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Original Article
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Impact of hysterectomy on analgesic, psychoactive and neuroactive drug use in women with endometriosis: nationwide cohort study

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Objective To evaluate how hysterectomy affects the prescription of analgesic, psychotropic and neuroactive drugs in women with endometriosis using population-based nationwide registers.

Design Nationwide cohort study.

Setting Swedish national registers, from 1 January 2009 to 31 December 2018.

Population Women with benign disease undergoing a total hysterectomy during the 4-year period of 2012–2015. Women with endometriosis (n = 1074) were identified and compared with women who did not have endometriosis (n = 10 890).

Methods Prospectively collected data from two population-based registers were linked: the Swedish National Quality Register of Gynaecological Surgery and the Swedish National Drug Register. Multivariate logistic regression was used as the main statistical method.

Main outcome measures Changes in drug prescription over time for 3 years prior to and 3 years after hysterectomy.

Results The frequency of prescription of analgesics was higher in women with endometriosis compared with women without endometriosis (OR 2.2, 95% CI 1.7–2.9). Among women with endometriosis, the prescription of analgesics (OR 1.0, 95% CI 0.8–1.2) did not decrease 3 years after hysterectomy compared with the 3 years prior to surgery. There was also a significantly higher rate of prescription of psychoactive (OR 1.6, 95% CI 1.4–2.0) and neuroactive drugs (OR 1.9, 95% CI 1.3–2.7) in the long term postoperatively.

Conclusions In women undergoing hysterectomy, endometriosis was associated with a higher prescription rate of analgesics. In the endometriosis group the prescription of analgesic, psychoactive and neuroactive drugs did not decrease when comparing prescription rates for the 3 years prior to and the 3 years after surgery.

Keywords Endometriosis, hysterectomy, pain, prescription.

Tweetable abstract In women with endometriosis, the long-term prescription of analgesics did not decrease after hysterectomy.

Linked article This article is commented on by S Latif and D Mavrelos, p. 856 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16514.

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Introduction

The management of pain associated with endometriosis is often challenging and a matter of controversy.[1] The true prevalence of endometriosis is unknown, as it is a surgical diagnosis and a number of patients will not have surgical confirmation of the diagnosis. Nonetheless, the prevalence of endometriosis in fertile women is estimated to be 5–10%, with higher estimates in women with pelvic pain and/or infertility (35–50%).[2,3] In a study on women having had a hysterectomy in 2016, 15.2% had a visually confirmed diagnosis of endometriosis.[4]

A cardinal symptom of endometriosis is severe and persistent abdominal pain,[2,5,6] with implications on daily function, social interactions, sexuality and psychological wellbeing.[7,8] The reason for endometriosis-related pain is elusive, but involves different pathways and may differ between patients. Endometriosis-associated pain is complex

and may be nociceptive, neuropathic or a combination of both.[6] Pain in endometriosis can be classified as acute or consistent pain, and can be cyclic or non-cyclic.[9] The chronic inflammation can lead to peripheral sensitisation, with axon growth at the site of the endometriosis lesion. The afferent nerve fibres from the lesion and the pelvic floor can merge in the spinal cord and thus be independent of input from the peripheral nerve. The neurons in the central nervous system can become hyper-responsive to even mild stimuli. This is termed central sensitisation and is common with chronic endometriosis pain.[10] As in other conditions with consistent pain, endometriosis can lead to anxiety, sleeping disorders and depression.[11] It is known that the severity of pain does not correlate with the American Society for Reproductive Medicine (ASRM) classification of endometriosis, further befuddling our understanding of the mechanisms involved.[12]

Hysterectomy is often considered a last option for patients with endometriosis-related pain.[13] When performing a hysterectomy on a woman with endometriosis, a bilateral salpingo-oophorectomy may reduce the risk of recurrence[14]. This must be weighed against the consequences of a premature menopause. Also, some studies have shown that a complete resection of the endometriosis nodules is more effective than hysterectomy alone.[15–17] The long-term pain-reducing effect of hysterectomy is unclear,[18] however, and severe continuing pain is a common reason for analgesic and opioid consumption. The overuse of opioids is a major public health problem and continuous intake is a risk factor for substance abuse.[19] The aim of the present study was to assess how hysterectomy affects the prescription of analgesic, psychotropic and neuroactive drugs in women with endometriosis using population-based nationwide registers.

Methods

Data were collected from two Swedish population-based registers: the Swedish National Quality Register of Gynaecological Surgery (GynOp) and the Swedish National Drug Register, with the latter supervised by the Swedish Board of Health and Welfare. GynOp was established in 1994 with 52/56 (93%) Swedish Gynaecological Departments reporting data to the register at the time of the study. This corresponds to a coverage of 86–89% of hysterectomies performed in Sweden. The data from GynOp are prospectively collected and reported both by patient and surgeon, and contain information on demographics as well as pre-, intra- and postoperative data. Data before and during surgery, as well as pre-discharge complications, are reported by the surgeon. The patient answers a preoperative questionnaire, as well as questionnaires at 2 months and 1 year after surgery. If the patient reports a complication during follow-up the surgeon will get a notification. The surgeon will then either meet the patient or read her medical journal and then register the complication.[20]

The Swedish national drug register contains national data on prescribed and retrieved drugs. It was established in 2005 and is a nationwide health-care register, supervised by the Swedish Board of Health and Welfare, and has a coverage of 97–100%, depending on the variable of interest.[21] In Sweden, only a small number of drugs used for self-care can be bought from the pharmacy without a prescription.

In GynOp we identified all women having had a total hysterectomy, with or without a salpingo-oophorectomy, from 1 January 2012 to 31 December 2015. We used codes from the International Statistical Classification of Diseases and Related Health Problems – Tenth Revision (ICD-10) to identify women with endometriosis (N80.1, N80.3 and N80.9, referred to as 'exposed') and those with no endometriosis diagnosis (referred to as 'unexposed'). The postoperative diagnosis held in the register was given only after a pathological examination of the specimen. Patients with a diagnosis of malignancy or hysterectomy for an obstetric complication were excluded. As prolapse as an indication for surgery often results in full prolapse surgery in addition to hysterectomy, this group of women were also excluded from the analysis. To avoid misclassification bias, we added two extra variables to find patients with endometriosis. Cases where the surgeon had entered 'difficulties during operation due to endometriosis' or 'severe endometriosis seen during operation' were also included in the endometriosis group, even if the preoperative indication or diagnosis did not state endometriosis. The comparison group consisted of women undergoing hysterectomy for any benign reason other than endometriosis. The most common ICD-10 code in this group was myoma (D25.9), abnormal uterine bleeding (N84.0, N85.0, N92.0 and N92.1), cervical dysplasia (D06.9, N87.0, N87.1, N87.2 and N87.9) or pathology in the adnexa (D27.9, N70.1, N83.0, N83.1, N83.2, N83.5, N83.9 and Q50.5). Study objects with patient-reported endometriosis but no ICD-10 code for endometriosis were excluded from the analysis. A few cases, where the surgeon had described intraoperative mild endometriosis, but without an ICD-10 code for endometriosis, were also excluded. The reason for this was to make sure that only patients with biopsy-proven endometriosis were included in the study. Women with adenomyosis were identified by the postoperative ICD-10 code (N80.0), based on histopathology. If women had concurrent endometriosis they were included in the exposed group, and we subsequently linked all patients with the drug register using the national registration number assigned to all Swedish residents. In order to investigate changes in the prescription of drugs over time, data were collected from a time period

3 years prior to and 3 years after surgery, from 1 January 2009 through to 31 December 2018.

Our primary outcome was to assess pre- and postoperative differences in the prescription of analgesic, psychotropic and neuroactive drugs in women with an endometriosis diagnosis undergoing hysterectomy. Our secondary outcome was to compare drug usage in women with endometriosis with a comparison group of women without endometriosis during the same time period. To exclude any prescription specifically for pain in the immediate postoperative period, and to observe the long-term effects on drug prescription, we compared prescriptions for 3 years and 1 year prior to surgery with prescriptions for 2 years and 3 years after surgery. The drugs were identified using the Anatomical Therapeutic Chemical Classification System (ATC code). In the group of patients using opioids prior to surgery we also tested the differences in World Health Defined Daily Dose (DDD), before and after surgery.[22]

We defined ten different drug groups: hormonal treatment for menopausal symptoms, with ATC codes G03C and G03F; hormonal treatment for endometriosis, including contraceptives, with ATC codes G02B, G03A, G03D, G03X, H01C, L02A and L02B; drugs containing opioids, with ATC code N02A; other analgesics, with ATC codes M01A, M01B, M02A and N02B; muscle relaxants, with ATC code M03B; antidepressant drugs, with ATC code N06A; sedative and sleeping pills, with ATC codes N05B and N05C; neuroleptic drugs, with ATC code N05A; anti-epileptic drugs, with ATC code N03A; and psychostimulants, with ATC code N06B. These drugs were put together into three main groups: analgesics (drugs containing opioids, other analgesics and muscle relaxants); psychoactive drugs (sedatives and sleeping pills and antidepressants); and neuroactive drugs (neuroleptic drugs, anti-epileptic drugs and psychostimulants).

Demographic and surgical variables were analysed with respect to an association with the following outcomes: age; body mass index (BMI); American Society of Anesthesiologists Physical Status classification (grouped as ASA classes 1–2 or 3–5); parity (grouped as 0, 1–2, ≥3 children); previous caesarean section; smoking habits; previous abdominal surgery; method of anaesthesia; antibiotics and thrombosis prophylaxis; mode of surgery (abdominal, laparoscopic, vaginal or robotic); concurrent salpingo-oophorectomy; concurrent procedures at the time of hysterectomy (e.g. suture of the ureter, enterorrhaphy, colostomy); weight of the uterus; operation time; conversion to laparotomy; intraoperative bleeding; hospital procedure volume; surgeon's notation of complicated surgery (yes/no); perioperative complications and postoperative complications (up to 1 year after surgery); and hormonal treatment pre- and postoperatively. As the intervention in the study was hysterectomy, surgical variables were specifically chosen from the register to adjust for confounding factors. Aside from surgery, hormonal treatment is the other major treatment option. The prescription of drugs was grouped into 1-year periods related to the date of the operation.

Patients were not involved in the development of this study.

Statistical analyses were conducted in STATA 13.0 (StataCorp LLC, College Station, TX, USA). Baseline characteristics are presented as medians with interquartile ranges (IQRs) for continuous variables and as frequencies and proportions for categorical variables. For the comparison between continuous variables in Table 1 we used quantile regression with 100 bootstrap samples, and for categorical variables we used logistic regression. Negative binomial regression was performed to compare median DDDs in the prescription of drugs containing opioids.

Results from the negative binomial regression model were presented as crude and adjusted incidence rate ratios (cIRR and aIRR, respectively) with 95% confidence intervals (95% CIs). $P < 0.05$ was considered significant. For the categorical end points, namely the pre- and postoperative prescription of drugs (analgesic, psychoactive and neuroactive drugs), univariate and multivariate logistic regression was used for the comparison of the prescription of drugs between exposed and unexposed women. To account for intraindividual dependence, the robust sandwich estimator for standard error was used. Demographic variables as well as perioperative data from Table 1 were adjusted for in the multivariate analysis. Variables with $P > 0.25$ were removed from the final model. Results from the univariate regression model are presented as crude odds ratios (cORs) and results from the multivariate regression model are presented as adjusted odds ratios (aORs), with 95% confidence intervals (95% CIs). When comparing the prescription of drugs before and after hysterectomy, the results were not adjusted for confounding factors as these were comparisons for the same individuals and were thus self-controlled. $P < 0.05$ were considered significant. A sensitivity analysis was performed including the cases where the surgeon had described intraoperative mild endometriosis, but without including an ICD-10 code for endometriosis, in the exposed group.

The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden and conform with the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines for reporting observational studies (www.strobe-statement.org).

Results

A flow chart for the study subjects is shown in Figure 1. Out of the 17 891 patients having had a hysterectomy in

Table 1. Baseline characteristics, including perioperative data for the study population

Baseline characteristics	No endometriosis (n = 10 890)*	Endometriosis (n = 1074)	OR/coef Q (0.5) (95% CI)
Age	47 (9)	44 (7)	−3 (−4.2 to −1.8)
Body mass index (kg/m^2)	26 (6)	26 (6)	0 (−0.6 to 0.6)
ASA 1–2	10 273 (94.3)	1030 (95.9)	1.4 (1.0 to 1.9)
Parity			
0	652 (6.0)	167 (15.6)	Ref.
1–2	3621 (33.3)	384 (35.8)	0.4 (0.3 to 0.5)
≥3	1917 (17.6)	112 (11.4)	0.2 (0.2 to 0.3)
Smoking	948 (8.7)	87 (8.1)	1.2 (1.0 to 1.6)
Caesarean section	1052 (9.7)	145 (13.5)	1.5 (1.2 to 1.8)
Previous abdominal surgery	3313 (30.4)	462 (43.0)	2.0 (1.4 to 2.9)
Preoperative hormonal treatment	5282 (50.8)	588 (66.6)	1.8 (1.6 to 2.1)
Postoperative hormonal treatment	481 (4.4)	224 (20.9)	5.7 (4.8 to 6.8)
Hysterectomy mode			
Abdominal	5932 (54.5)	617 (57.5)	Ref.
Vaginal	2750 (25.3)	59 (5.5)	0.2 (0.2 to 0.3)
Laparoscopic	1291 (11.9)	232 (21.6)	1.7 (1.5 to 2.0)
Robotic	916 (8.4)	166 (15.5)	1.7 (1.4 to 2.1)
Salpingo-oophorectomy	1619 (14.9)	287 (26.7)	2.0 (1.7 to 2.3)
Other concurrent surgery	696 (6.4)	236 (22.0)	3.9 (3.3 to 4.6)
Specimen size (g)	223 (379)	192 (222)	−33 (−45.3 to 20.7)
Complex surgery (surgeon reported)	3953 (36.3)	744 (69.3)	4.0 (3.5 to 4.5)
Hospital volume			
<50/year	1690 (15.5)	141 (13.1)	Ref.
50–150/year	6495 (59.6)	691 (64.3)	1.3 (1.1 to 1.5)
>150/year	2705 (24.8)	242 (22.5)	1.1 (0.9 to 1.3)
Duration of surgery (min)	89 (57)	117 (65)	28 (24.0 to 32.0)
Conversion rate	214 (2.0)	63 (5.9)	3.5 (2.6 to 4.6)
Estimated blood loss (ml)	100 (250)	200 (350)	100 (50.8 to 149.2)
Perioperative complications	356 (3.3)	62 (5.8)	1.8 (1.4 to 2.4)
Complications reported 1 year after surgery	1791 (16.4)	232 (21.6)	1.4 (1.2 to 1.6)

ASA, American Society of Anesthesiologists Physical Status Classification; coef Q (0.5), median difference from quantile regression; conversion rate, conversion to open abdominal hysterectomy; hospital volume, number of hysterectomies performed per year in the hospital; other concurrent surgery, e.g. suture of the ureter, enterorrhaphy, colostomy; pre- and postoperative hormonal treatment, hormonal treatment for endometriosis, including contraceptives (not including menopausal hormonal treatment).
Data are presented as median (interquartile range) or frequencies (proportions).
*Reference.

Sweden in 2012–2015, we identified 1074 patients with a diagnosis of endometriosis pre- and/or intraoperatively and 10 890 women without endometriosis. Table 1 presents baseline characteristics. Exposed women were more often nulliparous (OR 2.9, 95% CI 2.4–3.5), treated with preoperative (cOR 1.8, 95% CI 1.6–2.1) and postoperative (cOR 5.7, 95% CI 4.8–6.8) hormones, and had undergone previous abdominal surgery (cOR 2.0, 95% CI 1.4–2.9), to a greater extent, compared with unexposed women.

Perioperative data are shown in Table 1. Among women with endometriosis, surgery was more often considered complicated (cOR 4.0, 95% CI 3.5–4.5). This was confirmed by a number of objective variables, such as: concurrent surgery (cOR 3.9, 95% CI 3.3–4.6); conversion rate (cOR 3.5, 95% CI 2.6–4.6); intraoperative complications (cOR 1.8, 95% CI 1.4–2.4); and postoperative complications (cOR 1.4, 95% CI 1.2–1.6). For a comparative analysis, see Table S6.

For the whole time period, the overall prescription of analgesics was greater in exposed women compared with unexposed women (aOR 2.2, 95% CI 1.7–2.9) (Figure 2); however, there was no significant difference between exposed and unexposed women in the prescription of psychoactive (aOR 1.1, 95% CI 0.8–1.5) and neuroactive (aOR 1.6, 95% CI 0.7–3.6) drugs during this time period.

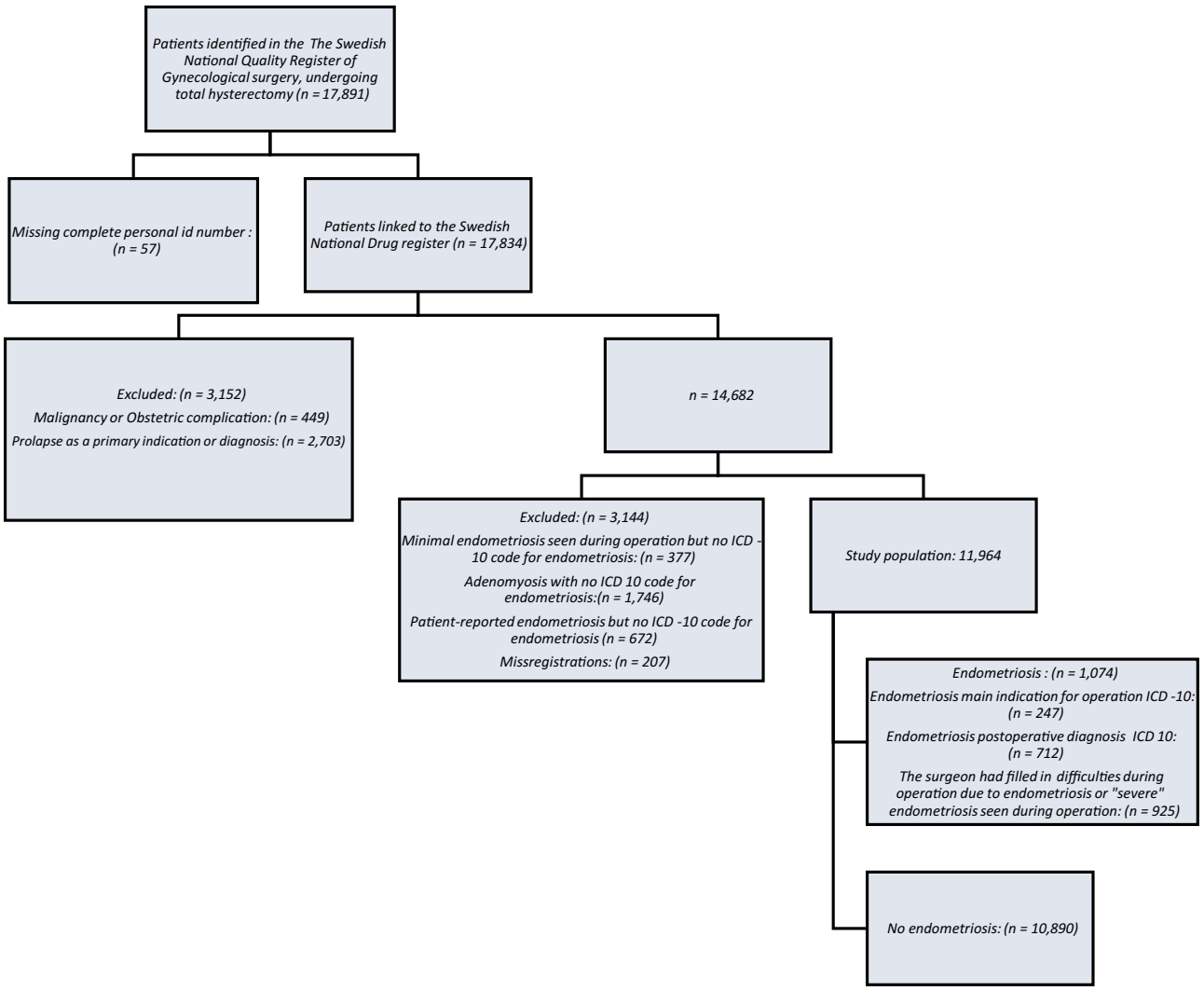
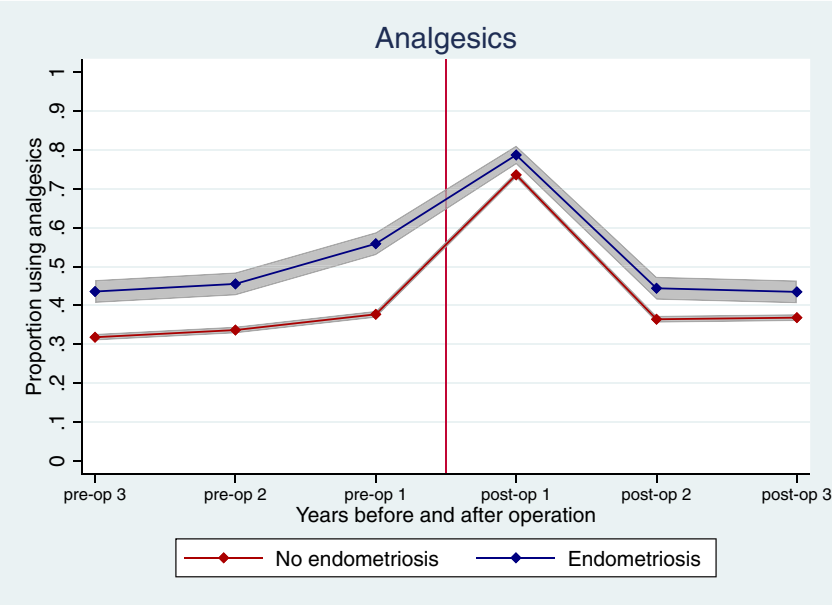


Figure 1. Flow chart of the study population.

Tables 2 and 3 present differences in the exposed group's use of analgesic, psychoactive and neuroactive drugs for 3 years prior to and 3 years after hysterectomy. In the exposed group there was no significant decrease in the use of analgesics comparing the 3 years before surgery with the 3 years after surgery (OR 1.0, 95% CI 0.8–1.2). The prescription of psychoactive (OR 1.6, 95% CI 1.4–2.0) and neuroactive (OR 1.9, 95% CI 1.3–2.7) drugs did in fact increase in the 3 years after hysterectomy, compared with the 3 years before hysterectomy.

Three subgroup analyses of specific drugs from the main groups of analgesic, neuroactive and psychoactive drugs are shown in Figure S1, which shows changes over time in the prescription of opioids, antidepressant drugs, sedatives and sleeping pills for both the exposed and unexposed groups. Drugs containing opioids followed the same pattern over time as analgesics overall. Opioids (aOR 1.6, 95% CI 1.0–2.5) and sedatives and sleeping pills (aOR 1.8, 95% CI 1.2–2.9) were prescribed to a greater extent to the exposed group than to the unexposed group. There was no significant difference in the frequency of prescription of antidepressants (aOR 1.6, 95% CI 1.0–2.6) between the groups. Comparing the 3 years prior to surgery with the 3 years after surgery in the exposed group, there was a significantly higher postoperative prescription of sedatives and sleeping pills (OR 1.7, 95% CI 1.4–2.1), as well as antidepressants (OR 1.4, 95% CI 1.2–1.8). There was no significant decrease in the prescription of opioids (OR 0.9, 95% CI 0.7–1.1).

A subanalysis of the dosage of opioids was performed. Exposed patients were prescribed a higher mean DDD of opioids compared with the unexposed group before and



*Endometriosis vs No endometriosis	cOR (95% CI)	[1]aOR (95% CI)	[2]aOR (95% CI)
Analgesics	2.1 (1.8-2.4)	2.2 (1.7-2.9)	2.3 (1.5-3.6)

Figure 2. Comparison of frequency of women with (n = 1074) or without (n = 10 890) endometriosis being prescribed analgesics, over time. Graph showing point estimate and 95% confidence interval (shadowed area). *A comparison of overall differences in frequency of women with or without endometriosis being prescribed analgesics over the time period of 6 years. 95% CI, 95% confidence interval; aOR, adjusted odds ratio; cOR, crude odds ratio; preop, before hysterectomy; postop, after hysterectomy. [1]Adjusted for all variables in Table 1 in a stepwise multivariate logistic regression model, removing variables with $P > 0.25$; [2]adjusted for all variables in Table 1. Numbers of observations in regression models: [1]aOR = 2016; [2]aOR = 917. For more details, see Table S6.

after surgery overall (aIRR 3.0, 95% CI 1.7–5.1). Furthermore, there was no significant decrease in the mean DDD for opioids 3 years after surgery, compared with 3 years before surgery, in women with endometriosis (IRR 0.9, 95% CI 0.8–1.1). The distribution of the DDD prescription of opioids was skewed, with a few women being prescribed very high doses of drugs containing opioids (data not shown).

Four different subgroups in the exposed group were analysed separately, comparing the prescription of opioids, non-opioids and analgesics overall for the 3 years prior to

Table 2. Comparing the frequency of women with endometriosis (n = 1074) using prescribed analgesics 3 years before and 3 years after hysterectomy

	3 years before hysterectomy*	3 years after hysterectomy	OR 95% CI
Non-opioids	410 (38.1)	417 (38.8)	1.0 (0.9–1.2)
Opioids	240 (22.4)	218 (20.3)	0.9 (0.7–1.1)
Analgesics overall	468 (43.6)	467 (43.5)	1.0 (0.8–1.2)

Non-opioids: aspirin, non-steroid anti-inflammatory drugs, paracetamol.
Data are presented as frequencies (proportions).
*Reference.

Table 3. Comparing the frequency of women with endometriosis (n = 1074) using prescribed psychoactive and neuroactive drugs 3 years before and 3 years after hysterectomy

	3 years before hysterectomy*	3 years after hysterectomy	OR 95% CI
Sedatives and sleeping pills	182 (17.0)	273 (25.4)	1.7 (1.4–2.1)
Antidepressants	210 (19.6)	277 (25.8)	1.4 (1.2–1.8)
Psychoactive drugs overall	307 (28.6)	425 (39.6)	1.6 (1.4–2.0)
Neuroactive drugs overall	44 (4.1)	79 (7.4)	1.9 (1.3–2.7)

Non-opioids: aspirin, non-steroid anti-inflammatory drugs, paracetamol.
Data are presented as frequencies (proportions).
*Reference.

versus the 3 years after hysterectomy. The subgroups consisted of exposed women with or without bilateral salpingo-oophorectomy, adenomyosis and hormonal treatment, respectively. Also, the exposed women were separated into two groups, with women noted by the surgeon as having minimal or mild endometriosis compared with women who were noted to have moderate or severe disease. None of the subgroup analyses differed in outcome compared with the results from the complete exposed group (data presented in Tables S1–S4).

Table S5 shows a sensitivity analysis performed to examine possible changes in the main results if women with minimal or mild endometriosis seen during operation but with no ICD-10 code for endometriosis ($n = 377$) were included in the exposed group. Data from this analysis did not differ from the results in the primarily defined exposed group.

Discussion

Main findings

We found that among women undergoing hysterectomy, endometriosis was associated with a higher degree of prescription of analgesics. In the endometriosis group the prescription of analgesic, psychoactive and neuroactive drugs did not decrease significantly after surgery. In fact, the prescription of psychoactive and neuroactive drugs increased. Furthermore, among women with endometriosis the average daily opioid usage did not decrease after surgery, and there was a small group of patients who had a very high consumption of opioids. In a subgroup analysis of specific drugs, we also observed that the frequency of patients with endometriosis who retrieved drugs containing antidepressants, sleeping pills and sedatives were higher compared with women without endometriosis. The prescription of sedatives and sleeping pills were even higher postoperatively compared with preoperatively. Even in the unexposed group, we found a surprisingly high consumption of analgesics. Interestingly, the difference in analgesic consumption between the two groups seems to diminish over time. This is mainly linked to an increase in the unexposed group, rather than to a decrease of analgesic consumption in the exposed group after surgery. The reasons for this are unclear but does not change the major findings of the study.

Strength and limitations

One strength of our study is that the patients' retrieval of drugs from pharmacies may be considered an objective measurement of perceived pain. Using the Swedish national drug register, with a low rate of missing data and complete national coverage, the study could minimise recall and ascertainment bias. The long follow-up period is also a strength. To some extent, classification bias may have influenced our results as we did not have information on the underlying diagnosis for specific drug prescriptions. Smaller packages of ibuprofen and acetaminophen can be bought over the counter in Sweden, and the consumption of these analgesics was not included in the study. We cannot exclude that some patients were misclassified with regards to exposure and ended up in the control group, which would underestimate the observed differences. A limitation of the study is the lack of data regarding the complete excision of endometriosis nodules, the resection of peritoneal endometriosis during surgery and the preoperative staging of endometriosis. To address this limitation, we used the variable 'concurrent' surgery and surgeon-reported 'complex surgery'. As this is an observational study there is a risk of residual confounding.

Logistic regression was chosen as the analytical method because it offers a way to adjust for background variables in a flexible and transparent way, with few assumptions.

Interpretation

Several prospective studies have shown that hysterectomy may reduce pain,[23–25] but there is a lack of data specifically on how hysterectomy affects pain in patients with endometriosis.[18] Prospective long-term studies are scarce, and few studies have studied the prescription of drugs in this group of patients.[26] The main result of our study is somewhat surprising and contrary to the common notion that hysterectomy, as a last measure, effectively relieves endometriosis-related pain. Nevertheless, the results are in line with two other national register studies on postoperative pain and patient-reported outcomes.[5,27] Hysterectomy is often considered the last option to treat endometriosis, as the procedure by its very nature ends reproduction. If hysterectomy does not decrease the need for analgesics postoperatively, the effectiveness of the procedure as an integral, albeit final, stage of endometriosis pain management becomes doubtful, however.

The definition of pain varies a lot, and women with endometriosis suffer from both acute and chronic pain, and with a severity that is often unrelated to the presence and extent of spread at surgery.[9,12] Pain in general may also be affected by psychiatric and somatic concurrent disorders, as well as by social and cultural factors. Our findings of an increased use of sedatives confirm the complexity of the association between endometriosis and pain after hysterectomy. The concept of pain in women with endometriosis is further complicated by the psychological impact of self-perception in relation to fertility, female identity and sexual function.[7,28] The prescription of drugs could be described as an objective measurement of how often a patient seeks medical attention for pain and how perceived pain persists over time. As such, drug

prescription may be considered a proxy measure that nonetheless increases our understanding of pain management in women with endometriosis. Recurring or remaining endometriotic nodules have been reported in 18–100% of cases after surgery.[29] Some studies imply that in order to reduce pain it is more important to remove the endometriosis lesions than to remove the uterus.[16] According to some studies, a hysterectomy without a concurrent salpingo-oophorectomy is not a definitive treatment for endometriosis.[29,30] In the exposed group in the present study, 26.7% had a salpingo-oophorectomy at the time of surgery, but adjusting for this in the statistical analysis showed no difference in outcome. Thus, different surgical approaches may influence the occurrence of postoperative pain, but at present there is no consensus as to which approach is the more effective. Neither the severity of the disease nor the presence of adenomyosis or hormonal treatment affected our results. Contrary to this finding, previous studies in women with adenomyosis have shown pain relief after hysterectomy. Nevertheless, a rather high proportion of patients will still suffer from persistent pain after surgery.[31] Also, hormonal treatment after surgery has shown a reduction in the recurrence of the disease,[13] but the effect on persistent pain after surgery is not clear.

The results of the present study might be linked to the complex mechanisms of chronic pain in women with endometriosis, such as peripheral and central sensitisation. Furthermore, these mechanisms could be exaggerated by diagnostic failures, resulting in delayed surgery.

Conclusion

In women undergoing hysterectomy, endometriosis was associated with a higher prescription of analgesics. In the endometriosis group, the prescription of analgesic, psychoactive and neuroactive drugs did not decrease, when comparing the 3 years prior to surgery with the 3 years after surgery.

Practical implications

Patients with endometriosis often end up with chronic pain,[11] and are at risk for the excessive use of addictive drugs.[32] Our hypothesis was that the prescription of analgesic and psychotropic drugs would decrease after surgery, especially in a long-term follow-up; however, our data did not support our hypothesis. At the same time, we recognise that the indication for hysterectomy is not solely based on the presence of pain. Patients often also have dysfunctional uterine bleeding, side effects from hormonal treatment and sometimes even an obstruction of the intestines or ureters, which may affect the decision to perform a hysterectomy. Healthcare professionals should counsel endometriosis patients before hysterectomy in order to set realistic expectations of pain reduction and the consumption of analgesic and psychoactive drugs after surgery. Being aware that surgery in itself may not remove the perceived need for analgesics after surgery may prepare the patient for alternative pain management strategies.

Research implications

This study raises questions about the surgical efficacy of hysterectomy in women with endometriosis-related pain. An area of interest for further studies would be to compare different surgical strategies, e.g. hysterectomy versus the removal of endometriotic nodules with regards to analgesic and psychoactive drug consumption. Also, the further evaluation and optimisation of pain management programmes may improve the standard of care for women with severe endometriosis pain and avoid continuous opioid use.

Disclosure of interests

MB has had a temporary assignment as a proctor in robotic surgery for Intuitive Surgical. ME has been awarded a research grant from Intuitive Surgical. DA, MWS and MP have no conflicts of interest to declare. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

MB designed the study, together with ME and DA. MB applied for ethical approval and collected data from the registers, with support from MP and ME. MP is head of the hysterectomy protocol, a division of the Swedish National Quality Register of Gynaecological Surgery. Also, MB, analysed the data with support from biostatisticians HH and ME. MB wrote the article. The article was revised by DA, ME, MP and MS, and they also approved the final version for publication.

Details of ethics approval

Ethical approval was obtained from the research ethics committee at Karolinska Institutet, Stockholm, registration number 2018/190-31 (2 April 2019). The patients receive written information about the registers and also give informed consent for data collection in the preoperative questionnaires. The information for patients states that data from the registers may be used for research. Patients always have the possibility to remove any personal data from the registers.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Comparison of the frequency of exposed (n = 1074) and unexposed (n = 10 890) women being prescribed drugs containing opioids, antidepressants, sedatives and sleeping pills over time.

Table S1. Comparison of the frequency of exposed women (n = 1074) with or without adenomyosis being prescribed analgesics 3 years before and 3 years after hysterectomy.

Table S2. Comparison of the frequency of exposed women (n = 1074) with or without bilateral salpingo-oophorectomy being prescribed analgesics 3 years before and 3 years after hysterectomy.

Table S3. Comparison of the frequency of exposed women (n = 1074) by severity of endometriosis disease being prescribed analgesics 3 years before and 3 years after hysterectomy.

Table S4. Comparison of the frequency of exposed women (n = 1074) with or without hormonal treatment for endometriosis being prescribed analgesics 3 years before and 3 years after hysterectomy.

Table S5. Sensitivity analysis including women with minimal endometriosis seen during surgery but with no ICD-10 code for endometriosis (n = 377) being prescribed analgesics 3 years before and 3 years after hysterectomy.

Table S6. Comparison of frequency of women with (n = 1074) or without (n = 10 890) endometriosis being prescribed analgesics, over time. ■

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