Endometriosis Cost Assessment (the EndoCost Study): A Cost-of-Illness Study Protocol

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Key Words
Endometriosis · Cost of illness · Healthcare cost · Productivity loss · Study protocol

Abstract
Aims: The EndoCost study aims to calculate the costs of endometriosis from a societal perspective. Methods: This multicentre, prevalence-based cost-of-illness analysis aggregates data on endometriosis costs and quality of life from a prospective hospital questionnaire and from both retrospective and prospective patient questionnaires. The EndoCost study comprises 12 representative tertiary care centres involved in the care of women with endometriosis in 10 countries. The sample includes patients with a laparoscopic and/or histological diagnosis of endometriosis and with at least 1 patient contact related to endometriosis during 2008. The EndoCost study measures direct healthcare costs (e.g. costs of medication, physician visits), direct non-healthcare costs (e.g. transportation costs), and indirect costs of productivity loss. Cost questions are developed specifically for the purpose of the EndoCost study. Quality of life is measured using the EuroQol-5D and relevant parts of the Global Study of Women’s Health instruments. Both aggregate analyses and country-specific analyses are planned for total costs per patient. Costs are broken down into cost drivers and into the various payers that incur costs. Conclusions: The cost estimates provided by the EndoCost cost-of-illness analysis may be used to justify the prioritisation of future research in endometriosis.

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 [1]. Endometriosis is associated with: severe dysmenorrhea; deep dyspareunia; chronic pelvic pain; ovulation pain; cyclical or peri-menstrual symptoms (e.g. bowel or bladder associated) with or without abnormal bleeding; infertility, and chronic fatigue. Some affected women, however, remain asymptomatic.
The estimated prevalence of endometriosis is 10% among women of reproductive age, rising to 30–50% in patients with infertility and/or pain [2]. Endometriosis is a complicated disease that often goes undiagnosed for years [3]. Medical or surgical treatment aims to reduce symptoms, and to remove or diminish disease. Medical treatment is based on hormonal suppression and appears to be effective in treating pain associated with endometriosis, though the side effects and cost profiles differ between medicines. Surgical treatment is effective in treating endometriosis-associated pain, and most likely also in treating endometriosis-associated subfertility [1]. However, recurrence of endometriosis after surgery and after cessation of medical therapies occurs regularly.

The endometriosis-associated costs to society are considerable but yet poorly identified, as are the costs to the individual when disease symptoms interfere with day-to-day life at work or at home [3]. Diagnostic and surgical procedures, medicines, fertility treatments and involvement of healthcare professionals all factor in when a woman presents with and/or is treated for symptoms suggestive of endometriosis. Societal costs not only consist of costs of appropriate treatment of diagnosed endometriosis, but also include costs of possible under-treatment as a result of delayed diagnosis and ‘hit and miss’ treatments [4–7].

In a context of spiralling healthcare costs and limited resources, public policy makers and healthcare payers are concerned about the costs of endometriosis. Cost estimates can underline the importance of endometriosis 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 cost-effectiveness of various approaches to diagnosing and treating endometriosis by examining their effectiveness in relation to their costs. A cost-of-illness study is a formal way of providing such cost estimates.

A disease, which has such a profound effect on society, needs to be recognised and dealt with by society, and public health initiatives need to be undertaken to generate awareness of the high prevalence and burden of endometriosis at all levels of society [5, 7]. Action for increased awareness and investment in research has so far resulted in unprecedented recognition of endometriosis by the European Parliament in 2005 and 2006 [7]. Inspired by this recognition, the Italian Senate has recognised endometriosis as a social disease and has produced a 5-year plan to improve treatment of endometriosis at a national level [7]. But to get further recognition, in more than one country, the calculation of endometriosis costs will be instrumental to trigger increased awareness of endometriosis among those who determine health policy and grant research funding.

Three review papers have been published in recent years underlining the lack of research on costs of endometriosis and that identifying several avenues for future research which the EndoCost study seeks to address [6, 8, 9]. To close the gaps identified in these papers in investigating the costs of endometriosis, the aim of the EndoCost study is to calculate the costs of endometriosis from a societal perspective. For this purpose, a prospective, prevalence-based, multicentre cost-of-illness analysis is set up to collect cost data using a bottom-up approach. This approach is combined with an assessment of endometriosis-related quality of life in participating patients. The cost estimates provided by this cost-of-illness analysis may be used to justify the prioritisation of future research in endometriosis.

The EndoCost Consortium decided to submit this study protocol for publication in order to raise awareness of endometriosis among policy makers and to encourage other researchers to carry out cost studies of endometriosis. The publication of a study protocol is seen by the Consortium as a natural step in the process of designing, conducting and reporting on a study. This study protocol presents detailed information about the different steps involved in designing the EndoCost study and may thereby inform the design of future cost studies of endometriosis.

**Materials and Methods**

The methodology of the EndoCost study is reported using the STROBE statement for reporting observational studies [10].

**Study Design**

The multicentre cost-of-illness analysis involves the identification, quantification, and valuation of resources related to endometriosis [11] from an international perspective. This prevalence-based study measures costs attributable to a group of women suffering from endometriosis during a 2-month period. A bottom-up approach aggregates data derived from three sources: a prospective hospital questionnaire measures hospital costs related to endometriosis, and two patient questionnaires identify costs and quality of life related to endometriosis prospectively and retrospectively.

Ethical approval for the EndoCost study was obtained from the ethical committee associated with each participating centre. Women are required to sign an informed consent form in order to participate in the EndoCost study.
Setting
The EndoCost study involved the establishment of a research network known as the EndoCost Consortium. In 2007, a letter of invitation was sent to all members of the Special Interest Group for Endometriosis and Endometrium of the European Society of Human Reproduction and Embryology (ESHRE) to join the EndoCost Consortium. The conditions to join the Consortium were: motivation to spend time on this study; good knowledge of written and spoken English; ability to get information from domestic health authorities, and willingness to attend a number of Consortium meetings. Twelve centres in ten countries signed up to be part of the EndoCost Consortium.

The EndoCost study wishes to provide cost estimates of endometriosis from multiple countries that differ in terms of the organisation and financing of their healthcare system, including Belgium, Denmark, France, Germany, Hungary, Italy, The Netherlands, Switzerland, the United Kingdom and the United States. Aggregate as well as country-specific cost estimates are to be calculated. Each participating country includes one or more representative of tertiary care centres involved in the care of gynaecological patients. Recognition of a representative centre is based on the recognition of this centre as a referral centre for patients with endometriosis-associated symptoms within and outside a country. For each country, a team of one or more gynaecologists and one health economic expert with a major interest in the epidemiologic, public health, and cost aspects of endometriosis participate in the EndoCost Consortium.

Participants
The study population includes women with a laparoscopic and/ or histological diagnosis of endometriosis and with at least one patient contact between January 1 and December 31, 2008, related to endometriosis-associated symptoms (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). The diagnosis of endometriosis was not necessarily made in this time period and patients who had been diagnosed earlier were included as long as they had one centre contact due to endometriosis during the calendar year of 2008. It was not required that endometriosis diagnosed by laparoscopy was confirmed by biopsy with positive histology. Patients with endometriosis proven after histological/histologic patients. Recognition of a representative centre is based on the recognition of this centre as a referral centre for patients with endometriosis-associated symptoms within and outside a country. For each country, a team of one or more gynaecologists and one health economic expert with a major interest in the epidemiologic, public health, and cost aspects of endometriosis participate in the EndoCost Consortium.

Variables
The EndoCost study measures direct healthcare costs (e.g. costs of medication, physician visits and hospitalisation) as well as direct non-healthcare costs (e.g. transportation costs, child care costs, etc.). Indirect non-healthcare costs relating to reduced productivity as a result of endometriosis and its treatment are included. These costs not only consist of the reduced productivity of the woman, but also of the loss of productivity of family/friends who take time off work to care for the woman. Other indirect non-healthcare costs such as the costs of support with household activities are documented.

Endometriosis costs are calculated from the societal perspective. This includes costs incurred by the healthcare payer (i.e. insurance funds or National Health Service), the patient/family (i.e. co-payment or full payment for medicines and/or care) and by the society at large (i.e. costs of reduced productivity).

The EndoCost Consortium is aware of the complexity involved in estimating the economic burden of endometriosis and, thus, the EndoCost study purports to attain a truthful and comprehensive representation of the costs of endometriosis. As an example, table 1 identifies the major cost items which need to be considered when calculating the costs of endometriosis from a societal perspective.

Data Sources/Measurement
Relevant questions regarding direct and indirect costs of endometriosis were compiled into one retrospective and one prospective patient questionnaire, and a prospective hospital questionnaire. In general, cost questions were developed specifically for the purpose of the EndoCost study by the participating health economists and gynaecologists, except for the Work Productivity and Activity Impairment Questionnaire [12]. Quality of life was measured using the EuroQol-5D [13] and relevant parts of the Global Study of Women’s Health (GSWH) instruments [14]. Copies of the questionnaires are available from the corresponding author on request.

The prospective hospital questionnaire measured the start and end dates of patient hospitalisations; the number of monitoring tests; the trade name, daily dosage, and number of days of patient medication; the number and type of outpatient physician consultations; the number and type of surgical procedures and/or infertility treatments; the number and type of other therapies from October 5 until November 30, 2009.

In the prospective patient questionnaire, questions related to the number and type of physician consultations; the trade name, daily dosage, and number of days of patient medication; the number of monitoring tests; the start and end dates of patient hospitalisations; the number and type of other therapies; the dates and number of hours of additional support with household activities; the dates, type and number of hours of informal care, and loss of productivity from October 5 until November 30, 2009. The productivity loss was measured using the Work Productivity and Activity Impairment Questionnaire [12]. This generic instrument considered the time lost from work (‘absenteeism’) as well as reduced productivity at work (‘presenteeism’). To register the evolution of health-related quality of life over time, the EuroQol-5D [13] instrument was filled in by patients on October 2, November 2 and November 30, 2009. The EuroQol-5D is a generic instrument which contains 5 dimensions of health-related quality of life: mobility, self-care, daily activities, pain/discomfort and depression/anxiety. Each dimension can be rated at three levels: no problems, some problems and major problems. The five dimensions can be summed into a health state.

The retrospective patient questionnaire enquired about the woman’s demographic characteristics and medical history (e.g.
Table 1. Costs of endometriosis

<table>
<thead>
<tr>
<th>Direct healthcare costs</th>
<th>diagnostic procedures</th>
<th>surgical procedures</th>
<th>healthcare providers</th>
<th>other</th>
<th>Direct non-healthcare costs</th>
<th>Indirect costs</th>
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<tbody>
<tr>
<td>medication</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Ultrasound scan (transvaginal/abdominal/transrectal)</td>
<td>Laparoscopy</td>
<td>General practitioner</td>
<td>Accident and emergency visit</td>
<td>Transportation to healthcare provider</td>
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<tr>
<td>Progestogen-only contraceptives</td>
<td>Ultrasound scan (kidney)</td>
<td>Laparotomy</td>
<td>Gynaecologist</td>
<td>Hospitalisation</td>
<td>Child care costs while in treatment</td>
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<tr>
<td>Combined oral contraceptive pill</td>
<td>Magnetic resonance imaging</td>
<td>Colposcopy</td>
<td>Nurse</td>
<td>Alternative medicine (e.g. homeopathy, acupuncture, nutrition)</td>
<td>Reduced productivity while at work</td>
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<td>Danazol</td>
<td>Computed tomography</td>
<td>Cyst aspiration</td>
<td>Urologist</td>
<td>In vitro fertilisation</td>
<td>Additional support with household activities</td>
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<tr>
<td>Gestrinone</td>
<td>Intravenous pelvigraphy</td>
<td>Hysterectomy</td>
<td>Gastroenterologist</td>
<td>Intrauterine</td>
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<td>Gonadotropin-releasing hormone agonists</td>
<td>Barium enema</td>
<td>Ovarian cystectomy</td>
<td>Anaesthetist</td>
<td>insemination</td>
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<td>Add-back hormone replacement therapy</td>
<td>Sigmoidoscopy</td>
<td>Adnecotomy</td>
<td>Radiologist</td>
<td>Hormonal stimulation</td>
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<tr>
<td>Mirena coil</td>
<td>Biopsy and histological examination (vaginal endometriosis, peritoneal endometriosis, ovarian endometriosis, bowel endometriosis)</td>
<td>Ovariectomy</td>
<td>Theatre staff</td>
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<td>Clomiphene citrate</td>
<td>Serum markers (CA 125)</td>
<td>Tubectomy</td>
<td>Haematologist</td>
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<td>Gonadotropins</td>
<td></td>
<td>Adhesiolysis</td>
<td>Counsellor</td>
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<td>Antibiotics</td>
<td>Bacteriology/culture</td>
<td>Resection endometriosis rectovaginal septum</td>
<td>Physiotherapist</td>
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<td>Antidepressants</td>
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<td>Resection bladder endometriosis</td>
<td>Psychiatrist</td>
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<td>Aromatase inhibitors</td>
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<td>Low anterior resection</td>
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<td>Resection small bowel</td>
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<td>Colostomy</td>
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<td>Ureter re-implantation</td>
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<td>Ureter-ureterostomy</td>
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<td>Nephrectomy</td>
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<td>Electrocoagulation peritoneal endometriosis</td>
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<td>Laser coagulation peritoneal endometriosis</td>
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<td>Laparoscopic uterosacral nerve ablation</td>
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<td></td>
<td>Endometrial ablation</td>
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age, weight, educational level, marital status, ethnic origin, year and type of first symptoms, year of endometriosis diagnosis; the number and type of lifetime surgical procedures; the number of lifetime cycles of infertility treatments; as well as the trade name and number of months of hormonal treatment; the number and type of physician consultations; the trade name, daily dosage, and number of days of patient medication; the number of monitoring tests; the start and end dates of patient hospitalisations; the number and type of other therapies; the dates and number of hours of support with household activities; the dates, type and number of hours of informal care; and productivity loss from August 6 until October 1, 2009. The impact of endometriosis on quality of life was measured by the GSWH instrument as this allowed comparison with this prospective study of naive patients [14]. The validated GSWH instrument is based on the Short Form-36 (SF-36), a generic 8-scale profile of physical and mental health [15], and the Endometriosis Health Profile-30 (EHP 30), a disease-specific instrument that measures health-related quality of life associated with endometriosis [16].

The questionnaires elicited data about the volume of resource use associated with endometriosis. To value resource use, price data were collected using the following principles.

1. Prices reflected unit costs based on actual resource use as much as possible. In the absence of unit cost data, charges based on official list prices were used.

2. Prices reflected the contribution of the healthcare payer and the patient co-payment.

3. Prices reflected generic costs. For example, the EndoCost study wished to collect the generic cost of an ultrasound examination, but not necessarily patient X’s ultrasound on a specific date. Each participating country’s health economist was responsible for collecting the price data using a standardised form in collaboration with the gynaecologist.

Utility values were calculated for the health states identified by the EuroQol-5D using a national health utility index. The utility values are used to compute quality-adjusted life years (QALYs), if combined with estimates of the time period for which a particular health state lasts. The QALY is an outcome measure that accounts for the quantity and quality of life, and that allows comparison of outcomes between diseases.

The questionnaires were piloted and reviewed for face and content validity by the members of the EndoCost Consortium and by 6 patients at the Katholieke Universiteit Leuven. Respondents discussed the relevance of questions, commented on their wording and interpretation, and checked whether all potential answers were included. As a result, medical terms were clarified, ambiguous questions were reformulated for greater clarity, and answer categories were added where appropriate.

Study Size

As is usual practice in cost-of-illness analyses, this study is designed to measure costs rather than test a specific hypothesis about costs and, therefore, no sample size calculations were conducted. Each referral centre identified eligible patients and 3,216 women were invited on August 31, 2009, to participate in the study and 1,450 women (response rate of 45%) provided informed consent in time to be mailed the questionnaires on September 24, 2009. This sample size is larger than previous studies on the costs of endometriosis that tended to include only a few hundred patients [6]. Data collection has now been completed and data analysis has just been started. Results of the EndoCost study will be reported over the course of the next years.

Statistical Methods

Data collection and input into the central database are carried out in each participating centre. Missing values are to be expected, but are minimised primarily by using several categories such as ‘not applicable’ and ‘not known’. Each centre may contact patients to supplement answers for missing values and standard statistical techniques are utilised to deal with missing data. Overall quality assurance of data entry and data analysis is carried out by the coordinating health economist (S.S.) at the University Hospital Leuven, the coordinating centre of the EndoCost study.

Statistical analyses are primarily of a descriptive nature. A descriptive analysis is carried out on the demographic characteristics of patients. Characteristics are reported as relative frequencies for categorical data, and as mean (±standard deviation) or median (and quartiles) for continuous data depending on the normality of the data.

Prospective and retrospective analyses are carried out separately. An aggregate analysis is planned for the volume of resource use and total costs. Costs per patient are computed by multiplying resource use by unit costs. The following cost measures are calculated: costs per patient, annual costs per patient, and costs per centre.

Costs per patient are computed and summarised using the following descriptive statistics: mean, standard deviation, median, 5th and 95th percentiles. Since costs do not usually follow a normal distribution, a robust confidence interval of the mean is also calculated. This interval is calculated by means of the bootstrapping method, a technique which does not require the assumption of normality [17].

Total costs are broken down into the major cost drivers (e.g. hospitalisation, medicines, productivity loss, etc) and into the major payers that incur those costs (insurance fund/National Health Service and patients). Country-specific analyses are conducted for total costs. Extrapolation from the sample to the whole country is not a goal of the study, while extrapolation from the sample to the annual cost per centre is possible.

Costs are expressed in euros. For those countries that do not have the euro, costs are converted into euros using purchasing power parity exchange rates, i.e. market exchange rates adjusted for differences in purchasing power between countries [18]. The price year is 2009.

Discussion

The EndoCost study purports to calculate the level of endometriosis costs, elicit the most important drivers of endometriosis costs, and identify factors that influence the level of endometriosis costs. Cost estimates may be used to raise awareness of endometriosis with policy makers, healthcare professionals, and research institutions in order to underline that early diagnosis and treatment, not ‘hit and miss treatments’, may reduce costs on a societal and personal level. The hypothesis is that
results from this study are fundamental in justifying significant investment in endometriosis research to understand disease mechanisms (pathogenesis and the pathophysiology of endometriosis-related pain and/or infertility) which may lead to improved diagnostics and therapeutics, which may in turn reduce the socio-economic impact of the disease.

To the best of the authors’ knowledge, the EndoCost study is the first international, multicentre cost-of-illness study assessing the costs of endometriosis from a societal perspective. Ideally, the true cost of a disease is measured by the additional burden imposed by that disease on society. This additional burden takes the form of increased resource utilisation by endometriosis patients, which exceeds the use of resources by the general population [19]. For this purpose, a case-control study design can be used to compare total costs of endometriosis patients with costs of an equivalent standardised population with a view to calculating the additional costs that can be attributed to endometriosis. Due to practical and resource constraints, the EndoCost study did not include a control population of patients without endometriosis. Instead, the EndoCost questionnaires enquired about the costs specifically related to endometriosis. However, it will be possible to compare the results of this study with national statistics regarding age- and gender-corrected ‘per capita’ spending on healthcare services.

Each participating country includes one or more representative tertiary care centres involved in women’s health. These centres typically have women with endometriosis referred to them and, therefore, our cost estimates can be expected to reflect ideal practice, but may be different from the costs of endometriosis observed in other centres, since more complex cases of endometriosis are normally referred to a tertiary care centre.

The two patient questionnaires identify costs and quality of life related to endometriosis prospectively and retrospectively. The retrospective assessment is important in order to get optimal data out of this study, although the investigators fully recognise the limitations of this method of data collection due to potential recall bias. Therefore, the retrospective questionnaire uses a recall period of only 2 months. This is in line with previous research recommendations when estimating costs due to illness [20].

The EndoCost study takes a prevalence-based approach, measuring endometriosis costs within a given time interval, rather than an incidence-based approach, quantifying lifetime costs of endometriosis from onset to death. An incidence-based approach would be better suited to take into account the recurrence of endometriosis and its associated costs. However, an international, multicentre cost analysis based on an incidence-based approach was not feasible due to practical and resource constraints.

This international study provides evidence of the costs of endometriosis in multiple countries. The reader should note that differences in the organisation and financing of healthcare systems are likely to influence reported cost estimates. Therefore, country-specific as well as aggregate cost estimates are to be calculated and country-specific estimates can be used to inform national health policy.

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