the diagnosis and treatment of endometriosis and its associated symptoms (i.e. infertility) and indirect costs associated with reduced quality of life and reduced ability to work.

The aim of this paper is to present the Belgian cost and quality of life results from the international WERF EndoCost study. Belgian-specific estimates are provided since differences in organization and financing of healthcare systems and differences in the management of endometriosis may hamper comparison between countries. Additionally, an in-depth analysis of the management of endometriosis in Belgium is carried out focusing on diagnosis, comorbidities, resource use and treatment of endometriosis under common clinical practice conditions.

## Materials and methods

A multicentre analysis was set up by the WERF EndoCost Consortium to provide cost and quality of life estimates of women with endometriosis-associated symptoms from different countries. The study protocol of the international

WERF EndoCost study is reported in detail elsewhere (Simoens et al., 2011a). Only a brief overview is provided here, with focus on the methods used for the Belgium-specific data collection.

## Study design and patients

A prospective prevalence-based cost-of-illness study was performed to measure resource use, costs and quality of life of women treated for endometriosis-associated symptoms in the Leuven University Fertility Center (University Hospitals Leuven, Belgium), a tertiary referral centre for endometriosis.

Women with a laparoscopic and/or histological diagnosis of endometriosis with at least one endometriosis related patient contact in the calendar year 2008 were enrolled in the study. The diagnosis was not necessarily made in this time period and patients with an earlier diagnosis of endometriosis were also included. Prior to enrolment, patients were informed about the study objective and gave their written informed consent. The study was approved by the ethical committee of University Hospitals Leuven (reference no. B32220085251, approved 23 December 2008).

## Data collection

Information on volume of healthcare resource use and health-related quality of life related to endometriosis and its associated symptoms was collected during a 2-month period (October–November 2009) from patients and physicians by means of prospective questionnaires. Patients were explicitly asked to include only aspects attributable to endometriosis. Demographics and clinical characteristics including age at first symptoms and type of initial symptoms were derived from retrospective patient questionnaires. A 29-item list was used to assess comorbidities. If available, data on endometriosis severity at first laparoscopic diagnosis were obtained according to the ASRM classification system (Canis et al., 1997).

Costing involved identification, measuring and valuing of relevant resources used during the measurement period and was performed using a bottom-up approach. The study took a societal perspective including costs incurred by the patient (i.e. co-payment or full payment for medicines and/or care), the National Institute for Health and Disability Insurance, and by society at large (i.e. costs of reduced productivity).

## Direct healthcare costs

Prospective patient questionnaires collected healthcare resource use data relating to: (i) outpatient physician visits including type of profession and number of visits; (ii) medication (both prescribed and over-the-counter) with trade name, daily dose and duration of administration; (iii) number and type of monitoring tests; (iv) number and duration of hospitalizations; (v) other treatments (i.e. psychologist visits) including description of treatment and number of hours; and (vi) informal care provided by family/friends (type and number of hours). The prospective hospital questionnaire elicited information about the number and type of

surgical procedures and infertility treatments (medically assisted reproduction including assisted reproductive technology (Zegers-Hochschild et al., 2009). Valuation of resource use was based on charges reflecting official list prices (including the third-party payer reimbursement and the woman's co-payment). Drug costs per unit of administration were calculated by dividing the cost per package (derived from the Belgian Centre for Pharmaco-therapeutic Information) by the number of units per package. Overall costs of medication were calculated by multiplying unit cost by the number of intakes.

### Direct non-healthcare costs

Patients were asked to report transportation costs to healthcare providers and costs from receiving additional support with household activities.

### Indirect non-healthcare costs

Indirect non-healthcare costs represented productivity loss related to work impairment. The general health version of the Work Productivity and Activity Impairment questionnaire (Reilly et al., 1993) was used to assess absenteeism (the percentage of work time missed), presenteeism (the percentage of impairment while at work) and overall work impairment in employed women because of endometriosis-associated symptoms and to assess the impact of symptoms on usual daily activities other than work. One-week productivity loss was valued using 2009 national estimates of gross weekly earnings (derived from Statistics Belgium).

### Quality of life

Health-related quality of life was measured using the generic preference-based EuroQol-5D instrument (The Euro-Qol Group, 1990). This instrument covers five dimensions of health-related quality of life including mobility, self-care, daily activities, pain/discomfort and anxiety/depression which can each be rated at three levels: 'no problems' (score 1), 'some problems' (score 2), and 'major problems' (score 3). Each combination of these dimensions and response scores represents a health state. Using the Belgian health utility index, these health states were valued on a 0–1 utility scale, with 0 representing death and 1 representing full health (Anon, 2012). Utility values were multiplied with the time period for which a particular health state lasts to compute quality-adjusted life years (QaLY).

### Statistical analysis

Descriptive statistics were used to describe demographic and clinical variables of patients and healthcare resource use; relative frequencies were used for categorical data and mean ( $\pm$ standard deviation (SD)) or median (range) for continuous data. Estimates of costs and health-related quality of life during October and November 2009 were multiplied by six to generate annual estimates. The price year was 2009 and costs were expressed in Euros. If resource use was unavailable, a conservative approach was used

and the associated cost was set to zero. Women were contacted to supplement answers for missing data and the mean imputation technique was used to deal with remaining missing data. Costs were described as mean, standard deviation, minimum/maximum and 95% confidence intervals. The chi-squared test and Mann–Whitney *U*-test were used to compare groups of patients assuming non-normality of data. All tests were two-sided and the level of significance was set at 0.05. Data were analysed using Statistical Package for the Social Sciences (SPSS for Windows, version 20, IBM SPSS Inc., USA).

## Results

### Patient characteristics and comorbidities

In total, 134 women with endometriosis-associated symptoms and a mean age (SD) of 33 years ( $\pm$ 4 years) were enrolled in the study. Demographic and clinical characteristics are summarized in Table 1. There was 94% of patients (126/134) who reported one or more comorbidities. The most frequently reported comorbidities were infertility (103/134, 77%), migraine (35/134, 26%) and depression (18/134, 13%).

### Diagnosis

Median age at which the first symptoms occurred was 26 (range 11–40). Seventy % of patients (94/134) presented with multiple symptoms. The frequency of initial symptoms is listed in Table 1. Dysmenorrhoea was the most common initial symptom in all patients and was present more frequently in adolescents and young adults under 21 years of age at first symptoms ( $P < 0.001$ ), while subfertility was more often present in the group aged above 21 years ( $P < 0.001$ ). Median age at the time of diagnosis was 29 years (range 14–43) after a median diagnostic delay of 2 years (range 0–33) between onset of symptoms and diagnosis of endometriosis. A prolonged delay in diagnosis was observed when symptoms started in adolescence and young adulthood under 21 years of age ( $P < 0.001$ ) and in patients presenting with dysmenorrhoea ( $P < 0.001$ ), while women with subfertility showed the shortest delay ( $P < 0.001$ ). A delay originated from the time delay between onset of symptoms and the patient's initiative for seeking help (median 1 (range 0–16) year). For dysmenorrhoea, a significantly longer delay was observed ( $P = 0.008$ ), while subfertility was associated with significantly shorter delays in seeking help ( $P = 0.003$ ).

### Resource use and treatment

The use of healthcare resources is summarized in Table 2. During the 2-month study period, 10% of patients (13/134) were hospitalized with a mean length of stay (SD) of 2 ( $\pm$ 1) days. Hospitalizations were linked to surgical procedures and/or infertility treatments. Of 134 patients, six patients (4%) underwent therapeutic surgery for endometriosis, seven patients (5%) were treated with IVF and three patients (2%) received intrauterine insemination. The number of

**Table 1** Demographic and clinical characteristics.

<i>Characteristic</i>	<i>No. of women</i>	<i>Study population</i>
Age (years)	134	33 ± 4 (21–44)
Height (cm)	133	168 ± 6 (153–184)
Weight (kg)	133	66 ± 11 (105–65)
Current marital status	134	
Single and living with partner		34 (25)
Married		87 (65)
Single and not living with partner		9 (7)
Divorced/separated		4 (3)
Ethnic origin	117	
Asian/Oriental		1 (1)
Hispanic or Latino		1 (1)
North/West European		105 (90)
East European		4 (3)
South European		4 (3)
Mixed race		2 (2)
Occupation	134	
Employee		114 (85)
Self-employed		12 (9)
Housewife/carer		6 (4)
In education		5 (4)
Voluntary work		2 (2)
Unable to work due to endometriosis		4 (3)
Unable to work due to other reasons		5 (4)
r-AFS-stage	134	
Minimal–mild (stage I–II)		13 (10)
Moderate–severe (stage III–IV)		33 (25)
Unknown		88 (66)
Age at first symptoms (years)	129	24 ± 7 (10–40)
Age at diagnosis (years)	131	29 ± 5 (14–43)
Diagnostic delay (years)	128	5 ± 6 0–33)
Initial symptoms	134	
Dysmenorrhoea		106 (79)
Deep dyspareunia		35 (26)
Pelvic pain		74 (55)
Ovulation pain		31 (23)
Cyclical or perimenstrual symptoms		57 (43)
Infertility		54 (40)
Fatigue		28 (21)
Comorbidities	134	
Infertility		103 (77)
Migraine		35 (26)
Depression		18 (13)
Eczema		16 (12)
Spine problems		15 (11)
Fibroid uterus		12 (9)
Asthma		11 (8)

Table 1 (continued)

Characteristic	No. of women	Study population
Scoliosis		9 (7)
Thyroid disease		8 (6)
Chronic fatigue syndrome		4 (3)
Deafness		3 (2)
Polycystic ovary syndrome		3 (2)

Values are mean  $\pm$  SD (range) or *n* (%).

Table 2 Direct healthcare resource use and costs in endometriosis patients.

Resource type	Resource used (%)	Quantity used in 2-month period	Cost per patient (€)	
			Mean $\pm$ SD	Range
Hospitalization	9.7	26 days	304.87 $\pm$ 1148.96	0–6834.78
Surgery	4	6	335.39 $\pm$ 2024.43	0–20367.12
Infertility treatment	7	10	487.74 $\pm$ 1904.03	0–9889.32
IVF	5	7	3120.73 $\pm$ 3120.73	0–9889.32
Intrauterine insemination	2	3	1087.73 $\pm$ 1087.73	0–4696.38
Physician visits	41	196	170.76 $\pm$ 278.13	0–1134.66
Obstetrics and gynaecology	30	136	114.97 $\pm$ 234.09	0–1019.52
General practitioner	15	48	41.24 $\pm$ 124.22	0–805.98
Gastroenterology	2	3	3.87 $\pm$ 25.69	0–172.98
Urology	2	3	2.54 $\pm$ 16.82	0–113.28
Emergency medicine	1	3	4.17 $\pm$ 48.22	0–558.18
Endocrinology	1	2	3.12 $\pm$ 25.48	0–209.34
General surgery	1	1	0.85 $\pm$ 9.79	0–113.28
Monitoring tests	41	221	601.42 $\pm$ 1185.91	0–6060.00
Blood tests	27	109	421.34 $\pm$ 909.82	0–4661.82
Ultrasound scans	29	101	150.55 $\pm$ 312.17	0–1398.18
Intravenous pyelogram	2	3	6.60 $\pm$ 43.78	0–294.84
Bacteriology culture	2	3	1.46 $\pm$ 12.57	0–130.56
Computed tomography	2	2	11.44 $\pm$ 93.30	0–766.62
Barium enema	2	2	8.80 $\pm$ 71.77	0–589.68
Sigmoidoscopy	1	1	1.22 $\pm$ 14.10	0–163.26
Other treatments	41	196	73.39 $\pm$ 258.13	0–2100.00
Medication	51	267	191.03 $\pm$ 511.80	0–3214.02
Nonsteroidal anti-inflammatory drug	20	51	4.21 $\pm$ 36.08	0–416.35
Combined oral contraceptives	16	38	1.94 $\pm$ 5.27	0–28.56
Progestins	16	36	2.80 $\pm$ 8.95	0–45.36
Analgesics	16	32	0.87 $\pm$ 4.07	0–37.44
Gonadotrophins	12	34	17.92 $\pm$ 59.11	0–385.97
Gonadorelin analogues	12	20	7.87 $\pm$ 42.65	0–277.94
Other	16	53	6.62 $\pm$ 34.05	0–304.08
Informal care	19	9814 h	73.24 $\pm$ 655.61	0–7569.00

Mean cost per patient is calculated based on the quantity of each particular resource item used during 2-month period and its unit cost and is generalized to an annual time frame.

outpatient visits per patient to physicians ranged from 0 to 10. Most of the patient visits were made to gynaecologists (136/196, 69%), followed by visits to general practitioners (48/196, 24%). Patient visits also included visits for therapies by other professionals like psychologists ( $n = 4$ , 16 visits), acupuncturists ( $n = 5$ , 11 visits), kinesiotherapists ( $n = 1$ , eight visits) and osteopaths ( $n = 3$ , seven visits).

Among reported medication, the most commonly used drugs were hormonal treatments (47/134 patients, 35%). Progestins and combined oral contraceptives accounted each for 16% of patients, and gonadotrophin-releasing hormone analogues were used in 12% of patients, 20% (26/134) used nonsteroidal anti-inflammatory drugs (NSAID) combined with hormonal treatment (15 patients) or in monotherapy (11 patients). Analgesics were used by 16% (20/134), including 11 patients who used analgesics in combination with hormonal treatments.

### Costs

Average annual total costs of endometriosis were estimated at €9872 (95% CI €7930–11,870) per patient (Table 3). Total costs were dominated by indirect costs of productivity loss (75%, €7434 per woman, 95% CI 5827–8997). Direct healthcare costs represented 23% (€2238, 95% CI 1567–3240) of total costs and were mainly ascribed to surgeries and infertility treatments (37%), monitoring tests (27%) and hospitalizations (14%). Medication and physician visits accounted for 9% and 8%, respectively, of direct healthcare costs. Table 3 shows total endometriosis-related direct healthcare costs broken down by category. Direct non-healthcare costs amounted to 2% of total costs and were caused by transportation costs to healthcare providers (71%) and additional help in household activities (29%). Factors that increased costs significantly included hospitalizations ( $P < 0.001$ ), surgeries ( $P < 0.001$ ), infertility treatments ( $P = 0.001$ ), pain ( $P < 0.001$ ) and symptoms of anxiety or depression ( $P < 0.001$ ). Comorbidities had no significant effect on endometriosis-associated costs.

### Quality of life

With respect to the five dimensions covered by the Euro-QoL-5D, 51% of women reported problems (i.e. response scores 2 or 3) with pain/discomfort, 28% reported problems with anxiety/depression, 27% reported problems with usual activities, 9% reported problems with mobility and 1% reported problems with self-care. Women with endometriosis-associated symptoms generated a mean  $\pm$  SD of  $0.82 \pm 0.18$  (range 0.23–1) QaLY over a 1-year period. Only 33% of women generated 1 QaLY, corresponding to the best possible health state, while 67% of women showed a reduction in quality of life due to endometriosis-associated symptoms.

### Discussion

To the best of the authors' knowledge, this is the first paper to report prospectively collected endometriosis-associated cost and quality of life data from a Belgian tertiary care centre, Leuven University Fertility Center, with regard to comorbidities, diagnosis, resource use and treatment. These results, with an average annual total cost of €9872 per patient (mainly driven by productivity loss) and 0.82 QaLY, are consistent with the results from the international WERF EndoCost study (Simoens et al., 2012). Ideally, costs originating from the time delay between onset of symptoms and diagnosis of endometriosis should also be considered, since delays of up to 33 years were recorded. The results of this study indicate that endometriosis is a complex and costly disease that places a significant burden on patients, the Belgian healthcare system and society.

Endometriosis still remains undiagnosed for years. The median diagnostic delay of 2 years (mean 5 years) between first presentation of symptoms and diagnosis was shorter than reported elsewhere (median 5–9 years; Ballard et al., 2006; Hadfield et al., 1996; Husby et al., 2003; Pugsley and Ballard, 2007), but large variations were observed according to women's age at first presentation of symptoms and the type of presenting symptoms. Adolescents and

**Table 3** Annual costs of endometriosis associated symptoms (2009).

Item	Mean $\pm$ SD	95% CI of the mean	Range
Direct healthcare costs	2237.83 $\pm$ 4711.71	1566.65–3240.14	0–28786.44
Physician visits	170.76 $\pm$ 278.13	127.88–215.53	0–1134.66
Medication	191.03 $\pm$ 511.80	98.36–275.07	0–3214.02
Monitoring tests	601.42 $\pm$ 1185.91	413.13–816.13	0–6060.00
Surgery	823.13 $\pm$ 2719.20	416.86–1357.88	0–20367.12
Other treatments	73.39 $\pm$ 258.13	32.78–117.05	0–2100.00
Informal care	73.24 $\pm$ 655.61	40.00–190.98	0–7569.00
Hospitalization	304.87 $\pm$ 1148.96	112.03–516.48	0–73,986
Direct non-healthcare costs	200.42 $\pm$ 590.72	117.21–321.15	0–5983.20
Transportation	142.28 $\pm$ 540.27	75.51–251.03	0–5983.20
Household support	58.14 $\pm$ 226.22	24.35–103.90	0–1440.00
Indirect costs	7433.62 $\pm$ 9094.41	5827.12–8996.58	0–356200.00
Total costs	9871.87 $\pm$ 11291.29	7930.47–11869.59	0–61450.44

young adults with early symptoms showed longer delays as well as women presenting with menstruation-related symptoms such as dysmenorrhoea. This can be explained by difficulties involved in distinguishing between abnormal menstruation, by menstrual symptoms being normalized by patients and doctors (Ballard et al., 2006), by stigmatization of menstrual problems (Seear, 2009) and by symptoms being suppressed through hormones (Ballard et al., 2006). By contrast, women presenting with subfertility showed the shortest delays in diagnosis. This subset of patients tends to call for assistance much quicker, and early referral to specialized centres also accelerates endometriosis diagnosis. For instance, in this study centre, patients with infertility for at least 1 year with regular menstrual cycles (and whose partners have a normal semen analysis) are recommended to undergo laparoscopic diagnostic investigation (Meuleman et al., 2009). Special attention should be paid to adolescents and young adults with menstruation-related symptoms such as dysmenorrhoea, as this might result in infertility later on (Janssen et al., 2013). Further efforts are needed to accelerate diagnosis of endometriosis by increasing awareness among women and healthcare providers and by early referral to specialized centres.

In the context of early diagnosis of endometriosis, transvaginal hydrolaparoscopy (THL) has been proposed (De Wilde and Brosens, 2012; Gordts et al., 1998) as a safe, efficacious and validated diagnostic technique for the exploration of women with unexplained infertility and for the diagnosis of endometriosis in comparison to standard laparoscopy. However, this technique has not yet routinely been introduced in most centres of reproductive medicine and is unlikely to facilitate early diagnosis of endometriosis for the following reasons. First, specific technical skills to perform THL can only be acquired in centres with a sufficiently large patient population, in view of the learning curve. Secondly, THL is usually carried out under conscious sedation (requiring a day care surgery set up, just like standard laparoscopy) and is associated with a low percentage (less than 1%) of bowel injury (De Wilde and Brosens, 2012), just like standard laparoscopy. Thirdly, equivalence or superiority of THL versus hysterosalpingography as the first-line investigation in infertile women has not been demonstrated (De Wilde and Brosens, 2012). Fourthly, advanced hydrosoneographic techniques have been developed as an alternative to the more invasive THL and the more painful hysterosalpingography to visualize both uterine cavity and tubal patency (Van Schoubroeck et al., 2013). Fifthly, although THL allows the visualization of filmy free-floating adhesions and micropolypoidal lesions on the ovarian surface, the clinical significance of these lesions are unclear. Sixthly, it is not possible during THL to evaluate the anterior vesicouterine compartment or to inspect completely the uterosacral and rectal areas for the presence of endometriosis, which may lead to underdiagnosis of endometriosis. Finally, it is not possible to excise endometriosis lesions at the time of THL, in contrast with standard laparoscopy combining diagnosis and therapy in one single surgical session during day care surgery for women with minimal to moderate endometriosis. This study centre offers standard diagnostic/operative laparoscopy and hysteroscopy to all infertile patients with a regular menstrual cycle whose male partner has normal sperm quality, regardless of pain symptoms or

transvaginal ultrasound results, since half of them have endometriosis and 40% of those without endometriosis have fertility-reducing pelvic pathology (Meuleman et al., 2009).

Women with endometriosis frequently suffer from comorbid conditions as recognized by other authors (Fuldeore et al., 2010; Sinaii et al., 2002). Amongst them, infertility was the most considerable one, affecting three-quarters of patients in this study. This observation is not surprising in view of the fact that patients were recruited in the Leuven University Fertility Center and the strong association and possibly causal relationship between the presence of endometriosis and infertility (D'Hooghe et al., 2003). The prevalence rate of infertility observed in the current study was higher than those obtained from database studies (5.5–11.6%; Fuldeore et al., 2010; Mirkin et al., 2007). However, infertility rates in endometriosis as high as 30–50% have also been published (Holoch and Lessey, 2010). In the current centre, the prevalence of endometriosis in subfertile women with a regular cycle whose partner has normal sperm quality has been reported to be about 50% (Meuleman et al., 2009).

Comorbidities such as autoimmune diseases, fibromyalgia and chronic fatigue syndrome were less frequently reported in this study, but have also been linked to endometriosis (Sinaii et al., 2002). The presence of comorbidities did not significantly add to healthcare costs, although others (Mirkin et al., 2007) have found that comorbidities are responsible for an increase of costs with approximately 15–50% in women with endometriosis.

Although not responsible for major costs, medication is being used in the majority of patients. Two main categories were distinguished: hormonal treatments and NSAID/analgesics. To date, there is inconclusive evidence to show that NSAID and analgesics are effective in managing pain caused by endometriosis (Allen et al., 2009) but they are often used in the medical treatment of dysmenorrhoea or other inflammatory diseases, although long-term treatment is not recommended. According to current guidelines on hormonal treatments, combined oral contraceptives, danazol, gestrinone, medroxyprogesterone acetate and gonadoreline analogues seem to be equally effective against pain and their choice should therefore be based on costs and side effects (Kennedy et al., 2005). A notable proportion of patients treated with hormones required additional consumption of NSAID or analgesics, indicating that unsatisfactory symptom control is achieved by hormones alone. This is also reflected in quality of life estimates where more than half of patients reported experiencing pain, which could also explain the high number of physician visits per patient and their need for alternative treatments.

Limitations of the EndoCost studies have been addressed before (Simoens et al., 2012) and are briefly summarized here. In the first place, patient selection could have been biased since only symptomatic endometriosis patients were included in the study; in spite of this, a broad selection of patients was chosen by including both newly diagnosed patients and women with a previous diagnosis of endometriosis. Secondly, patients were recruited in a tertiary referral centre for infertility and endometriosis, therefore relatively more infertile patients (since a diagnostic laparoscopy was performed early in the diagnostic work-up) or more severe cases of endometriosis could have been included; in

addition, several patients already had a diagnosis of endometriosis when referred to this centre, so ASRM staging at first diagnosis was frequently lacking. Thirdly, resource use was self-reported by patients and patients were explicitly asked to only include endometriosis-related resource use; in order to avoid recall bias, data were collected prospectively within a short 2-month period, but yet long enough to record cyclical and perimenstrual symptoms of endometriosis.

In conclusion, this study showed that total endometriosis-associated costs are dominated by indirect costs from work productivity loss and driven by infertility treatments, surgeries, hospitalizations, anxiety and pain. Earlier diagnosis and more appropriate treatment of endometriosis may decrease productivity loss and healthcare consumption and consequently reduce total costs to patients and society.

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## References

- Allen, C., Hopewell, S., Prentice, A., Gregory, D., 2009. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst. Rev.*, CD004753.
- Ballard, K., Lowton, K., Wright, J., 2006. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. *Fertil. Steril.* 86, 1296–1301.
- Canis, M., Donnez, J.G., Guzik, D.S., Halme, J.K., Rock, J.A., Schenken, R.S., Vernon, M.W., 1997. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil. Steril.* 67, 817–821.
- de Wilde, R.L., Brosens, I., 2012. Rationale of first-line endoscopy-based fertility exploration using transvaginal hydrolaparoscopy and minihysteroscopy. *Hum. Reprod.* 27, 2247–2253.
- D'Hooghe, T.M., Debrock, S., Hill, J.A., Meuleman, C., 2003. Endometriosis and subfertility: is the relationship resolved? *Semin. Reprod. Med.* 21, 243–254.
- Eskenazi, B., Warner, M.L., 1997. Epidemiology of endometriosis. *Obstet. Gynecol. Clin. North Am.* 24, 235–258.
- Fuldeore, M., Wu, N., Boulanger, L., Chwalisz, K., Marx, S., 2010. Prevalence rate and direct cost of surgical procedures among women with newly diagnosed endometriosis. *Hum. Reprod.* 25, 1158–1159.
- Gao, X., Outley, J., Botteman, M., Spalding, J., Simon, J.A., Pashos, C.L., 2006. Economic burden of endometriosis. *Fertil. Steril.* 86, 1561–1572.
- Gordts, S., Campo, R., Rombauts, L., Brosens, I., 1998. Transvaginal salpingoscopy: an office procedure for infertility investigation. *Fertil. Steril.* 70, 523–526.
- Guo, S.W., 2009. Recurrence of endometriosis and its control. *Hum. Reprod. Update* 15, 441–461.
- Hadfield, R., Mardon, H., Barlow, D., Kennedy, S., 1996. Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. *Hum. Reprod.* 11, 878–880.
- Holoch, K.J., Lessey, B.A., 2010. Endometriosis and infertility. *Clin. Obstet. Gynecol.* 53, 429–438.
- Husby, G.K., Haugen, R.S., Moen, M.H., 2003. Diagnostic delay in women with pain and endometriosis. *Acta Obstet. Gynecol. Scand.* 82, 649–653.
- Janssen, E.B., Rijkers, A.C., Hoppenbrouwers, K., Meuleman, C., D'Hooghe, T.M., 2013. Prevalence of endometriosis diagnosed by laparoscopy in adolescents with dysmenorrhea or chronic pelvic pain: a systematic review. *Hum. Reprod. Update* 19, 570–582.
- Kennedy, S., Bergqvist, A., Chapron, C., d'Hooghe, T., Dunselman, G., Greb, R., Hummelshoj, L., Prentice, A., Saridogan, E., 2005. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum. Reprod.* 20, 2698–2704.
- Meuleman, C., Vandenabeele, B., Fieuws, S., Spiessens, C., Timmerman, D., D'Hooghe, T., 2009. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil. Steril.* 92, 68–74.
- Mirkin, D., Murphy-Barron, C., Iwasaki, K., 2007. Actuarial analysis of private payer administrative claims data for women with endometriosis. *J. Manag. Care Pharm.* 13, 262–272.
- Pugsley, Z., Ballard, K., 2007. Management of endometriosis in general practice: the pathway to diagnosis. *Br. J. Gen. Pract.* 57, 470–476.
- Reilly, M.C., Zbrozek, A.S., Dukes, E.M., 1993. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 4, 353–365.
- Rogers, P.A.W., D'Hooghe, T.M., Fazleabas, A., Gargett, C.E., Giudice, L.C., Montgomery, G.W., Rombauts, L., Salamonsen, L.A., Zondervan, K.T., 2009. Priorities for endometriosis research: recommendations from an international consensus workshop. *Reprod. Sci.* 16, 335–346.
- Seear, K., 2009. The etiquette of endometriosis: stigmatisation, menstrual concealment and the diagnostic delay. *Soc. Sci. Med.* 69, 1220–1227.
- Simoens, S., Hummelshoj, L., d'Hooghe, T., 2007. Endometriosis: cost estimates and methodological perspective. *Hum. Reprod. Update* 13, 395–404.
- Simoens, S., Hummelshoj, L., Dunselman, G., Brandes, I., Dirksen, C., d'Hooghe, T., 2011a. Endometriosis cost assessment (the EndoCost study): a cost-of-illness study protocol. *Gynecol. Obstet. Invest.* 71, 170–176.
- Simoens, S., Meuleman, C., d'Hooghe, T., 2011b. Non-health-care costs associated with endometriosis. *Hum. Reprod.* 26, 2363–2367.
- Simoens, S., Dunselman, G., Dirksen, C., Hummelshoj, L., Bokor, A., Brandes, I., Brodzsky, V., Canis, M., Colombo, G.L., DeLeire, T., Falcone, T., Graham, B., Halis, G., Horne, A., Kanj, O., Kjer, J.J., Kristensen, J., Lebovic, D., Muller, M., Vigano, P., Wullschlegler, M., d'Hooghe, T., 2012. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum. Reprod.* 27, 1292–1299.
- Sinaai, N., Cleary, S.D., Ballweg, M.L., Nieman, L.K., Stratton, P., 2002. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum. Reprod.* 17, 2715–2724.
- The EuroQol Group, 1990. Euroqol – a new facility for the measurement of health-related quality-of-life. *Health Policy* 16, 199–208.
- Van Schoubroeck, D., Van den Bosch, T., Meuleman, C., Tomassetti, C., D'Hooghe, T., Timmerman, D., 2013. The use of a new gel-foam for the evaluation of tubal patency. *Gynecol. Obstet. Invest.* 75, 152–156.



Zegers-Hochschild, F., Adamson, G.D., de Mouzon, J., Ishihara, O., Mansour, R., Nygren, K., Sullivan, E., van der Poel, S., 2009. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary on ART terminology, 2009. *Hum. Reprod.* 24, 2683–2687.

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