

Hospital care of endometriosis in Spain: a retrospective multicenter analysis of patient characteristics and costs

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Author contributions

JD contributed to the investigation by analyzing and interpreting the burden associated to endometriosis in Spain and was a major contribution in the intellectual content revision. AM analyzed the current situation of endometriosis in Spain, interpreted the statistical data and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Abstract

Background: Despite the potential serious outcomes associated to endometriosis, few data is available describing the real clinical practice and costs. The aim of this study was to evaluate the characteristics of patients diagnosed with endometriosis in Spanish, to measure incidence within the hospital setting and the associated medical costs.

Methods: Admission records of patients with endometriosis registered between 2009 and 2018 were obtained from a Spanish hospital discharge database and analyzed in a retrospective multicenter study.

Results: Data corresponded primarily to inpatient admissions, with a median length of stay of 3 days. Length of stay correlated with patients' age. Admissions were mainly associated to surgical procedures, namely local excision or destruction of lesions. The majority of secondary diagnoses registered corresponded to inflammatory disease of female pelvic organs; 9.2% of patients presented neoplasms of uterus and only 0.9% registered ovarian neoplasms. Mean admission cost was €3566 over the study period.

Conclusions: The majority of admissions reviewed in this study corresponded to the removal of ovarian lesions, although data suggested a decrease in the number of cases that were treated as hospital inpatient admissions over the study period. Older patients, surgical procedures and lengthier admissions were associated with higher medical costs.

Keywords: Endometriosis; hospital incidence; direct medical costs; Spain.

1. Introduction

Endometriosis is a complex syndrome, with potentially serious outcomes including pelvic pain and infertility. Its classical definition was based on the presence of endometrial tissue outside of the uterus, however, a wide spectrum of clinical features has been associated with the disease. Despite it being found mainly in pelvic tissues, this chronic inflammatory syndrome can affect numerous tissues, which led to consider it a systemic disease [1].

Endometriosis is estimated to affect around 10% of women [1]. Despite the efforts made in the past two decades, its pathogenesis remains poorly understood. In addition, specific serum biomarkers for endometriosis are not yet available, with the current diagnostic standard being the laparoscopic visualization of the disease [1]. Microscopic lesions may remain undiagnosed after laparoscopy, and a wide number of patients are diagnosed via imaging ultrasound, which leaves many cases undiagnosed [2]. In this direction, the use of high-resolution magnetic resonance imaging (MRI) has been proposed as a solution for the detection of deep infiltrating endometriosis, yet ultrasound remains the most common approach [2].

Similarly to its diagnosis, the management of patients with endometriosis presents several shortcomings; effective therapeutic interventions are lacking to treat the wide range of symptoms associated with endometriosis. Consensus guideline recommendations focus on the diagnosis of the disease, the hormonal treatment and the removal of lesions to treat endometriosis-related pain, and the treatment of the

reduced fertility associated [3-6]; however, the symptoms treated with hormonal treatment often recur after discontinuation, and the eradication of lesions via laparoscopy is not always possible or desired [7-9].

The first comprehensive guideline published by the Spanish Ministry of Health in 2013 recommended to refer any suspicious cases to a secondary care specialist (hospital based) where the diagnosis can be confirmed by transvaginal ultrasound, followed by MRI or laparoscopy if considered necessary [10]. Subsequent visits are recommended for disease monitoring or further surgery if required [10]. This document was updated in 2020, integrating recommendations from several Spanish regions, the guide from the French Ministry of Health (HAS) from 2017, and the United Kingdom National institute for Health and Care Excellence (NICE) guidelines published in 2017 [11-13]. In addition to previous recommendations, this document specified the possibility to initiate treatment (hormonal or AINE) in primary care, prior monitoring in secondary care centers (gynecology services), and the engagement of a multidisciplinary team when considering surgery in digestive endometriosis; to focus on the patient's life quality was also recommended [13]. Similarly, the working group on Endometriosis, part of the Spanish society of Fertility published specific guidelines for the patient in reproductive age [14].

Despite the efforts to provide integrated comprehensive guidelines few data is available evaluating the real clinical practice in Spain, and the characteristics of the patients that are affected by this disease. Additionally, the substantial medical costs that are assumed to be associated with endometriosis have not been quantified, while large variations exist in medical expenses between different countries [15].

The objective of this study was to evaluate the profile of patients diagnosed with endometriosis in Spanish hospitals between 2009 and 2018, to measure incidence within the hospital setting and the associated medical costs.

2. Methods

2.1. Study setting

Records of ambulatory visits and inpatient admissions registered in Spanish hospitals and other specialized care centers between 1 Jan 2009 and 31 Dec 2018 were analyzed in a retrospective multicenter study. Records were obtained from a Spanish National discharge database, which covers 90% of hospitals in Spain with data from all Spanish regions. The database includes data codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) the year 2016 [16,17]. Centers are responsible for data codification, evaluation and confidentiality. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated.

2.2. Data extraction

All records of ambulatory visits and hospital admissions in which endometriosis was listed as the admission motive were claimed using the corresponding ICD-9 and ICD-10 codes: 617 and N80, respectively (Table 1). Admission records did not contain any parameters identifying healthcare centers or medical history that were previously recorded to maintain records anonymized, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was no access to identifying information; in this context the

Spanish legislation does not require patient consent and ethics committee approval [18].

2.3. Study variables

The variables analyzed were: patients' age, date of admission, type of admission, date of discharge, type of discharge, readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), primary diagnosis, up to 20 secondary diagnoses registered during the admission, medical procedures and total admission cost. Admission costs were not available for the year 2018 at the time of the study.

2.4. Data analysis

The primary diagnosis was used to classify patients according to the tissue affected with endometriosis in three main groups: patients with adenomyosis, patients with ovarian endometriosis and those with endometriosis of other sites. Patient characteristics were examined in the first admission registered per patient, whereas admission details and costs were analyzed using all admission files.

Age-adjusted hospitalization rate was measured as the annual number of women admitted with endometriosis within the total number of admission files in the database.

Direct medical costs of specialized healthcare were extracted from the database, where they are assigned according to the standardized average expenses of admissions and medical procedures determined by the Spanish Ministry of Health (include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources).

Normality was tested with the Kolmogorov-Smirnov test. Frequencies and percentages are presented for dichotomous variables and mean or median and interquartile range (IQR) were calculated for continuous variables. The Spearman correlation test was used to test correlation between patient's age and length of hospital stay. Two-tailed non-parametric independent t-test (Mann-Whitney U test) or one-way analysis of variance (Kruskal-Wallis test) were used as appropriate, with a $p < 0.05$ considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP. 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

3. Results

Inclusion criteria claimed 44,331 admission files, corresponding to 41,118 individual patients with a median patient age of 37 years (IQR=11) (Figure 1A). Patients' age increased significantly over the study period (35 in 2009 vs. 39 in 2018; $p < 0.0001$).

The majority of reviewed files corresponded to inpatient admissions (99.5%), and median length of hospital stay (LOHS) was 3 days (IQR=2). LOHS correlated with patient's age ($p < 0.0001$) (Figure 1B). Most of the admissions identified in the database were programmed (80.8%), while 18.6% of admissions were not programmed or urgent. Readmission rate was 4.8% over the study period.

The age-adjusted hospitalization rate of endometriosis measured in this database was 12.5 cases per 10,000 patients, decreasing over the study period ($p < 0.0001$). The registration of ovarian endometriosis decreased over the study period ($p < 0.0001$), whereas the diagnosis of adenomyosis and endometriosis of other tissues increased ($p < 0.0001$) (Figure 2A).

A wide variety of medical conditions were registered as secondary diagnoses in patients' admission files Table 2. Neoplasms of uterus and ovary were found in 9.2% and 0.9% of patients, respectively. Malignant neoplasms were found in only 0.2% of the patients. The most frequent secondary conditions as registered in this database were inflammatory diseases of female pelvic organs (21.7%)

To evaluate the cases of endometriosis in multiple tissues, subsequent endometriosis diagnoses were analyzed by first diagnosis (Table 3); 69.2% of patients admitted with endometriosis of the fallopian tube and 59.0% of those with endometriosis of the pelvic peritoneum were diagnosed with ovarian endometriosis.

The majority of procedures registered (73.3%) were surgical procedures, and 26.7% were other medical procedures (Table 4). Overall, the majority of admissions (96.8%) registered operations on ovaries: 52.7% of procedures corresponded to the local excision or destruction of ovarian lesion or tissue, 30.3% were unilateral or bilateral oophorectomies and 10.3% the lysis of adhesions of ovary and fallopian tube. This varied according to the tissue that was affected by endometriosis.

The medical costs associated to endometriosis at the hospital level were evaluated. Each admission file included a total admission cost, based on procedures and other expenses related to the admission. Mean admission cost was €3566 over the study period. The mean costs per admission were €3778, €3433 and €4020 for adenomyosis, ovarian endometriosis and other endometriosis types, respectively (Table 5). Seventy-one percent of all the costs were registered in patients primarily admitted with ovarian endometriosis, whereas the higher costs per admission were registered in patients admitted due to intestine endometriosis, reaching the €8052. Longer hospital stays

were associated with higher costs; the same association was found in programmed admissions, those associated to surgical procedures and patients' age.

The evolution of admission costs over time revealed significant fluctuations (Figure 2B). Mean cost decreased significantly between 2012 and 2014 ($p < 0.0001$), and increased between 2014 and 2017 ($p < 0.0001$).

4. Discussion

This study aimed to describe the characteristics of women with endometriosis attended in Spanish hospitals and to review main medical procedures and costs. Over the past decade, efforts have focused on unifying the criteria for the diagnosis and management of endometriosis, with the release of comprehensive guidelines and specific protocols [10,11,14]. However, the current application of such guidelines and real patient management at the hospital level have not been reviewed. This study reviewed novel data on the incidence of endometriosis at the hospital level, and revealed several shortcomings in the diagnosis and codification of coexisting conditions and comorbidities associated to endometriosis in such settings.

Admission files corresponding to 41,118 individual patients were reviewed in this study. Median age was 37 years, with a minority of patients assumed to be postmenopausal; median age increased over the study period.

Total hospitalization rate decreased over the period of study; this data is in contrast with epidemiological studies that suggest a general increase in the diagnosis of endometriosis, and could indicate that inpatient hospital care for this disease is becoming less common [19]. Most of the hospital admissions analyzed herein corresponded to inpatient admissions associated to surgical procedures, with a median length of stay of 3 days. LOHS increased with patients' age, a correlation that has been

previously described in the United States in a population of women receiving surgery for with advanced endometriosis [20]. The disease stage could not be determined in this database, however, the local excision or destruction of ovarian lesions or tissue, oophorectomies and the lysis of adhesions of ovaries and fallopian tube were the most common medical procedures.

There is general consensus that the ideal therapeutic approach should be discussed and decided with the patient, considering the totality of symptoms and the patients' priorities, keeping in mind that radical surgery may be required in certain cases [9]. Nonetheless, previous results indicate that patients' life quality can potentially improve after radical surgery for endometriosis [21].

Patients' quality of life should be at the center in the treatment of endometriosis. In this context, one of the factors to consider is the comorbidity level of the patient. A comprehensive literature review of all studies reporting an association between endometriosis and other diseases suggested a higher risk of several chronic diseases in patients with endometriosis; specifically, patients' with endometriosis displayed an increased risk of ovarian and breast cancers, melanoma, asthma and other conditions [22]. Interestingly, 9.2% of the patients included in this study were diagnosed with uterine neoplasms, whereas the proportion of patients that registered ovarian neoplasms was relatively low. Endometriosis has been associated with an increase in the risk of non-serous and low-grade ovarian cancer, however, it must be noted that the absolute risk of this cancer type remains small [22-24]; the relation with uterine or endometrial cancer has been previously described although an increased risk of this cancer type in patients with endometriosis remains to be confirmed [25,26]. Most

frequent secondary conditions in this population were inflammatory and non-inflammatory disorders of pelvic organs, this included ovarian and fallopian tube cysts. In terms of medical costs, hospital care of endometriosis represented a mean cost of €3566 per patient. Length of stay, nature of admission, surgical procedures and patients' age were associated with higher medical costs, and ovarian endometriosis accounted for the biggest portion of costs, while being the most common form registered. Comparably, hospital-associated costs of endometriosis in Canada between 2008 and 2013 were €2669 (US \$3143), with most of the costs registered in patients with ovarian endometriosis and adenomyosis [27]. A comparable annual healthcare cost was found in 2007 in a meta-analysis (€2378; US \$2801), while this was €3113 per woman in a study with patients from 10 European countries and the United States in 2009 [28,29]. In contrast, in an independent study measuring hospital charges in the United States, mean cost per patient reach the €33,682 (US \$39,662) in 2014-2015 [30]; however, significant geographic variation has been documented in medical costs attributed to endometriosis, which must be taken into account when interpreting these results [15].

Finally, hospital costs in Spain experimented a significant decrease between 2012 and 2014, which could be associated with the economic crisis that had great effects on the Spanish medical and pharmaceutical expenditure [31].

It is plausible that a number of limitations could have influenced the results obtained. This study was hospital based, which may limit data inclusion to those patients with severe endometriosis; accordingly, results cannot be extrapolated to the general population with endometriosis. Additionally, any patients admitted with pelvic pain due to endometriosis in which this code was not registered could not be included in

the study. Other limitations derived from data codification must be considered, including the lack of specific codes that indicate disease severity and deficiencies in the coding of comorbidities. Moreover, data inclusion was limited to a ratio of 1.1 admissions per patient and generally corresponded to inpatient care; a random admission sample is provided in the database, limiting the analysis of patient long-term management, although it permits to evaluate individual admission characteristics and costs.

5. Conclusions

Admissions for endometriosis in the hospital settings are principally associated to the removal of ovarian lesions, requiring hospital stays of 3 days. Data suggests a possible decrease in the number of cases that are treated as hospital inpatient admissions in Spain. This study also revealed that hospital-based data codification in endometriosis can be improved, particularly focusing in patients' comorbidities; in this context, the incidence of uterine and endometrial cancer in this population should be further explored.

6. Transparency section

6.1. Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

6.2. Data availability statement

Data sharing is restricted due to legal stipulations, yet the data that support the findings of this study is fully available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for

researchers who meet the criteria for access to confidential data at:
<https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm>.

6.3. Declaration of funding

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6.4. Declaration of financial and other interest

The authors declare that they have no competing interests.

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8. Figures

Figure 1 A) Age distribution of the patient population. B) Linear fit of length of hospital stay per patients' age with 95% confidence bands.

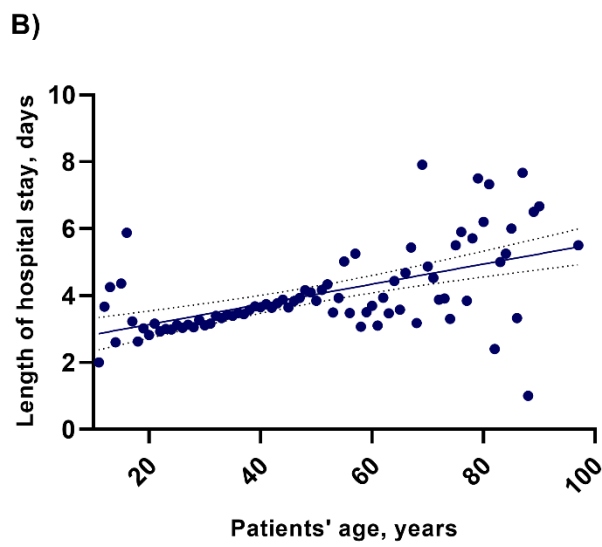
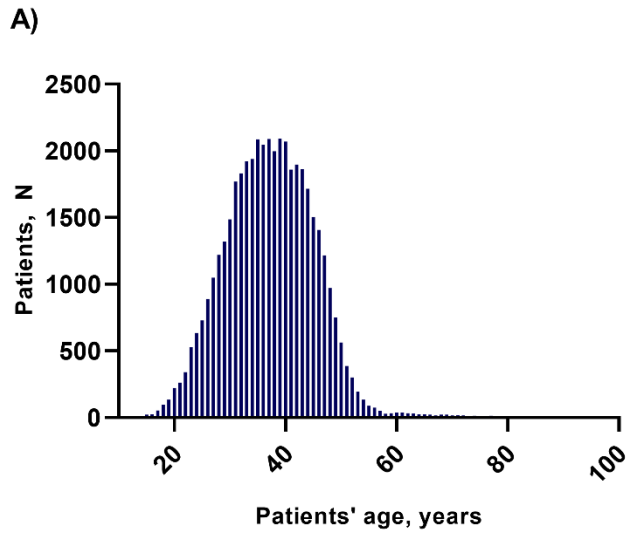
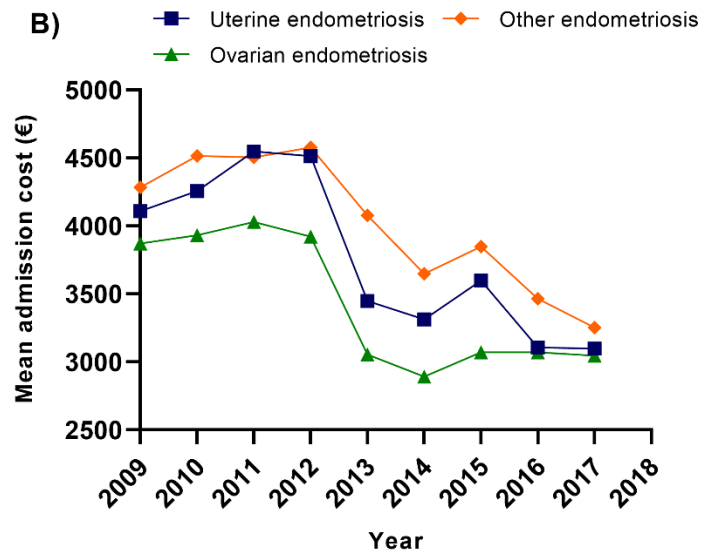
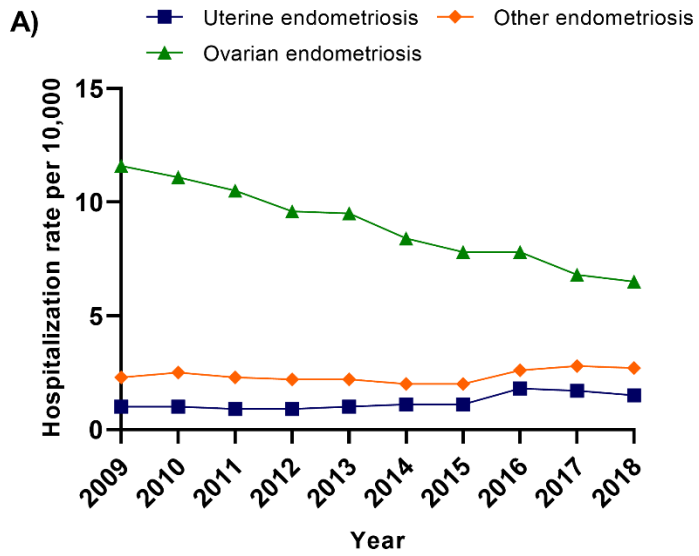


Figure 2 A) Hospitalization rate per 10,000 admissions per tissue over the study period (2009-2018). B) Mean cost per admission over time in patients with adenomyosis, ovarian or other endometriosis (2009-2017).



9. Tables

Table 1 International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) and 10th version (ICD-10) codes.

Description	ICD-9 codes	ICD-10 codes
Adenomyosis (endometriosis of uterus)	617.0	N80.0
Endometriosis of ovary	617.1	N80.1
Endometriosis of fallopian tube	617.2	N80.2
Endometriosis of pelvic peritoneum	617.3	N80.3
Endometriosis of rectovaginal septum and vagina	617.4	N80.4
Endometriosis of intestine	617.5	N80.5
Endometriosis in scar of skin	617.6	N80.6
Endometriosis of other specified sites	617.8	N80.8
Endometriosis, site unspecified	617.9	N80.9

Table 2 Characteristics of patients included in the study.

	Total, % (N=41,118)	Adenomyosis, % (N=3591)	Ovarian endometriosis, % (N=30,081)	Other endometriosis, % (N=7446)
Median age, years (IQR)	37 (11)	43 (9)	37 (11)	37 (10)
<i>Secondary diagnoses, %</i>	-	-	-	-

Neoplasm of uterus	9.2	18.7	8.8	5.9
Neoplasm of ovary	0.9	1.5	0.9	0.6
Neoplasms of other sites	0.7	1.0	0.6	0.8
Thyroid disorder	4.2	6.0	3.9	4.5
Diabetes mellitus	1.2	2.6	1.0	1.1
Overweight and obesity	2.4	4.1	2.3	1.9
Iron deficiency anemias	1.9	6.9	1.5	1.5
Other and unspecified anemias	4.2	6.5	4.1	3.5
Depressive disorder	1.5	2.8	1.3	1.5
Anxiety disorders	2.1	3.4	1.8	2.3
Tobacco use disorder	7.8	7.5	8.0	6.9
Nonessential hypertension	3.6	8.1	3.0	3.6
Inflammatory Disease Of Female Pelvic Organs	21.7	21.9	23.0	16.2
Non inflammatory disorders of ovary, fallopian tube and broad ligament (i.e. cyst)	8.0	11.6	7.9	6.6
Disorders of uterus not elsewhere classified (i.e. polyp, synechia, atrophy)	3.3	11.9	2.5	2.1
Dysmenorrhea or unspecified pain of female genital organs	2.7	4.4	2.2	3.6
Disorders of menstruation and other abnormal bleeding from female genital tract	1.5	10.2	0.7	1.0
Female infertility	3.1	1.1	3.4	2.9

Table 3 Correlation among tissues affected by endometriosis.

Secondary diagnoses, %	Adeno myosis of ovary	fallopi an tube	periton eum	ginal septum , vagina	intestin e	in scar of skin	other specific d sites	unspeci fied
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First diagnosis									
Adenomyosis	-	24.3	6.4	6.5	3.1	4.6	0.1	2.5	0.5
Endometriosis of ovary	3.3	-	4.7	6.5	1.6	1.8	0.0	1.3	0.4
Endometriosis of fallopian tube	13.0	69.2	-	12.9	4.5	8.3	0.0	3.4	0.3
Endometriosis of pelvic peritoneum	8.1	59.0	8.0	-	6.2	8.1	0.1	5.0	0.6
Endometriosis of rectovaginal septum and vagina	12.8	49.1	9.2	20.4	-	14.8	0.0	7.6	0.6
Endometriosis of intestine	14.6	42.7	13.1	20.6	11.4	-	0.1	9.9	0.6
Endometriosis in scar of skin	0.8	2.6	0.2	1.0	0.0	0.2	-	2.2	0.4
Endometriosis of other specified sites	7.0	26.2	4.6	11.2	5.1	8.7	0.7	-	0.5
Endometriosis, site unspecified	0.8	4.4	0.3	0.8	0.2	0.3	0.1	0.3	-

Table 4 Surgical and medical procedures registered during the admission.

	Total, % (N=44,331)	Adenomyosis, % (N=3839)	Ovarian endometriosis, % (N=32,216)	Other endometriosis, % (N=8276)

<i>Surgical procedures</i>	-	-	-	-
Diagnostic procedures on intestine (i.e. endoscopy, biopsy)	0.7	0.7	0.3	2.5
Excision, destruction or repair of lesion or tissue of intestine	2.8	3.0	1.0	10.3
Operations on rectum, recto sigmoid and perirectal tissue (i.e. excision, tissue resection)	1.8	2.3	0.8	6.1
Diagnostic procedures of abdominal region (i.e. biopsy)	9.0	8.6	7.3	16.9
Lysis of peritoneal adhesions	9.6	7.8	9.7	10.1
Operations on urinary bladder and urinary tract (i.e. biopsy, excision, lysis of lesion)	4.9	8.0	3.1	11.1
Diagnostic procedures on ovaries	2.3	0.6	2.8	0.9
Local excision or destruction of ovarian lesion or tissue	52.7	7.6	65.8	15.9
Unilateral or bilateral oophorectomy	30.3	37.9	31.8	20.5
Lysis of adhesions of ovary and fallopian tube	10.3	4.0	11.8	6.7
Procedures on fallopian tubes	13.6	12.3	13.5	14.3
Operations of uterus (i.e. incision, excision, uterus removal)	21.4	87.1	14.0	24.5
Operations of vagina (i.e. excision, tissue repair)	2.0	3.3	1.0	5.5
Procedures on skin and subcutaneous tissue (i.e. incision, biopsy)	1.2	0.4	0.3	5.2
<i>Medical procedures</i>	-	-	-	-
Diagnostic radiology	2.2	3.2	1.7	4.0
Other radio diagnostic and related techniques	22.3	20.0	20.1	33.0
Evaluation, consultation and examination	3.4	4.2	3.1	4.3
Microscopic examination of sample	7.9	10.0	7.4	8.8
Blood transfusion	2.0	4.4	1.8	2.1
Injection or infusion of therapeutic or prophylactic substance	21.1	25.2	19.8	24.8
Contraception prescription	2.7	2.7	2.8	2.6

Table 5 Mean direct medical costs in hospital settings per patient group.

	Total, €	Adenomyosis, €	Ovarian endometriosis,	Other endometriosis,
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			€	€
Mean admission cost	3566	3778	3433	4020
Admissions ≤ 3 days	3343	3359	3319	3458
Admissions > 3 days	4150	4070	3939	4737
Urgent admissions	3092	2853	2886	3652
Programmed admissions	3737	3884	3627	4173
Surgical procedures	3822	4046	3688	4426
Medical procedures	1774	1816	1662	2004
≤ 37 years of age	3541	3394	3463	3895
> 37 years of age	3708	3837	3559	4189