

SECTION 1

Keynote lectures

CHAPTER 1

Health economics of endometriosis

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Overview

Background: Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction and is associated with pain, subfertility, and impaired quality of life. The condition is found mainly in women of reproductive age, from all ethnic and social groups. The estimated prevalence of the disease is 10% among women of reproductive age, making it more common than diabetes in this population.

Objective: The aim of this chapter is to describe the overall economic impact of endometriosis, including both direct costs associated with specific diagnosis and treatment and indirect costs associated with reduced work productivity, loss in earned income, social withdrawal, relational stress, and psychological disorders such as depression.

Methodology: This review is based mainly on the content of two systematic reviews evaluating the economic impact of endometriosis [1, 2] and on a recently published actuarial analysis of private payer administrative claims data for women with endometriosis [3].

Results: Direct endometriosis-related costs are considerable, appear to be driven by hospitalizations, and have increased to 61% between 1993 and 2002 in the USA, despite a decline in the endometriosis-related hospital length of stay during the same period. Studies evaluating the cost of endometriosis in infertile patients and the indirect endometriosis-associated costs are largely lacking. Assuming a 10% prevalence rate of endometriosis among women of reproductive age, it has been estimated

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that the annual costs of endometriosis attained \$22 billion in the USA only in 2002. In this age group, these costs are considerably higher than those related to Crohn's disease, migraine, and hypertension and are comparable to the cost of diabetes. Furthermore, endometriosis-related costs are increasing, in contrast with the decreasing direct costs associated with pelvic inflammatory disease. Due to the added cost related to comorbid conditions like interstitial cystitis, depression, migraine, irritable bowel syndrome, chronic fatigue syndrome, abdominal pain, and infertility, women with endometriosis incurred total direct medical costs that were, on average, 63% higher than medical costs for the average women in a commercially insured group in the USA in 2004.

Conclusion and future perspectives: Endometriosis has an important economic impact, but the methodological value of the few existing cost studies is limited. The following recommendations can be made for future research regarding the cost of endometriosis: distinction between the disease endometriosis and the associated symptoms such as pain and infertility; differentiation of cost according to various degrees of endometriosis; cost related to endometriosis in adolescents; prospective longitudinal follow-up study of patients from the moment of diagnosis until menopause, including cost of complications, recurrences, ambulatory care, medication, etc.; calculation of indirect cost related to endometriosis (loss of work, etc.); prospective collection of primary data on actual healthcare resource use by endometriosis patients on a national and an international level, based on a well-defined list of the major cost items and of comorbid conditions.

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 [4]. Endometriosis is associated with severe dysmenorrhea, deep dyspareunia, chronic pelvic pain (CPP), 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 [2]. The prevalence of endometriosis in women with infertility and pelvic pain is about 30% and up to 50–60%, respectively [5].

Endometriosis is a painful, chronic disease affecting millions of women and girls worldwide. Although the prevalence of endometriosis is well

documented in women living in the developed world, studies on the prevalence of this disease among African women are still wanting [6]. The current view is that endometriosis rarely affects women of African descent. However, in African-American women in the USA, endometriosis is one of the common indications for major gynecological surgery and hysterectomy, and is associated with a long hospital stay and high hospital charges [6, 7–9]. Endometriosis may be more commonly found in infertile Caucasian or African-American women (born and living in North America) than in African-indigenous women (born and living in Africa), but it is likely that the true prevalence of endometriosis in African-indigenous women is underreported due to inadequate facilities and demands of specialized skills for adequate assessment of the pelvis, recognition of the various types, and appearances of the disease. Understanding the prevalence of endometriosis among African women will be instrumental in proper management of this disease in the African continent [6].

The estimated prevalence of endometriosis is 10% among women of reproductive age [10], making it more common than diabetes in this population [11]. Endometriosis is a complicated disease that often goes undiagnosed for years [1]. There is no cure for endometriosis, and recurrence of endometriosis after surgery and after cessation of medical therapies occurs regularly. Persistent and/or chronic diseases like endometriosis come with a price, although what the cost is to the individual, and to society, is very difficult to calculate [12]. The endometriosis-associated costs to society, including delayed diagnosis and “hit-and-miss” treatments [2, 13, 14], 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 [15]. Diagnostic and surgical procedures, drugs, fertility treatments, and involvement of healthcare professionals all factor in when a woman presents with and/or is treated for symptoms suggestive of endometriosis. However, it is not sufficient to just look at the cost of all of these treatments but also to evaluate the impact of the disease on her life and ability to work because of either hit-and-miss treatments or inadequate management of her symptoms [12]. The aim of this chapter is to describe the financial impact of endometriosis.

Methodology

Recently, two major reviews have been published regarding the economic impact of endometriosis [1, 2]. In view of the important impact which such papers may have on public health policy internationally, it is important to address any potential conflicts of interest that the authors of these reviews

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may have had. The first paper [1] was coauthored by six authors from the USA, including five authors associated with three private companies related to health services or the pharmaceutical industry (Health Economic Research and Quality of Life Evaluation Services, Abt Associates, Inc., Bethesda, Maryland and Lexington, Massachusetts, USA; Pharmerit North America, LLC, Bethesda, Maryland, USA; TAP Pharmaceutical Products Inc., Lake Forest, Illinois, USA) and one author associated with an academic institution (Women's Health Research Center, George Washington University, Washington, DC, USA). The second paper [2] was written by two academicians from Leuven University, Belgium (Research Centre for Pharmaceutical Care and Pharmaco-economics and Leuven University Fertility Center, University Hospitals Gasthuisberg), and by the owner of the Web site www.endometriosis.org, a Web site designed to provide information for patients, health professionals, and lay people interested in endometriosis. In their conflict of interest statement [2], the authors acknowledged that financial support for this study was received from the Serono pharmaceutical company (Serono, Geneva, Switzerland). It was also mentioned that one of the coauthors, Thomas D'Hooghe, held the Serono chair for Reproductive Medicine at Leuven University Hospital Gasthuisberg [2]. However, the study sponsor, Serono, had no role in study design, data collection, data analysis, data interpretation, or writing of the report and the authors had no conflicts of interest that were relevant to the content of this chapter [2].

The authors of both reviews used a systematic literature search of publicly available electronic databases since 1990 till 2004 [1] or till October 2006 [2]. Both authors used keywords like endometriosis, costs, and productivity [1, 2]. However, the keywords cost of illness, cost analysis, and economic burden were used only by one group [2], and the keywords insurance, pain, and quality of life were used only by the other group [1]. Both authors [1, 2] assessed the economic burden of endometriosis: the overall economic impact of endometriosis, the direct costs associated with specific treatments, and the indirect costs of endometriosis associated with reduced work productivity. In addition, the authors of the first review [1] assessed for patients with a principal diagnosis of endometriosis the inpatient costs obtained from analyses of the Healthcare Cost and Utilization Project (HCUP), the National Inpatient Sample (NIS), and the HUCP Kid's Inpatient Database (KID) and the outpatient costs obtained from the National Ambulatory Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS). In addition, the objective of the second review [2] was to determine the level and drivers of endometriosis costs, to appraise the methodological quality of cost studies, and to propose directions for designing future studies of the costs of

endometriosis. In both papers, 13 papers were finally included in the analysis, but remarkably only 6 of 13 papers included in the second review [2] were included in the first review [1], and 7 out of 13 papers were included in the first review [1] but not in the second review [2]. This can be partially but not fully explained by the fact that the authors of the second review [2] excluded 7 papers 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.

Results

Both reviews suggested that the economic impact of endometriosis to society is considerable, although published information is scarce and future studies are needed.

Direct costs

Direct costs included direct costs related to healthcare resource use (e.g., medication, diagnostic and surgical procedures, visits to healthcare providers, and hospitalization) and direct nonhealthcare costs (e.g., transportation to the healthcare provider) [2].

Kunz *et al.* [16] indicated that annual direct healthcare costs of endometriosis are substantial, amounting to \$2801 per patient. These direct costs were broken down into hospitalization costs (90%) and outpatient costs (10%), suggesting that inpatient costs are the primary driver of direct costs of endometriosis [2, 16]. Focusing on patients hospitalized for endometriosis, two studies observed that annual inpatient costs per patient nearly doubled from \$7855 in 1993 to \$12,644 in 2002, despite a steady decline in the length of hospital stay during this period of time [1, 8, 17]. In contrast, the direct costs associated with pelvic inflammatory disease have decreased from \$3.1 billion in 1994 to \$1.06 billion in 1998 [18].

Direct costs of medical treatment of endometriosis

Pearson and Pickersgill [19] evaluated the costs of the most commonly used medical treatments of endometriosis in the United Kingdom. The cost of 6 months of treatment amounted to \$11–\$18 with progestogen-only contraceptives, \$8 with the combined oral contraceptive pill, \$225 with danazol, \$945 with gestrinone, \$1035 and \$1145 with goserelin with and without add-back hormone replacement therapy, respectively. Within the class of gonadotropin-releasing hormone (GnRH) agonists, a cost advantage of treatment with nafarelin acetate as compared with leuprolide acetate has been reported [20]. Direct healthcare costs of 6 months of treatment

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amounted to \$2241 per patient with nafarelin acetate and \$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 [2].

Direct costs associated with surgical interventions

Hysterectomy, laparoscopy, and laparotomy are commonly performed on patients with endometriosis, with hysterectomy the most frequently performed [1]. Zhao *et al.* [8] published that a total abdominal hysterectomy was the most commonly performed procedure, accounting for 55–60% of surgical procedures for women with endometriosis. A total abdominal hysterectomy was associated with higher mean total charges when compared to laparotomy and to other uterus-related operations in 1991 and 1992 [1, 8]. In 2002, total abdominal hysterectomy, with endometriosis as the principal diagnosis, was the most frequently used hysterectomy technique and most costly compared to other techniques [1].

Besides hysterectomy, laparoscopy, and laparotomy are other surgical procedures that are often performed for patients with endometriosis [1]. Compared to laparotomy, laparoscopy generally results in quicker recovery, decreased morbidity, and lower costs [1]. Focusing on inpatient costs, a cost analysis found that laparotomy (\$9533) was nearly twice as expensive as laparoscopy (\$5014) [2, 21]. To the best of our knowledge, there are no publications documenting the costs of assisted reproductive technology in infertile patients with endometriosis [2].

Medical approach versus surgical approach

Direct cost analyses of endometriosis in patients presenting with CPP suggest that medical treatment of endometriosis with GnRH agonist therapy may be less expensive than a surgical treatment [2]. However, the lower costs of medical treatment need to be balanced by additional costs due to higher recurrence rates of endometriosis after medical treatment when compared with surgical treatment [2, 5, 22, 23]. 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 CPP [2].

The question arises as to whether economic savings can be generated by nonsurgical diagnosis and medical treatment which would allow patients to be cared for in primary care and which could prevent a surgical approach

with hospitalization. The answer is no, because currently there is no reliable nonsurgical diagnostic test for endometriosis. Diagnosis requires laparoscopy, preferably with histological confirmation [4]. 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 [2, 4].

Ambulatory resource use

Analysis of the 2002 NAMCS/NHAMCS data [1] revealed that more than 600,000 ambulatory patient visits related to endometriosis occurred in 2002, including 80% physician office visits (15% by women younger than 21 years), 8% emergency department visits (6% by women younger than 21 years), and 12% hospital outpatient visits (11% by women younger than 21 years). Mean and median patient ages for these visits were 27–33 years. Patients younger than 56 years accounted for 85, 100, and 100% of all physician office visits, emergency department visits, and hospital outpatient visits, respectively [1]. Furthermore, analysis of the NAMCS/NHAMCS data in 2002 revealed that there were an estimated 6.5 million physician office visits, emergency department visits, and hospital outpatient visits with pelvic pain as the principal diagnosis [1].

Chronic pelvic pain

Based on data from the 1995–1996 NAMCS and NHAMCS, endometriosis and pelvic pain patients had the highest risk of emergency department visits among all obstetric and gynecologic conditions studied, and this risk was more than two times greater for young women aged 18–29 years compared with women aged 30–44 years [1, 24]. However, this information is not endometriosis specific, since it grouped pelvic pain and endometriosis together [1].

Adolescent endometriosis

No studies are available in the literature quantifying the cost of adolescent endometriosis [1, 2]. Analysis of data from NAMCS/NHAMCS in 2002 showed that women younger than 24 years constituted more than 20% of all outpatient visits for endometriosis. Furthermore, the HCUP KID database showed that in 1997 and in 2002, adolescents 10–17 years of age had hospitalizations due to endometriosis [1]. Adolescents with pelvic pain refractory to treatment with nonsteroidal anti-inflammatory drugs and/or with contraception are estimated to have endometriosis in about 50% (D'Hooghe *et al.*, unpublished data).

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Factors affecting costs

In addition to difficulties involved in diagnosing endometriosis, costs appear to be influenced by the patient profile, the specific diagnosis of endometriosis, and the principal procedure performed [2]. An analysis of inpatient endometriosis treatment showed that costs were higher in older women and in African-American women as compared with Caucasian women [2]. 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 [2, 8].

Indirect costs

Endometriosis is a chronic disease that targets the young, working-age population [1]. Social, indirect, and intangible costs also contribute to the overall economic consequences of endometriosis [1]. These costs include, but are not limited to, time lost from work, loss in work productivity, loss in earned income, social withdrawal, and psychological disorders such as depression, which may manifest as a consequence of endometriosis [1, 2].

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 from 19.2 to 86.4 hours per patient per year [2, 16, 25]. The productivity loss of 86.4 hours translated into annual indirect costs of \$1023 per patient [2].

Indirect costs associated with adolescent endometriosis are probably considerable due to school absences, and behavioral and psychosocial consequences, but not well known [1, 2]. It appears that 25% of all excessive school absences in adolescent girls can be attributed to dysmenorrhea or pelvic pain.

CPP, in particular, is a prominent symptom in patients with endometriosis [1]. CPP can be incapacitating to the extent that nearly 24% of women with CPP reported bed stays of 2.5 days per month, 22% reported CPP-related sexual dysfunction, and more than 25% reported dyspareunia [1, 25]. Hummelshoj *et al.* [14] reported that 78% of symptomatic women with endometriosis lose an average of 5.3 days per month at work due to the symptoms, with 36% having had their job affected ($n = 2518$), to the extent that 41% had given up or lost their jobs due to illness, 37% have reduced their hours, 23% have changed their jobs, and 6% are on disability benefits [14]. These authors also found that 72% ($n = 5064$) reported relationship problems, with 10% saying that it caused a split, 11% saying that it was difficult to look after their children, and 34% saying that it caused significant problems with their partner. These data are similar to results from a North

American survey from 1998 ($n = 4000$) [26], where outcomes responses were (7 years apart, in a different study group, and with a different study design) worryingly similar [14].

Endometriosis is a disease with high morbidity and considerable physical and emotional disability [1]. Patients with endometriosis experience increased levels of depression and anxiety compared to patients without endometriosis [1, 27–31]. It is clear that issues surrounding pain and quality of life in women with endometriosis have an impact not only on the affected individual but also on her family, and on society in general [14].

Comparative cost of endometriosis and other chronic diseases

Based on a review of cost estimates in the USA [2], annual healthcare costs and costs of productivity loss associated with endometriosis during the year 2002 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 in the same year in the USA [2]. In a recent retrospective review of administrative data for commercial payers of a US insurance company [3], the extrapolated cost per patient per month (PPPM) was \$791: about double as high as the average cost PPPM (\$485), and higher than or similar to the cost PPPM for high-profile conditions such as hypertension (\$500), diabetes (\$916), and rheumatoid arthritis (\$1121). These costs could be explained by the high hospital admission rate and the surgical procedures. Furthermore, due to the added cost related to comorbid conditions like interstitial cystitis, depression, migraine, irritable bowel syndrome, chronic fatigue syndrome, abdominal pain, and infertility, women with endometriosis incurred total direct medical costs that were, on average, 63% higher than medical costs for the average women in a commercially insured group [3].

Guidelines for future research regarding health economics of endometriosis

Methodological analysis of the available evidence has shown important shortcomings [1, 2]. Few studies have reported on cost estimates by key symptoms attributable to endometriosis [1]. 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 CPP [2].

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Evidence of endometriosis costs in infertile patients is largely lacking. Cost estimates in the literature available were biased due to the absence of a control group of patients without endometriosis, inadequate consideration of endometriosis recurrence, and restricted scope of costs [2].

It has been recommended [2] that the following guidelines should be taken into account when designing future cost studies of endometriosis. Firstly, a distinction should be made between the disease endometriosis and the associated symptoms such as pain and infertility. Secondly, costs should be differentiated according to the various degrees (minimal, mild, moderate, or severe) of endometriosis, as specified in the classification system of the American Society for Reproductive Medicine [32]. Thirdly, there is an unmet need to determine the cost related to endometriosis in adolescents. Fourthly, prospective longitudinal follow-up studies are needed from the moment of diagnosis until menopause, including cost of diagnosis, surgical and medical treatment, complications, recurrences, ambulatory care, etc. Fifthly, a prospective calculation of indirect costs related to endometriosis (loss of work, impaired quality of life, etc.) is mandatory. Sixthly, a prospective collection of primary data on actual healthcare resource use by endometriosis patients is needed on a national and an international level, based on a well-defined list of the major cost items and comorbid conditions like interstitial cystitis, depression, migraine, irritable bowel syndrome, chronic fatigue syndrome, abdominal pain, and infertility.

Calculation of endometriosis cost is needed for increased awareness of endometriosis in politics determining health policy and research funding

Public health initiatives must be undertaken to generate awareness of the high prevalence and impact of endometriosis across all societies and at all levels [14]. A disease which has such a profound effect on society needs to be recognized and dealt with by society [15]. Action, commenced at grassroot level, for increased awareness and investment in research has resulted in unprecedented recognition of endometriosis by the European Parliament in 2005 and 2006, offering a welcome assurance to the scientific community [15]. Inspired by the actions of the European Parliament, the Italian Senate has recognized endometriosis as a social disease and has produced a 5-year plan to improve treatment of endometriosis at a national level [15]. This initiative heralds a new era of strategic alliances between patients, physicians, scientists, and legislators, where all the stakeholders

work together to address disease impact and disease resolution at a personal level and for society as a whole [15]. It is now time for the European Union to heed the call for action set out in the 2005 Written Declaration and the recommendations by the Italian Senate, and support national governments through the provision of resources and regulations, and for the rest of the European Community's countries—indeed countries across the world—to follow the Italian example and recognize endometriosis as a disease that needs to be dealt with by society as a whole [15].

The alliances, which have been formed as a result of the EU and Italian initiatives, are an important step forward in addressing all aspects of the disease, including a call for action to

1. fund causal and preventive research;
2. fund national and international awareness campaigns to reduce time to diagnosis, reduce "hit-and-miss" treatments, and ensure timely multidisciplinary expert care;
3. establish national and international registries to monitor morbidity and effectiveness of treatment with a subsequent aim to preserve fertility, improve quality of life, and reduce personal and socioeconomic burden [15]; and
4. recognize that a chronic, multifactorial disease such as endometriosis needs to be treated in centers of excellence by a multidisciplinary team, and work toward the establishment of such centers based on peer-reviewed treatment guidelines [12, 15].

In clinical excellence, those who excel practice according to guidelines of evidence-based medicine and according to quality management with the patient as their central focus [12]. This mantra becomes the aim when establishing centers, networks, or regions of excellence within the discipline of endometriosis [12]. Early referral to a center of expertise, which is skilled in the effective diagnosis and management of endometriosis, is therefore bound to have a profound impact on the reduction of healthcare (and individual) cost by

1. reducing the time to diagnosis and the time wasted to see numerous healthcare professionals;
2. subsequently reducing the time before individualized specialist care is invoked;
3. subsequently reducing expensive hit-and-miss treatments; and
4. subsequently reducing expensive fertility treatments if the disease is under control before fertility is impaired.

We therefore propose that networks and centers of excellence within a multidisciplinary context are the only way forward to ensure that women

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with persistent/chronic endometriosis receive consistent, evidence-based, and cost-efficient care within a framework that is able to provide excellence, continuity of care, a multidisciplinary approach, research, training, and cost effectiveness [12].

Conflict of interest statement

Professor D'Hooghe holds the Merck Serono chair for Reproductive Medicine at Leuven University Hospital Gasthuisberg since 2005, but Merck Serono Pharmaceuticals had no role in designing or writing of this chapter. The authors have no conflicts of interest that are relevant to the content of this chapter.

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