Original Article

Germany Endometriosis Pattern Changes; Prevalence and Therapy over 2010 and 2019 Years: A Retrospective Cross-Sectional Study

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Abstract

Background: The aim of this study was to investigate whether the prevalence and the therapy patterns of endometriosis differ in 2010 and 2019.

Materials and Methods: This retrospective cross-sectional study was based on the data from the IQVIA Disease Analyzer database and included women with at least one visit to one of the 136 private gynecologist practices in Germany in 2010 or 2019. The prevalence of endometriosis as well as prevalence of each endometriosis therapy such as Dienogest, other Progestins than Dienogest, and Gonadotropin-Releasing Hormones, was calculated in both years.

Results: The present study included 346,249 women documented in 2010 and 343,486 women documented in 2019. The prevalence of endometriosis increased from 0.53% in 2010 to 0.66% in 2019 (P<0.001). The proportion of endometriosis patients treated with Dienogest increased significantly between 2010 and 2019 (18.1 vs. 35.0%). The proportion of women prescribed other Progestins than Dienogest has not significantly changed between 2010 and 2019 (8.4 vs. 8.3%). Gonadotropin-releasing hormones were prescribed only rarely in both 2010 and 2019, with a significant decrease in prescriptions between these two years (3.7 vs. 2.0%).

Conclusion: There were significant changes in the prevalence and medical therapeutic patterns of endometriosis in 2010 versus 2019 reflecting changes in therapy guidelines and possibly in diagnostic methods.

Keywords: Dienogest, Endometriosis, Gonadotropin-Releasing Hormones, Prevalence, Progestin

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Introduction

Endometriosis, a chronic disease, is defined as the presence of functional endometrial mucosa outside the uterine cavity, often in the pelvis, but also more rarely in locations such as the pericardium, pleura cavity and even in the brain tissue. It is one of the most common benign gynecological diseases in pre-menopausal women. Symptoms of endometriosis re included pelvic pain, dysmenorrhea, periovulatory pain, dyspareunia, dyschezia, dysuria and infertility. Endometriosis affects approximately 5-10% of reproductive age woman, which equates to around 190 million women worldwide, with prevalence peaking between 25 and 35 years of age (1-3).

Despite of benign proliferative nature, endometriosis shares certain characteristics with neoplastic processes, including inflammatory state, invasion of adjacent tissues, induction of angiogenesis, and resistance to apoptosis (4).

Further research, new therapeutic options have come to the market. Subsequent of this improved knowledge, awareness of endometriosis has increased in the medical communities and the general population. Although therapeutic options have improved, one of the main problems has been remained : correct diagnosis. According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines (2014), the gold standard endometriosis diagnosis is a combination of laparoscopy visualization and histological confirmation subsequent: endometrial glands and/or stroma existence (5).

The laparoscopic surgery is defined as a gold standard for diagnosis, while it is invasive and costly, and endometriosis remains undiagnosed (6).

Despite of various therapeutic options for this condition, medical therapy is placed in the secondary stage after surgical treatment , a gold standard (7-9).

Several medical therapies aim to create a hypoestrogen-

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ic state in the endometriosis affected women Examples of these treatments include gonadotropin-releasing hormone agonist (GnRHa), GnRH antagonist (GnRH-ant) and synthetic androgens (10).

Since laparoscopy is often perceived as excessively invasive by patients, especially young women, it seems impractical as a first-line diagnostic tool. As a result, investigators have sought to identify non-invasive tools such as biomarkers for early diagnosis that might prevent or delay the progression of endometriosis (7). However, a study in 2016 that tested various biomarkers for clinical reliability showed that none of the tested biomarkers had a clinical reliability that was comparable to the current gold standard (8).

Overall, the therapeutic approach for endometriosis must be adapted individually for each patient, as age, fertility, desire to have children, family planning measures, degree of pain and personal impairment and the mode of action and side effects of the medications vary from patient to patient. Above all, it is essential to weigh up the side effects of the preparations.

The aim of this study is to investigate whether the prevalence and the therapy patterns of endometriosis was different in 2010 and 2019.

Materials and Methods

This retrospective cross-sectional study was based on data from the Disease Analyzer database (IQVIA), which includes diagnoses, drug prescriptions, and basic demographic data obtained directly and in anonymous format from computer systems used in the practices of general practitioners and specialists. The database covers approximately 3% of all outpatient practices in Germany. Diagnoses, prescriptions, and the quality of reported data are monitored by IQVIA on an ongoing basis. IQVIA uses summary statistics from all doctors in Germany published yearly by the German Medical Association to determine the panel design according to specialist group, German federal state, community size category, and physician age. This sampling method is appropriate for obtaining a representative database of general and specialized practices (11).

This study included girls and women (14 years or older) with at least one visit to one of the 136 private gynecologist practices in Germany in 2010 or 2019. The selection of the study samples from the database is shown in the Figure 1. The first outcome of the study was the change in the prevalence of endometriosis diagnosis (ICD 10: N80) in the year 2019 compared to 2010. The prevalence was defined as the number of women diagnosed with endometriosis in the selected year divided by the total number of women with at least one visit in the same year. The second outcome was the change in the endometriosis therapy prevalence as estimated for three treatments: Dienogest (ATC: G03DB08), other Progestins than Dienogest (ATC: G03DA04), and Gonadotropin-releasing hormones (ATC: L02AE). The therapy prevalence was defined as the number of women with at least one prescription of a defined drug in the selected year divided by the total number of women with diagnosed with endometriosis in the same year. Both prevalence analyses were also calculated by age group (age 14-20 years, age 21-30 years, age 31-40 years, age 41-50 years, age >50 years).

Totally, all data were analyzed using chi-squared tests for categorical variables and t tests for continuous variables. Chi-squared tests were used to compare endometriosis prevalence and the prevalence of defined treatments. Analyses were carried out using SAS version 9.4 (SAS Institute, Cary, USA).

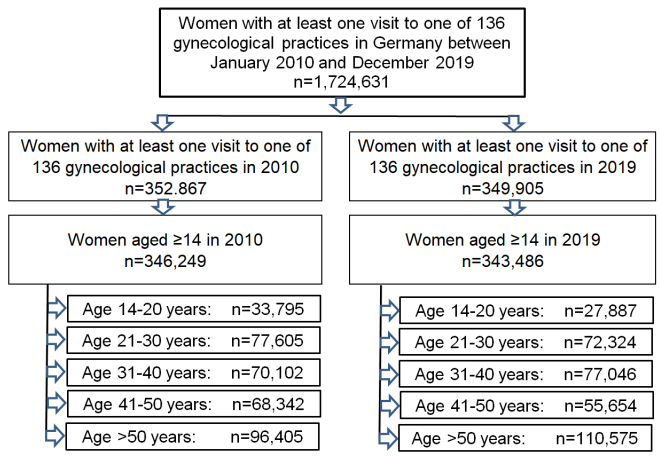

Fig.1: Selection of study sample.

Ethical statement

German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical Ethics Committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no institutional review board approval was required for the use of this database or the completion of this study.

Results

Prevalence of endometriosis

The present study included 346,249 girls and women documented in 2010 and 343,486 women documented in 2019 who visited one of 136 gynecologist practices. In total, 1,830 women had a documented diagnosis of endometriosis in 2010 and 2,272 in 2019, resulting in a prevalence of 0.53% in 2010 versus 0.66% in 2019 (P<0.001). The prevalence significantly increased from 2010 to 2019 in all age groups investigated with the exception of the group aged 14-20 years (Fig.2).

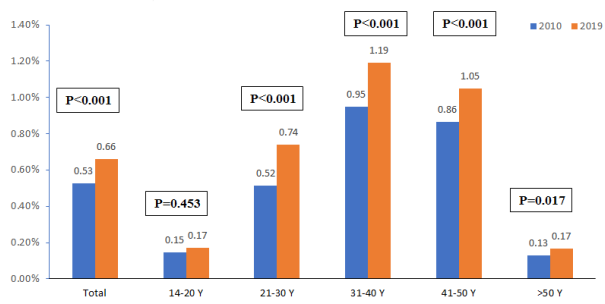

Fig.2: Prevalence of endometriosis diagnosis in the gynecological practices in the Germany in 2010 and 2019.

Baseline characteristics of study patients

The basic characteristics of our patients are displayed in the Table 1. There were no significant differences between 2010 and 2019 in terms of mean age (37.6 years vs. 37.1 years), history of hysterectomy (6.8 vs. 7.8%) and history of other surgical treatment for endometriosis (21.0 vs. 21.3%), respectively. The most common endometriosis diagnosis was unspecified endometriosis (ICD-10: N80.9) with 59.5 in 2010 vs. 61.3% in 2019, followed by endometriosis of the uterus (ICD-10: N80.0), which occurred slightly less frequently in 2019 (13.3%) than in 2010 (16.9%).

Treatment prevalence

Table 2 shows the results of the treatment prevalence analysis. The proportion of women with other Progestins than Dienogest prescription has not changed significantly between 2010 and 2019 (8.4 vs. 8.3%, P=0.912). The proportion of endometriosis patients treated with Dienogest increased significantly between 2010 and 2019 (18.1 vs. 35.0%, P<0.001). Although this increase was observed in all age groups, the proportion of patients treated with Dienogest was highest in the youngest age group (60.4%) and lowest in women >50 years (15.6%). Gonadotropin-releasing hormones were prescribed rarely in both 2010 and 2019, with a significant decrease in prescriptions by 2019 (3.7 vs. 2.0%, P<0.001).

Table 1: Baseline characteristics of our patients

Variable	2010 (n=1, 830)	2019 (n=2, 272)	P value
Mean age in years (standard deviation)	37.6 (SD: 9.3)	37.1 (SD: 9.8)	0.183
Age 14-20 Y	50 (2.7)	48 (2.1)	<0.001
Age 21-30 Y	400 (21.9)	536 (23.6)	
Age 31-40 Y	666 (36.4)	917 (40.4)	
Age 41-50 Y	591 (32.3)	585 (25.8)	
Age >50 Y	123 (6.7)	186 (8.1)	
Endometriosis diagnosis code			
Endometriosis of uterus (N80.0)	309 (16.9)	302 (13.3)	0.001
Endometriosis of ovary (N80.1)	117 (6.4)	174 (7.7)	0.117
Endometriosis of pelvic peritoneum (N80.3)	164 (9.0)	244 (10.7)	0.059
Other endometriosis (N80.2, N80.4, N80.8, N80.5, N80.6)	152 (8.3)	159 (7.0)	0.116
Endometriosis, unspecified (N80.9)	1,088 (59.5)	1,393 (61.3)	0.226
History of hysterectomy	124 (6.8)	177 (7.8)	0.216
History of other surgical treatment for endometriosis	385 (21.0)	484 (21.3)	0.837
Symptoms documented in the year of endometriosis diagnosis			
Abnormal uterine and vaginal bleeding (N91-N93)	432 (22.3)	537 (23.6)	0.232
Pain and other conditions associated with female genital organs and menstrual cycle (N94)	760 (41.5)	843 (37.1)	0.004

Data are presented as mean (SD) or n (%).

Table 2: Medication treatment of women diagnosed with endometriosis diagnosis in gynecological practices in the Germany in 2010 and 2019

Age group	Progestins others than Dienogest			Dienogest			Gonadotropin-releasing hormone		
	2010	2019	P value	2010	2019	P value	2010	2019	P value
All women	154 (8.4)	189 (8.3)	0.912	332 (18.1)	796 (35.0)	<0.001	68 (3.7)	45 (2.0)	<0.001
Age 14-20 Y	4 (8.0)	1 (2.1)	0.183	19 (38.0)	29 (60.4)	0.027	3 (6.0)	0 (0.0)	0.085
Age 21-30 Y	48 (12.0)	47 (8.8)	0.105	93 (23.3)	221 (41.2)	<0.001	28 (7.0)	7 (1.3)	<0.001
Age 31-40 Y	59 (8.9)	96 (10.5)	0.243	123 (18.5)	320 (34.9)	<0.001	25 (3.5)	32 (3.5)	0.969
Age 41-50 Y	41 (6.9)	36 (6.2)	0.587	79 (13.4)	197 (33.7)	<0.001	13 (2.2)	6 (1.0)	0.110
Age >50 Y	3 (2.4)	9 (4.8)	0.285	8 (6.5)	29 (15.6)	0.016	1 (0.8)	0 (0.0)	0.218

Data are presented as n (%).

Discussion

This retrospective study shows that the prevalence of endometriosis increased significantly between 2010 and 2019. Furthermore, the proportion of endometriosis patients treated with Dienogest increased substantially between 2010 and 2019, while the proportion of women prescribed other Progestins than Dienogest and Gonadotropin-releasing hormones has not changed significantly.

The prevalence of women with endometriosis and those receiving endometriosis therapy found in this study is lower than other studies, 0.53% and 0.66% vs. up to 10%, respectively (12, 13). This significant difference in the prevalence is most likely due to the different layout of these studies. Some studies include the general population, whereas others focus on women in a high-risk population, for example infertile women (13, 14). The prevalence given in the ESHRE guideline falls within the range of 2 to 10% (5), whereas the guideline of the Association of the Scientific Medical Societies in German (15) shows a prevalence of 0.8% to 2%. Although prevalence differs among studies, most studies have two findings in common (5, 15). First, there are a large number of patients with undetected endometriosis, which may result from misdiagnosis, non-diagnosis or incorrect coding of endometriosis. Second, there is a general trend indicating that the overall prevalence of the disease is increasing over the years. This trend may be influenced by new diagnosis standards and guidelines for the ICD-10 classification of endometriosis or the increased relevance and awareness of endometriosis over the last decade. The growing prevalence of endometriosis is a positive trend. Period pain is not seen solely as an incidental secondary symptom of menstruation, but may be increasingly understood as a part of the pathology of endometriosis and used for diagnosis. In the majority of patients, the suspected diagnosis is made on the basis of a thorough history supported by clinical examination, including vaginal ultrasound and, less frequently, accompanied by MRI or laparoscopy (16).

Drug therapy is not claimed to cure the condition, although is rather considered as a symptomatic and suppressive approach. The therapy need to be tailored individually to each patient in terms of its duration and side effects. In addition, a rapid recurrence of symptoms and disease is observed when therapy is discontinued (9).

The essential principle of hormonal therapy for endometriosis is the induction of therapeutic amenorrhea (15). As seen in the study, Dienogest seem to be the treatment of choice for most patients (17). A narrative literature review and expert commentary by Murji et al. (17) stated that Dienogest in a 2 mg doses presents an effective and tolerable alternative to surgical intervention for the long-term management of endometriosis, offering several important advantages over combined oral contraceptive pills. Studies have provided evidence of the effectiveness of Dienogest in several respects. These effects showed that a 2 mg/day dose of Dienogest inhibits ovulation and downregulates proinflammatory cytokines, including IL-6 and IL-8, and monocyte chemoattractant protein-1 (17, 18). Another study showed that Dienogest has a direct inhibitory effect on aromatase expression in endometrial cells (19), while a further paper found that Dienogest may have the ability to overcome Progestins resistance by directly increasing the Progestin receptor-B (20). The guideline for the treatment of endometriosis by the AWMF states that Dienogest reduces the pain associated with endometriosis by inducing decidualization and atrophy of endometriosis lesions, suppressing growth mediated by matrix metalloproteinases and inhibiting angiogenesis. To date, only Dienogest and Gonadotropin-releasing hormones have been approved for hormonal therapy, in German-speaking countries (DGGG, OEGGG, SGGG) (14). The consensus-based recommendations for the treatment of endometriosis by the AWMF suggest Dienogest as a first-line substance only. Treatment with GnRH or other Progestins than Dienogest is only suggested as a second-line therapy, which could explain the following: Comparing guidelines from 2010 and 2019, the recommendation for GnRH has changed so that other substances such as Dienogest are preferred. This shift is due to the negative side effects of GnRH, which include hot flashes or metabolic abnormalities (15, 21). This study shows that the total number of patients treated with GnRH in 2010 and in 2019 was far below the number treated with Dienogest or other Progestins, at 3.7 and 2%, respectively, compared to 8.4 and 8.3% respectively for other Progestins and 18.1 and 35% respectively for Dienogest. GnRH caused a 4-6% decrease in the bone mineral density (BMD) after 24 weeks of treatment in comparison with a decrease of just 0.5-2.7% in the BMD in the women who were treated with Dienogest without add-back therapy. While both drugs induce a hypoestrogenic state that falls outside the recommended therapeutic window of 20-60 pg/mg this state is more moderate level with Dienogest than with GnRH or even other Progestins (22).

This study has several limitations. Since endometriosis diagnosis was based on the ICD codes and not on the biological data, the prevalence of endometriosis might have been underestimated. Furthermore, no information was available on how endometriosis diagnoses were made, the symptoms exhibited by patients, and how treatment responses were evaluated by gynecologists. Moreover, even if women included in this study were also treated in hospitals, we did not have access to the related data. The next limitation is a lack of several variables which were not documented in the database used, which include smoking behavior, alcohol use, family status, family history of endometriosis and other risk factors. Finally, we were able to analyze prescriptions for different drugs, but not laparoscopy, which as already mentioned is the gold standard in the treatment of endometriosis. The main strength of this work was the number of patients and gynecologists included.

Conclusion

There were significant changes in the prevalence and

medical therapeutic patterns of endometriosis between 2010 and 2019, reflecting changes in therapy guidelines and possibly in diagnostic methods.

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Authors' Contributions

J.G., K.K., M.D., M.K.; Study conception and design. J.G., K.K.; Analysis performance. J.G.; Writing first draft of the manuscript. All authors commented on previous versions of the manuscript, read, and approved the final manuscript.

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