

Endometriosis: cost estimates and methodological perspective

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This article aims to provide a systematic review of estimates and methodology of studies quantifying the costs of endometriosis. Included studies were cost-of-illness analyses quantifying the economic impact of endometriosis and cost analyses calculating diagnostic and treatment costs of endometriosis. Annual healthcare costs and costs of productivity loss associated with endometriosis have been estimated at \$2801 and \$1023 per patient, respectively. Extrapolating these findings to the US population, this study calculated that annual costs of endometriosis attained \$22 billion in 2002 assuming a 10% prevalence rate among women of reproductive age. These costs are considerably higher than those related to Crohn's disease or to migraine. To date, it is not possible to determine whether a medical approach is less expensive than a surgical approach to treating endometriosis in patients presenting with chronic pelvic pain. Evidence of endometriosis costs in infertile patients is largely lacking. Cost estimates were biased due to the absence of a control group of patients without endometriosis, inadequate consideration of endometriosis recurrence and restricted scope of costs. There is a need for more and better-designed studies that carry out longitudinal analyses of patients until the cessation of their symptoms or that model the chronic nature of endometriosis.

Keywords: cost estimates; endometriosis; GnRH agonists; laparoscopy

Introduction

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction. The condition is predominantly found in women of reproductive age, from all ethnic and social groups. The associated symptoms can impact on general physical, mental and social well-being (Kennedy *et al.*, 2005). Endometriosis is associated with severe dysmenorrhoea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding, infertility and chronic fatigue. Some affected women, however, remain asymptomatic.

Despite significant improvement in recent years regarding our understanding of the disease, the pathogenesis of endometriosis is still unclear. Retrograde menstruation followed by implantation of viable endometrial cells onto the peritoneum and the pelvic organs, seems to be a key step. However, retrograde menstruation is a universal phenomenon, occurring in at least 76–90% of women undergoing peritoneal dialysis and laparoscopy (Blumenkrantz *et al.*, 1981; Halme *et al.*, 1984), but not all of them develop endometriosis, suggesting that other factors must be involved in determining susceptibility to the disease. Substantial evidence indicates that immunological, inflammatory, genetic and environmental factors play major roles in this process (Zondervan *et al.*, 2001; Mihalyi *et al.*, 2005).

The appearance of endometriosis ranges from small peritoneal lesions to large ovarian endometriotic cysts (endometriomas), and extensive fibrosis and adhesions leading to significant distortion of pelvic anatomy. In a considerable number of cases, endometriosis is progressive (D'Hooghe and Hill, 1996; D'Hooghe *et al.*, 1996). Peritoneal lesions mainly result in pain symptoms but are also associated with subfertility, whereas the more severe forms may cause pain and impair fertility and may lead to pelvic organ dysfunction often requiring extensive surgery. Disease severity is usually classified into four stages (I–IV or minimal to severe), using the revised American Fertility Society (rAFS) system (American Society for Reproductive Medicine, 1996), based on the observations acquired during laparoscopy. However, there is no correlation between the classification system(s) and the type or severity of pain symptoms, although a negative correlation has been reported between the degree of endometriosis and the occurrence of pregnancy following surgery (D'Hooghe *et al.*, 2003a).

The diagnosis of endometriosis may be suspected based on symptoms alone. However, frequently these symptoms are similar or identical to those of other gynaecological or gastrointestinal disorders. As yet, diagnostic approaches such as ultrasound, magnetic resonance imaging (MRI) or blood tests have not been able to deliver satisfactory diagnostic power (Kennedy *et al.*, 2005), thus, the only way to conclusively diagnose endometriosis is laparoscopic surgery with histological confirmation.

Medical or surgical treatment aims to reduce symptoms, and to remove or diminish disease. Medical treatment is based on hormonal suppression, and treatment with progestins, danazol, gestri-none or GnRH agonists appears to be effective in treating pain associated with endometriosis, though their side effects and cost profiles differ (Kennedy *et al.*, 2005). However, conception is not possible during medical treatment, treatment is prolonged (usually for six months), and symptoms are likely to recur following treatment cessation. Surgical treatment is effective in treating endometriosis-associated pain, and is also likely to be used in treating endometriosis-associated subfertility (Marcoux *et al.*, 1997). Finally, it should be noted that the effectiveness of treatment is in part related to the severity of endometriosis, especially in the case of surgery.

There is an extensive medical literature with respect to the diagnosis and treatment of endometriosis (Huntington and Gilmour, 2005). In a context of spiraling health care costs and limited resources, public policy makers and health care payers are also concerned about the costs of endometriosis. Cost estimates can underline the importance of a disease to society when considered alongside its impact on morbidity and mortality and when compared with the economic burden of other diseases. Furthermore, cost studies may allow the identification of the drivers of diagnosis and treatment costs. Finally, cost data can be fed into economic evaluations, so that decision makers can ascertain the efficiency of various approaches to diagnosing and treating endometriosis by examining their effectiveness in relation to their costs.

The aim of this article is to provide a systematic review of the international literature exploring the costs of endometriosis. The objectives of the literature review are three-fold: (i) to determine the level and drivers of endometriosis costs; (ii) to appraise the methodological quality of cost studies and (iii) to propose directions for designing future studies of the costs of endometriosis. The cost estimates and methodological perspective provided by this article can be used to determine priorities for and inform future research on endometriosis.

Materials and methods

Search strategy

Studies were identified by searching the following electronic databases up to October 2006: PubMed, EMBASE, CINAHL, Social Science and Citation Index, Cochrane Library, National Health Service Economic Evaluation Database and EconLit. Search terms included 'endometriosis', 'costs', 'cost-of-illness', 'cost analysis', 'economic burden', 'productivity' alone and in combination with each other. Additionally, the bibliographies of included studies were checked for other relevant studies. The review focused on studies published between 1990 and 2006 in English. Earlier studies were considered to yield cost estimates of limited practical relevance due to likely changes over time in diagnosis and treatment modalities of endometriosis and in the organization and financing of the health care system.

Inclusion criteria

Information about endometriosis costs was derived from cost-of-illness analyses and cost analyses. A cost-of-illness analysis quantifies the economic burden of endometriosis to society by measuring the costs of diagnosing and treating endometriosis as well as the

costs arising as a result of endometriosis (for instance, productivity loss due to time taken off work). A cost analysis compares two or more approaches to diagnosis and treatment of endometriosis (for instance, medical versus surgical therapy).

Studies that enrolled patients suffering from illnesses associated with endometriosis (e.g. pelvic pain, dysmenorrhoea and infertility) were included if they reported costs related to diagnosis and treatment of endometriosis. To qualify for inclusion, studies had to draw on primary data or a cost model, and had to report costs or charges. Also, inclusion was restricted to articles published in peer-reviewed journals. Congress abstracts were not considered because they do not provide sufficient detail of methodology and results.

Data analysis

A data extraction form was completed by the lead author for each study. This form collected information about authors, country, year of costing and estimates of direct and indirect costs. To compare costs between studies, costs were actualized to 2002 values (unless indicated otherwise) using a rate of inflation based on the evolution of the Consumer Price Index (OECD, 2006). All costs were expressed in US dollars using average market exchange rates for the year 2002 (OECD, 2006).

Assessment of methodological quality

A qualitative appraisal was carried out of the methodological quality of cost studies. An appraisal form was filled in by the lead author for each study focusing on sample, epidemiological approach, data collection, design, scope of included costs, time horizon and sensitivity analysis. With respect to the sample, studies can be based on a representative national sample or can enroll a specific group of patients. The epidemiological approach can take the form of a prevalence-based study, which measures costs attributable to a group of patients suffering from endometriosis during a given time interval. Alternatively, an incidence-based study quantifies lifetime costs of endometriosis from onset to death. Data can be collected prospectively/retrospectively from patient medical records, a survey, a claims database or the literature.

Cost studies can be designed as a case series following up patients suffering from endometriosis, a case-control study comparing patients with/without endometriosis, or a cohort study contrasting options for diagnosis and treatment of endometriosis patients. Studies can measure direct costs related to healthcare resource use (e.g. medication, diagnostic and surgical procedures, visits to healthcare providers and hospitalization), direct non-healthcare costs (e.g. transportation to the healthcare provider) and indirect costs arising from time lost from work or reduced productivity at work. Estimates can be presented as charges based on official list prices or costs based on actual resource use. Finally, the robustness of cost estimates can be tested by conducting a sensitivity analysis to account for uncertainty around key estimates and assumptions made during the identification and valuation of costs.

Results

The literature search did not identify any potentially relevant studies written in languages other than English, but did generate 20 articles written in English. Seven articles were excluded because they were published prior to 1990, they did not report cost data, or they presented costs of diagnosis and treatment of chronic pelvic pain or infertility rather than endometriosis

(Boling *et al.*, 1988; Davies *et al.*, 1992; Gant, 1992; Blackwell and William Mercer Actuarial Team, 2000; Philips *et al.*, 2000; Winkel, 2000; Ojha *et al.*, 2003). Thirteen studies met our inclusion criteria: four cost-of-illness analyses of endometriosis (Kunz *et al.*, 1995; Mathias *et al.*, 1996; Zhao *et al.*, 1998a; Gao *et al.*, 2006), two cost analyses of endometriosis (Zhao *et al.*, 1998b; Pearson and Pickersgill, 2004), five cost analyses of endometriosis in patients presenting with chronic pelvic pain (Surrey, 1997; Heinrichs and Henzl, 1998; Glazer, 1999; Kephart, 1999; Winkel, 1999) and two cost analyses of endometriosis in infertile patients (Luciano *et al.*, 1992; Bodner *et al.*, 1996). All but two studies were set in the USA (Bodner *et al.*, 1996; Pearson and Pickersgill, 2004).

Cost studies of endometriosis

Direct costs

Few cost-of-illness analyses measured direct healthcare costs of endometriosis. One study indicated that annual direct healthcare costs of endometriosis are substantial, amounting to \$2801 per patient. These direct costs were broken down into hospitalization costs of \$2518 (90%) and outpatient costs of \$283 (10%), suggesting that inpatient costs are the primary driver of direct costs of endometriosis (Kunz *et al.*, 1995). Focusing on patients hospitalized for endometriosis, two studies observed that annual inpatient costs per patient nearly doubled from \$6597 in 1991 to \$12 644 in 2002 (Zhao *et al.*, 1998a; Gao *et al.*, 2006).

Direct costs of medical treatment of endometriosis were quantified by two cost analyses. One analysis contrasted costs of the most commonly used medical treatments of endometriosis in the UK (Pearson and Pickersgill, 2004). Costs of six months of treatment amounted to \$11–18 with progestogen-only contraceptives, \$8 with the combined oral contraceptive pill, \$225 with danazol, \$945 with gestrinone and \$1035 and \$1145 with goserelin with and without add-back hormone replacement therapy, respectively. Within the class of GnRH agonists, a study detected a cost advantage of treatment with nafarelin acetate when compared with leuprolide acetate (Zhao *et al.*, 1998b). Direct healthcare costs of six months of treatment amounted to \$2241 per patient with nafarelin acetate, whereas \$2623 with leuprolide acetate ($P < 0.05$). This cost difference arose from lower drug costs with nafarelin acetate ($P < 0.001$). There were no significant differences between medical treatments with nafarelin acetate and leuprolide acetate in terms of costs of outpatient drugs other than nafarelin and leuprolide acetate, outpatient services and inpatient admissions.

Five cost analyses modelled the direct healthcare costs associated with diagnosis and treatment of endometriosis in patients presenting with chronic pelvic pain (Surrey, 1997; Heinrichs and Henzl, 1998; Glazer, 1999; Kephart, 1999; Winkel, 1999). Analyses compared surgical with medical approaches. Figure 1 suggests that GnRH agonist therapy (with leuprolide acetate) was less expensive than laparoscopy. Variations in cost estimates originated from differences in the duration and costs of GnRH agonist therapy, allowance for recurrence of symptoms or not, the proportion of patients who have recurrent symptoms and treatment options for recurrent symptoms.

There is little evidence of costs of treating endometriosis in infertile patients. Focusing on inpatient costs, a cost analysis

found that laparotomy (\$9533) was nearly twice as expensive as laparoscopy (\$5014) (Luciano *et al.*, 1992). Evidence presented by a Scottish cost analysis was in favour of expectant management when compared with medical management, with costs of treating a patient during six months amounting to \$697 with expectant management and \$1162 with medical management (Bodner *et al.*, 1996).

Indirect costs

Little is known about the productivity loss associated with endometriosis, although available estimates from cost-of-illness analyses suggest that endometriosis may impose considerable indirect costs. Estimates of the number of hours missed from work due to endometriosis ranged 19.2–86.4 h per patient per year (Kunz *et al.*, 1995; Mathias *et al.*, 1996). The productivity loss of 86.4 h translated into annual indirect costs of \$1023 per patient.

Factors affecting costs

Diagnosing endometriosis on the basis of symptoms is rendered difficult by the fact that the presentation of endometriosis is variable, each of the symptoms can have other causes (for example, irritable bowel syndrome or pelvic inflammatory disease), and a significant proportion of affected women are asymptomatic (Kennedy *et al.*, 2005). The ability to diagnose endometriosis by means of laparoscopy depends on the surgeon's skills and experience. As a result, 3–12 years may pass between symptom onset and definitive diagnosis (Arruda *et al.*, 2003; Husby *et al.*, 2003). During this time period, unnecessary investigations and treatments are likely to be initiated, thus representing a cost of obtaining a diagnosis for women presenting with symptoms that may have several different causes. Better diagnostic methods would alleviate some of the distress felt between symptom onset and diagnosis and treatment, although the net effect on costs is unclear. As cost studies enrol patients who have been identified to suffer from endometriosis, they under-report the economic burden of endometriosis.

In addition to difficulties involved in diagnosing endometriosis, costs appear to be influenced by the patient profile, specific diagnosis of endometriosis and principal procedure performed. An analysis of inpatient endometriosis treatment showed that costs were higher in older women and in African-American women as compared with Caucasian women. The specific diagnosis appears to play a role: endometriosis of the intestine and of the skin was associated with higher and lower inpatient costs, respectively, than endometriosis at other sites (Zhao *et al.*, 1998a). Of the surgical interventions of endometriosis, total abdominal hysterectomy generated higher inpatient costs than other procedures (Zhao *et al.*, 1998a; Gao *et al.*, 2006). Studies did not report endometriosis severity of included patients, except for one study which sampled patients with moderate to severe endometriosis (Luciano *et al.*, 1992). Therefore, it is not possible to examine whether there is a relationship between endometriosis severity and costs.

Estimating US costs

It is possible to estimate costs arising from endometriosis for the US population in 2002. A cost-of-illness study found annual direct healthcare costs of \$2801 per patient (outpatient and hospital care amounted to 10 and 90% of costs, respectively) and annual

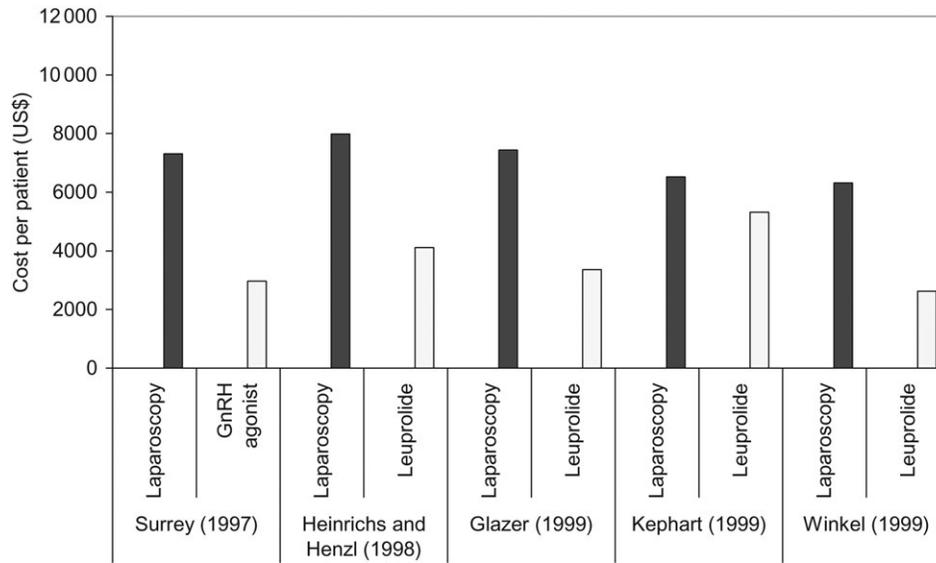


Figure 1: Direct costs of endometriosis diagnosis and treatment (2002 values)

indirect costs of \$1023 per patient (Kunz *et al.*, 1995). The number of women suffering from endometriosis was computed by multiplying the number of US women of reproductive age with the prevalence of endometriosis. There were 61.9 million women aged 15–44 years in the USA in 2002 (US Bureau of the Census, 2005). Estimates of the prevalence of endometriosis among women of reproductive age vary greatly from 1% to 50%, but a rate of 10% is frequently reported in the literature (Child and Tan, 2001; Vigano *et al.*, 2004). Employed women incur indirect costs of time lost from work due to endometriosis. A study found that 89% of women suffering from endometriosis were employed (Kunz *et al.*, 1995). Our analysis used a conservative employment rate of 75%.

Estimates of direct costs were calculated by multiplying the number of women aged 15–44 years in the USA (61.9 million women) with the prevalence rate of endometriosis (1, 10 or 50%) and annual direct healthcare costs per patient (\$2801). These direct costs can be divided into outpatient costs (10% of direct costs) and hospital care costs (90%). Estimates of indirect costs were computed by multiplying the number of women aged 15–44 years (61.9 million women) with the prevalence rate of endometriosis (1, 10 or 50%), annual indirect costs per patient (\$1023) and the employment rate (75%).

Table 1 presents estimates of endometriosis costs for the USA in 2002. Total costs are substantial and ranged \$2–110 billion depending on prevalence rates. Direct healthcare costs make up 78% of total costs arising from endometriosis. Annual indirect costs of time lost from work due to endometriosis amounted to \$0.5–24 billion. The approach outlined here can also be used to estimate costs arising from endometriosis for other populations in different years.

Quality of cost studies of endometriosis

Table 2 presents methodological characteristics of included cost studies. Four studies which drew on primary data enrolled national samples (Mathias *et al.*, 1996; Zhao *et al.*, 1998a,b; Gao *et al.*, 2006). The size of the samples enrolled in these studies was

large, samples were representative of the population and cost estimates could be extrapolated to the USA (Zhao *et al.*, 1998a,b; Gao *et al.*, 2006). Alternatively, three studies analysed a specific group of patients (Luciano *et al.*, 1992; Kunz *et al.*, 1995; Bodner *et al.*, 1996), limiting the ability to generalize cost estimates. The skewed nature of cost data and variability in costs between patients inhibits the robustness of cost estimates derived from two studies with a small sample size (Luciano *et al.*, 1992; Bodner *et al.*, 1996). Modelling studies were based on hypothetical patients suffering from endometriosis (Surrey, 1997; Heinrichs and Henzl, 1998; Glazer, 1999; Kephart, 1999; Winkel, 1999; Pearson and Pickersgill, 2004).

All studies adopted a prevalence approach. The majority of studies measured endometriosis costs during a time period of six months (Bodner *et al.*, 1996; Surrey, 1997; Zhao *et al.*, 1998b; Glazer, 1999; Kephart, 1999; Winkel, 1999; Pearson and Pickersgill, 2004) and up to five years in one study (Heinrichs and Henzl, 1998). This period was too short to account for the chronic nature of endometriosis, which may afflict women during their reproductive years. Some studies failed to consider recurrence (Luciano *et al.*, 1992; Bodner *et al.*, 1996; Surrey, 1997; Zhao *et al.*, 1998a,b; Kephart, 1999; Pearson and Pickersgill, 2004; Gao *et al.*, 2006), while others assumed equal recurrence rates with medical and surgical treatment (Heinrichs and Henzl, 1998).

Table 1: Estimated endometriosis costs in the USA in 2002

Description	Annual costs (million US \$)		
	Prevalence rate of 1%	Prevalence rate of 10%	Prevalence rate of 50%
Direct costs	1733	17 331	86 655
Outpatient costs	173	1733	8665
Hospitalization costs	1560	15 598	77 989
Indirect costs	475	4747	23 737
Total costs	2208	22 078	110 391

Table 2: Methodology of studies measuring costs of endometriosis

Sample	Epidemiological approach	Data collection	Design	Scope of included costs	Time horizon	Costs/charges	Year of costing	Original currency	Sensitivity analysis	Reference
Cost-of-illness analyses of endometriosis										
3303 endometriosis patients enrolled in Medicaid programme	Prevalence	Retrospective analysis of claims data	Case series	Direct healthcare costs and indirect costs	1 year	Charges	1992	US dollars	No	Kunz <i>et al.</i> (1995)
74 endometriosis patients aged 18–50 years	Prevalence	Prospective analysis of survey data	Case series	Indirect costs	1 month	Charges	1994	US dollars	No	Mathias <i>et al.</i> (1996)
Representative national sample of patients with first diagnosis of endometriosis	Prevalence	Retrospective analysis of claims data	Case series	Direct inpatient costs	Hospital admission	Charges	1991 and 1992	US dollars	No	Zhao <i>et al.</i> (1998a)
Representative national sample of patients with first diagnosis of endometriosis	Prevalence	Retrospective analysis of claims data	Case series	Direct inpatient costs	Hospital admission	Charges	2002	US dollars	No	Gao <i>et al.</i> (in press)
Cost analyses of endometriosis										
457 patients with first diagnosis of endometriosis	Prevalence	Retrospective analysis of claims data	Cohort study	Direct healthcare costs	6 months	Charges	1994	US dollars	No	Zhao <i>et al.</i> (1998b)
Hypothetical endometriosis patient	Prevalence	Unit charge data derived from National Health Service, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	6 months	Charges	2002	Pounds sterling	No	Pearson and Pickersgill (2004)
Cost analyses of endometriosis in patients presenting with chronic pelvic pain										
Hypothetical endometriosis patient	Prevalence	Unit charge data derived from clinic, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	6 months	Charges	1996	US dollars	No	Surrey (1997)

Continued

Table 2: *Continued*

Sample	Epidemiological approach	Data collection	Design	Scope of included costs	Time horizon	Costs/charges	Year of costing	Original currency	Sensitivity analysis	Reference
Hypothetical cohort of 70 endometriosis patients	Prevalence	Unit charge data derived from clinic, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	5 years	Charges	1997	US dollars	No	Heinrichs and Henzl (1998)
Hypothetical cohort of 80 endometriosis patients	Prevalence	Unit charge data derived from literature, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	6 months	Charges	1998	US dollars	No	Glazer (1999)
Hypothetical cohort of 43 endometriosis patients	Prevalence	Unit charge data derived from clinic, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	6 months	Charges	1998	US dollars	No	Kephart (1999)
Hypothetical endometriosis patient	Prevalence	Unit charge data derived from clinic, resource use data derived from literature	Cohort study based on modelling	Direct healthcare costs	6 months	Charges	1998	US dollars	No	Winkel (1999)
Cost analyses of endometriosis in infertile patients 120 patients with moderate to severe endometriosis	Prevalence	Unit charge data derived from clinic, resource use data derived from patient medical records	Cohort study	Direct inpatient costs	Hospital admission	Charges	1989	US dollars	No	Luciano <i>et al.</i> (1992)
56 endometriosis patients	Prevalence	Unit cost data derived from clinic, resource use data derived from patient medical records	Cohort study	Direct healthcare costs	6 months	Costs	1993	Pounds sterling	Yes	Bodner <i>et al.</i> (1996)

Endometriosis has a high likelihood of recurrence following treatment cessation, with the literature indicating that the rate of recurrence after surgery is up to 40% after five years and that medical therapy has higher recurrence rates than surgical therapy (Wellbery, 1999; D'Hooghe *et al.*, 2003b; Winkel, 2003; Kennedy *et al.*, 2005).

With respect to the source of data on healthcare resource use, studies gathered data from patient medical records (Luciano *et al.*, 1992; Bodner *et al.*, 1996), the literature (Surrey, 1997; Heinrichs and Henzl, 1998; Glazer, 1999; Kephart, 1999; Winkel, 1999; Pearson and Pickersgill, 2004), a claims database (Kunz *et al.*, 1995; Zhao *et al.*, 1998a,b; Gao *et al.*, 2006) or from a survey (Mathias *et al.*, 1996). When drawing on data from patient medical records or the literature, cost estimates were calculated by multiplying healthcare resource use with unit charges in all but one study (Bodner *et al.*, 1996). As charge data tended to pertain to specific institution(s), cost estimates cannot be generalized to other institutions, other parts of the country in which the study was set or other countries. A retrospective analysis of claims data benefits from comprehensiveness of information on healthcare resource use, but may suffer from missing data and incorrect diagnostic coding of claims. A survey can be an efficient method to study a representative sample, but reliability of survey data may be hindered by patients' ability to recall healthcare resource use.

All cost-of-illness analyses identified patients suffering from endometriosis, but did not have a control group of patients without endometriosis. Such case series that focus on identified patients only may be misleading in the case of endometriosis, where diagnosis is complex and attribution of healthcare resource use to the disease is difficult. A case-control study comparing patients with/without endometriosis seems better suited in that it is more inclusive and allows identification of additional healthcare resource use related to endometriosis. Cost analyses took the form of cohort studies based on primary data (Luciano *et al.*, 1992; Bodner *et al.*, 1996; Zhao *et al.*, 1998b) or a cost model (Surrey, 1997; Heinrichs and Henzl, 1998; Glazer, 1999; Kephart, 1999; Winkel, 1999; Pearson and Pickersgill, 2004). Cost estimates derived from primary data reflect real-world practice. Studies adopting a modelling approach evaluated standard protocols for diagnosis and treatment of endometriosis. Cost estimates derived from such protocols do not fully take into account variation in clinical practice and, hence, may not be realistic.

Differences in unit costs and perspective may make it difficult for analysts to transfer published cost estimates to their own analysis. Transferability is enhanced when studies report resource utilization and unit costs separately. A description of resource utilization underpinning cost estimates was provided in all but one study (Bodner *et al.*, 1996). This enables analysts to combine published estimates of resource utilization with unit costs pertaining to their analysis in order to estimate costs of endometriosis.

Studies generally measured direct healthcare costs associated with endometriosis, although some analyses were restricted to direct inpatient costs (Luciano *et al.*, 1992; Zhao *et al.*, 1998a; Gao *et al.*, 2006). No study considered direct non-healthcare costs associated with transportation to the healthcare provider or child care costs. Two studies explored indirect costs related to productivity loss of endometriosis (Kunz *et al.*, 1995; Mathias *et al.*,

1996). However, these studies focused on productivity loss as a result of absence from work, but did not consider reduced productivity while at work. The lack of attention to measuring indirect costs is a major concern given that patients suffering from endometriosis tend to belong to the working-age population (Bain, 2006). All but one study calculated charges (Bodner *et al.*, 1996) and, thus, did not accurately estimate underlying costs of actual healthcare resource use associated with endometriosis. Only one study explored the robustness of cost estimates to changes in key variables (e.g. unit charges, recurrence rate) by carrying out a one-way sensitivity analysis (Bodner *et al.*, 1996). However, undertaking a one-way sensitivity analysis is unlikely to adequately account for uncertainty (Drummond *et al.*, 2005).

Discussion

This article presented estimates and appraised the methodological quality of published studies on the costs of endometriosis, and provides recommendations for future research. The body of evidence on endometriosis costs was limited. Few studies computed costs associated with endometriosis. Studies contrasting different approaches to diagnosis and treatment of endometriosis in patients presenting with chronic pelvic pain or infertility were rare. Moreover, existing studies suffered from a number of methodological limitations, thus producing biased cost estimates.

Our study estimated that annual endometriosis costs in the USA in 2002 were ~\$22 billion assuming a prevalence of 10% in reproductive age women, and varying between \$2–110 billion assuming a prevalence rate between 1% and 50% (see Table 1). In order to fully appreciate these costs, it is important to compare them with published cost estimates for other diseases in the USA in 2002. When comparing costs of diseases, caution needs to be exercised as the methods used to derive cost estimates may differ between studies and diseases. Crohn's disease seems to be a good comparator as its treatment involves expensive medication and can draw on a medical or a surgical approach as is the case with endometriosis. Estimates of total annual costs of Crohn's disease were \$865 million (Sandler *et al.*, 2002). Migraine exhibits similarities to endometriosis in that it is a chronic condition, with a cyclic pattern, affecting individuals in a similar age group, and is more prevalent in women than in men. The annual economic burden of migraine was estimated at \$13–17 billion (Goldberg, 2005).

Cost analyses of endometriosis in patients presenting with chronic pelvic pain suggest that diagnosis and initial treatment with medicines may be less expensive than using a surgical approach. The question arises as to whether economic savings can be generated by non-surgical diagnosis and medical treatment that allows patients to be cared for in primary care and that prevents hospitalization and a surgical approach? The answer is no. First of all, there is currently no reliable non-surgical diagnostic test for endometriosis. Thus diagnosis requires laparoscopy, preferably with histological confirmation. If endometriosis is present at laparoscopy, it is recommended that it is surgically removed at the same time as diagnosis, as an effective treatment for endometriosis-associated subfertility and pain (Kennedy *et al.*, 2005).

Secondly, the lower costs of medical treatment need to be balanced by additional costs due to higher recurrence rates of endometriosis with medical when compared with surgical

treatment (Wellbery, 1999; D’Hooghe *et al.*, 2003b; Winkel, 2003). Existing studies have failed to adequately account for the chronic nature of endometriosis. Therefore, to date, it is unclear whether a medical approach is less expensive than a surgical approach to treating endometriosis in patients presenting with chronic pelvic pain.

In light of the methodological limitations of the few existing cost studies as reported in the previous section, the following avenues are proposed for designing future cost studies of endometriosis:

- (i) There is a need to distinguish between the disease endometriosis and the main symptoms (pain and subfertility) associated with endometriosis. To examine the costs associated with endometriosis itself, studies need to compare patients with endometriosis and pelvic pain to patients with a normal pelvis and pain or compare patients with endometriosis and infertility to patients with a normal pelvis and infertility. A case-control study design comparing patients with/without endometriosis seems to be suited for this purpose.
- (ii) Studies need to report the profile of included patients to enable readers to assess generalisability of cost estimates to their setting or patient population. This is necessary because costs are associated with patient characteristics (Zhao *et al.*, 1998a). In particular, research is required to compute costs for different degrees of endometriosis severity as the relationship between endometriosis severity and costs is still unclear. Also, even though adolescents as young as 10.5 years of age may develop endometriosis

(Gambone *et al.*, 2002), no studies that calculated costs of endometriosis in this patient population were found. Future research needs to focus specifically on the adolescent population.

- (iii) Studies need to adopt an incidence approach and compute costs for women who may suffer from recurrent episodes of endometriosis.
- (iv) Studies need to set up a prospective collection of primary data on healthcare resource use and costs. This type of analysis can be considered to be more reliable than retrospective analyses of patient medical records or claims databases. Alternatively, modelling approaches can be considered providing they are based on high-quality data, closely reflect real-life practice and the evolution of endometriosis in patients and test the robustness of cost estimates through extensive sensitivity analyses.
- (v) The economic impact of endometriosis on patients, the healthcare system and society is difficult to determine. Therefore, Table 3 identifies the major cost items that need to be considered when calculating the costs of endometriosis from a societal perspective. In addition to direct healthcare costs, future studies need to focus on eliciting direct non-healthcare costs and indirect costs. With respect to the latter, more attention needs to be paid to calculating the indirect costs of days lost to education and work and the costs of reduced ability to carry out normal everyday activities.
- (vi) Studies need to move away from using charge data based on official list prices towards measuring costs based on

Table 3: Items to be considered in cost studies of endometriosis

Direct healthcare costs					Direct non-healthcare costs	Indirect costs
Medication	Diagnostic procedures	Surgical procedures	Healthcare providers	Other		
NSAIDs	Ultrasound scan	Laparoscopy	General practitioner	Accident and Emergency visit	Transportation to healthcare provider	Absence from work
Progestogen-only contraceptives	Internal scan	Laparotomy	Gynaecologist	Hospitalization	Child care costs while in treatment	Reduced productivity while at work
Combined oral contraceptive pill	MRI	Hysteroscopy	Nurse	Alternative medicine (e.g. homeopathy, acupuncture and nutrition)		Time lost from education
Danazol	Blood tests	Hysterectomy	Urologist			Reduced ability to carry out day-to-day activities
Gestrinone	Swabs	Endometrial ablation	Gastro-enterologist			
GnRH analogues	Barium enema	Theatre costs	Anaesthetist			
Add-back hormone replacement therapy	Sigmoidoscopy		Radiologist			
Mirena coil	Endoscopy		Theatre staff			
Antibiotics	Bone scans		Haematologist			
Anti-depressants	X-rays		Counsellor Physiotherapist Psychiatrist			

actual resource use. This is because, for example, charges for surgical treatment of endometriosis in hospital may not accurately reflect actual expenditure on administration, billing, capital depreciation, maintenance, laundry and other hospital services related to the surgical procedure. Alternatively, in studies that measure charges, these need to be converted into costs by means of cost-to-charge ratios. Such adjustment by cost-to-charge ratios is regularly used in cost studies set in the USA (Drummond *et al.*, 2005).

- (vii) Future studies need to contrast different approaches to medical diagnosis and treatment of endometriosis, compare various approaches to surgical diagnosis and treatment and contrast medical with surgical approaches.

Conclusions

Endometriosis imposes a substantial economic burden on society. The high burden originates from the time delay between onset of symptoms and diagnosis, costly medical and surgical treatments, the chronic nature of endometriosis and the indirect costs associated with reduced quality of life and ability to work. Increasing awareness of the disease, cutting the time to diagnosis and providing centralized evidence-based specialized care are crucial steps in reducing the morbidity, health care expenditure and lost productivity associated with endometriosis. The substantial economic burden underlines the need for further research into cost-effective approaches to diagnosing and treating endometriosis.

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Conflict of interest statement

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