Pelvic Endometriosis Diagnosed in an Entire Nation Over 20 Years

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The annual incidence of pelvic endometriosis among women aged 15–49 years was ascertained for the Icelandic population between 1981 and 2000 by using Iceland's extensive record linkage systems. Comprehensive, state-financed health care and unique personal identification numbers enabled care to be tracked from first diagnosis. To identify cases, a centralized discharge-code registry was searched, as well as all hospital databases and, for individual patients, all hospital records. Each case of visually diagnosed and histologically verified endometriosis was cross-checked against the nationwide pathology registry. The revised American Society for Reproductive Medicine classification system was used for staging. Recorded was type of operation at diagnosis and presence of disease at 5 sites: deep pelvis, appendages, central pelvis, vesicouterine pouch, and ovaries. A total of 1,383 women were diagnosed surgically, with histologic verification of 811 (58.6%). All but 6 cases could be staged; 297 (36.9%) had minimal/mild and 508 (63.1%) had moderate/severe disease. The estimates of crude annual incidence were 0.1% for visually confirmed and 0.06% for histologically verified endometriosis, and respective age-standardized annual incidence was 0.1% and 0.05% for women aged 15–49 years. The most common site was the ovary, followed by deep pelvis, central pelvis, appendages, and vesicouterine pouch.

endometriosis; histology; incidence; population; surgical procedures, operative

Iceland has a small, homogenous, Nordic-Caucasian population. Genetic diversity is nonetheless comparable to that of larger populations (13). The population has numbered from 231,000 in 1981 to 281,000 in 2000, the period that this study spanned. In that time, as many as two-thirds of the population lived in the capital area of Reykjavik, where there is one average-size university hospital (Landspitali University Hospital) with all types of diagnostic facilities and specialized staff. In addition, 4 smaller hospitals were staffed by 1–3 gynecologists in other parts of the country, and 6 hospitals were served by surgeons and visiting gynecologists. Limited private operating facilities existed. The population is well educated, with a good standard of living. A state social security scheme covers visits to general practitioners and medical specialists at a low patient fee, and hospital admissions and operative procedures are free of charge or low cost.

The aim of this study was to estimate the incidence of visually confirmed and histologically verified endometriosis in the pelvic cavity and to describe where the disease is predominantly located.

MATERIALS AND METHODS

The sources of data for identifying cases were 1) the computerized records of the Discharge Diagnosis Register for Landspitali University Hospital and most of the larger and some smaller district hospitals; 2) local paper databases with diagnostic codes and operation-theater registers from remaining smaller hospitals and 2 private clinics not linked to the centralized registry; and 3) the centralized, computerized, countrywide Pathology Registry at Landspitali coded 76500 (Systematized Nomenclature of Medicine system; SNOMED). In the 3 revisions of the International Classification of Diseases (ICD) in use during the study period, 1981–2000, the diagnostic codes of interest were ICD-8, code 625.3; ICD-9, codes 617.0–617.9; and ICD-10, codes N80.0–N80.9. Complete paper hospital records, case notes, descriptions of operative procedures, and pathology reports were obtained for all potential cases and were scrutinized for laparoscopic or surgical visually confirmed and histologically verified diagnoses of endometriosis compatible with ICD-10 codes N80.0–N80.4, except adenomyosis and endometriosis of the vagina. Patients who were first diagnosed with endometriosis before 1981 were excluded. All women residents of Iceland during the study period aged 15–69 years were included. Most previous studies on endometriosis included cases up to age 49 years, so we report specifically on diagnosis up to and including that age.

During the whole study period, laparoscopic diagnosis was practiced with up-to-date equipment in units staffed by gynecologists, while open surgery was also used there and in the surgical units. Laser treatment for endometriosis was not used, and magnetic resonance imaging was not available. In 1990, video-laparoscopy techniques were introduced at the university hospital and gradually in other hospitals. With the comprehensive health care system, it is likely that women with acute or chronic pelvic pain, fertility problems, dyspareunia, or other symptoms will have sought medical assistance and been diagnosed. Sterilization by tubal ligation may also have led to discovery of asymptomatic endometriosis. All Icelandic residents have unique personal identification numbers used in the national and all other main registries, in the computerized Discharge Diagnosis Register, and when attending smaller hospitals or private clinics. This identifier enabled tracking of patients and ensured that individuals with multiple diagnoses were counted only once at the age at earliest diagnosis. In this paper, we thus report on the age at which endometriosis was visually and/or histologically confirmed, not age at disease onset.

From the paper hospital records and the operation notes, the type of operation(s) undergone by the patient (laparotomy, laparoscopy, or other) was recorded, as well as organs removed (data not shown). We staged only those patients with histologically verified endometriosis because of incomplete information in the hospital records and operation notes concerning those with a visually confirmed diagnosis only. The revised American Society for Reproductive Medicine classification (14) was used, and cases were classified as stage I–II (minimal/mild; 1 to 15 points) or stage III–IV (moderate/severe; 16 to >40 points). Staging was done by the same person (J. T. G.; consultation with R. T. G. if in doubt) and was based on both operative notes and pathology records where relevant.

The location of lesions in each case was noted, and the main involvement area was determined by dividing the locations into 5 groups: vesicouterine (bladder peritoneum, peritoneum anteriorly on the uterus, vesicouterine pouch), deep pelvis (rectovaginal septum, rectouterine pouch (of Douglas), uterosacral ligaments), central pelvis (pelvic peritoneal walls above uterosacral ligaments, peritoneum posteriorly on the uterus, inside parametrial tissues), appendages (broad ligaments, ovarian ligaments, Fallopian tubes, mesosalpinx), and ovarian. If lesions were located in more than one place, the location giving the highest score with the staging system was selected as the main one at diagnosis given the possibility that the same score might be given for different locations. Therefore, in this paper, the total number of locations is greater than the number of women.

To estimate the incidence rate of endometriosis, the numerator used was the number of women with a laparoscopic or open surgical procedure and either a visually confirmed or histologically verified diagnosis. The denominator was the midyear number of different age groups of women in the Icelandic population during 1981–2000, derived from Statistics Iceland (15). It was not possible to exclude from the denominator prevalent cases of endometriosis that had been diagnosed before the study period. We had no resources to identify, and thus be able to exclude from the denominator, those women who had undergone hysterectomy or oophorectomy, and it was not known whether these women used hormone therapy. Use of hormone therapy by postmenopausal women was not known and could not be adjusted for. Age-specific rates (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, and 65–69 years) were calculated by using age at first diagnosis. Most previous epidemiologic studies on endometriosis have reported cases during the fertile period of women or approximately
at premenopausal age. We included cases up to the age of 69 years and here divide the material into women up to age 49 years or age 69 years for comparison with previous studies. Rates were standardized with the World Standard (16) and the annual incidence estimated per 10,000 person-years. Pearson’s correlation coefficient (\( R \)) was calculated to find whether incidence rates were related to year of diagnosis.

The study was approved by the National Bioethics Committee and the Icelandic Data Protection Commission, as well as by respective hospital authorities.

**RESULTS**

A total of 1,428 women were diagnosed with endometriosis. Of these, 45 were excluded; for 42, the location was outside the pelvic cavity (minor pelvis) (cervix, vagina, colon, intrarectal, ileum, appendix, diaphragma, and intracavitary uterine myoma), and, for 3, diagnosis was made after age 69 years, leaving a study group of 1,383 women (Figure 1). Primary diagnosis was by laparotomy for 589 women (some commenced as laparoscopy), by laparoscopy for 778, and by other surgical procedures for 16 (vaginal hysterectomy and ovarian cyst aspiration). Histologic verification was available for 811 women, and 572 were visually confirmed only.

In the age range 15–49 years, 1,303 women met the inclusion criteria; for 739 of these women, disease was histologically verified (Table 1). The crude incidence of all endometriosis was 10.0/10,000 person-years; for histologically verified endometriosis, the incidence was 5.7/10,000 person-years (Table 1). Age at diagnosis ranged from 17 to 68 years, with a mean of 35 years (standard deviation, 9.26; median, 34.6). For histologically verified cases, the mean age was 38 years (standard deviation, 9.31; median, 37.5). The proportion of cases diagnosed after age 40 years was 27.4% (21.8% of histologically verified cases). Age-specific incidence was high in the age groups 30–34, 35–39, and 40–44 years at 13.4, 13.3, and 13.2/10,000 person-years, respectively. Age-specific incidence was highest for age 40–44 years during the latter half of the period (1991–2000) compared with the first half (1981–1990) (Figure 2). Age-specific incidence was higher in all 5-year age groups in the latter compared with the first half, except for the age group 30–34 years.

Age-standardized annual incidence per 10,000 person-years (World Standard (16) million) for women 15–49 years of age was calculated for all visually confirmed and separately for histologically verified endometriosis (Figure 3). Age-standardized incidence for visually confirmed diagnosis increased during the study period (\( R = 0.48, P = 0.03 \)), while histologically verified diagnosis did not (\( R = 0.16, P = 0.51 \)). For women aged 15–69 years, the age-standardized annual incidence exhibited a similar pattern (not shown in Figure 3) for both visually confirmed diagnosis (\( R = 0.56, P = 0.01 \)) and histologically verified diagnosis (\( R = 0.37, P = 0.11 \)).

For the 1,383 women, it was not possible to assign a major location for the disease in 294 of them. For the other 1,089 women, 1,147 main locations were assigned. The most common main location was the ovaries (\( n = 723 \)), followed by the deep pelvis (\( n = 195 \)), central pelvis (\( n = 104 \)), appendages (\( n = 78 \)), and vesicouterine pouch (\( n = 47 \)). The distribution of the main locations of all lesions and histologically verified lesions is shown in Table 2. For the histologically verified cases, it was not possible to decide on the main location in 51 women, leaving 760 women with 776 main locations. For the 572 visually confirmed cases, it was not possible to decide on the main location in 243 women, leaving 329 women with 371 main locations.

Among the histologically verified cases, 297 had stage I–II (minimal/mild) and 508 had stage III–IV (moderate/severe) disease; for 6 women, staging was not possible (\( n = 805 \) women with stageable disease). Most cases with predominant disease in the appendages and central pelvis were classified as minimal/mild (82.9%: 102/123). The majority of ovarian lesions (76.7%: 445/580) were classified as moderate/severe. The youngest woman diagnosed with predominantly ovarian disease was age 17 years, and 19.1% (111/580) were less than age 30 years. Deep pelvic cases tended to be minimal/mild (71.0%: 39/55).

**DISCUSSION**

This study assessed the incidence of surgically diagnosed endometriosis, both visually confirmed and histologically verified, in a whole nation over a considerable length of time. The women studied had more severe and symptomatic disease (including infertility) that led to an operative diagnosis. Although the population is not large, it is well defined and homogenous. Record keeping and access to health care have been good, and comprehensive, computerized diagnosis lists based on international coding could be cross-checked against centralized pathology records.

The information on number of women and the age distribution of the population, derived from the constantly updated data from Statistics Iceland, enabled us to follow the steady increase in the younger age groups (15). It is unknown whether the change in age distribution may have affected the temporal patterns of surgery in the population. The estimated incidence of visually confirmed endometriosis increased slightly, attributed mainly to an increase among women over the age of 35 years; however, histologically verified endometriosis did not increase over time. In addition, it was possible to show the main location of the disease and its severity. Histologic verification represents a certain “gold standard,” whereas visual diagnosis alone is less certain. A study from the United Kingdom (17) showed that 76% of consultant gynecologists considered themselves confident about visualizing endometriotic lesions at diagnostic laparoscopy, although only 6% reported performing confirmatory biopsies. We not only searched for all diagnosed cases but also focused on women for whom the disease was confirmed by histology, a high proportion in this population, partly because of frequent laparotomy.

In this population, it was an advantage that hospital care was free of charge through the state social security system, except for small charges for day-care admission at the end of
the study period. Expenses for infertility evaluation were also covered. Therefore, women with symptoms did not have a financial barrier to seeking qualified care. There is only a small chance that asymptomatic endometriosis found incidentally will become symptomatic later (18), nor will it matter unless associated with subfertility (17). In other women, lesions may heal spontaneously without a medical diagnosis ever being made. These women would be unlikely to be included among the cases in this clinical analysis; however, their endometriosis may nevertheless have been related to infertility, particularly if otherwise asymptomatic.

It is possible that, in this study, small lesions may not have been noticed or described by the surgeon or gynecologist at laparotomy or when using less advanced laparoscopy equipment during the first half of the study period. Modern video-laparoscopy increased the chance of small lesions (fresh and scarred) being noticed if the surgeon was alert to this possibility or considered it significant (19), which may partly explain the rise in incidence with time of visually diagnosed endometriosis. However, major clinical lesions (stage III–IV) are unlikely to have been missed, except possibly in the rectovaginal septum. With the dual verification methods used to search for clinical and histopathologic evidence, the number of missed cases is likely to include only a relatively small number of women with mainly minimal or mild disease who would have been diagnosed by visual inspection alone. All cases verified by histopathology should have been included. These women can be expected to have suffered most from the presence of endometriosis and be those with disease of major clinical relevance.

Lastly, women undergoing hysterectomy and particularly oophorectomy during the period would theoretically have had a smaller chance of developing endometriosis. The rates of hysterectomy grew somewhat during the study period in the country, reaching 390/100,000 women, but affected mainly women over the age of 35 years, and rates of oophorectomy were stable (J. A. Gudmundsson, Landspitali University Hospital, unpublished survey, with permission). This occurrence would not have affected the denominator to a degree that might have changed the incidence estimates.

The true incidence of endometriosis may never be known, but perhaps the best previous incidence estimates have come from population studies: 2 conducted on all diagnosed cases in Rochester and Olmsted County, Minnesota (4, 6); 2 performed on Scandinavian populations, although with different methods (5, 7); and the cohort of the Nurses’ Health Study II (8). The 4 populations were similar to the one in the present study, primarily Nordic/Caucasian (4–7); however, endometriosis seems to differ between ethnic groups (7, 8).
In the 2 Minnesota studies, performed during different time intervals, the annual incidence was 0.25% for women aged 15–44 years, and the methods used for these estimations were similar to those used in the present study (4, 6). The Norwegian study (5) was based on a defined population (aged 40–42 years) and an affirmative answer to the question, Have you been treated for endometriosis during the last 12 months? The annual incidence was 0.3% (5). The Swedish population study was based on the Swedish National Hospital Discharge Register for detection of cases (aged 20–41 years), thus lacking information on outpatient care, which perhaps explains decreased hospitalization rates during the study period (1990–2004). However, the age-adjusted incidence for women born in a Western country was 0.1%, as in the present study (7). Compared with other studies based on hospital discharge diagnosis, the strength of the Swedish study was that, because of the population register and individual personal identification numbers, it was possible to base estimates on number of cases rather than number of discharges (7).

The Nurses’ Health Study II was a questionnaire study on a specific socioeconomic group aged 25–42 years, where past infertility was an exclusion criterion, yielding a crude incidence of 0.24% (8). Endometriosis was laparoscopically confirmed according to the patients’ own report, with no mention of other surgical procedures. Our crude annual incidence was 0.1% for a visually confirmed diagnosis and 0.06% for histologically verified endometriosis.
With the revised American Society for Reproductive Medicine classification (14), we assessed where the most severe disease was located in histologically verified cases only. This may be considered a drawback, but the classification was retrospective, so including only securely identified disease seemed justifiable even though it may have led to selection of more severe disease. Moreover, pain symptoms are not strongly correlated with revised American Society for Reproductive Medicine staging. To our knowledge, this approach has not been used in the same way before, but it confirmed that the ovaries are by far the most frequent location. However, that could be an overestimation because the ovaries, compared with other anatomic sites, are easily inspected at laparoscopy and are more accessible for biopsy. Incomplete descriptions made it impossible to locate endometriosis lesions in 294 women. This limitation weakens these descriptive data and may not wholly equate with the clinical presentation, but it still points to the ovaries as the organs most often affected by what, in a clinicopathological sense, is the most severe disease but the easiest to eliminate by excisional surgery.

The strict definitions of visually confirmed and histologically verified diagnosis strengthen our study. We were able to include all women aged 15–69 years for altogether 1.3 million person-years. Furthermore, the National Registry and universal use of the personal identification number enabled us to manage multiple contacts with the health care sector and to determine age at first diagnosis. In addition, we included all hospitals and private clinics in which surgical procedures that are a prerequisite for diagnosis could be performed, thus ensuring identification of cases from inpatient and outpatient care. Numbers for each age group were available, and all paper hospital records could be scrutinized. Lastly, the study was conducted in a country with comprehensive and state-financed health care, including infertility treatment, with no or only low fees for outpatient services, hospital admissions, and operative procedures, providing a low threshold for seeking medical attention.

A limitation was that different symptoms or indications for the surgical procedures were not investigated, including fertility problems. The incidence rates must be considered underestimated given that endometriosis may be asymptomatic during long periods and can be self-healing. It is possible that some surgeons performing laparoscopy did not list endometriosis as a postoperative diagnosis if the woman was asymptomatic or when the endometriosis was secondary to another primary diagnosis. The study also has the inherent weakness of retrospective studies based on hospital records that are not always gathered systematically. Thus, important information may be missing. As an example, we were not able to stage 6 cases of histologically verified endometriosis. Therefore, we did not attempt to stage visually confirmed cases, as stated previously.

Table 2. Numbers and Proportions, by Site, of the Main 1,147 Classifiable Locations of Visually Confirmed Endometriosis and Histologically Verified Endometriosis in the Icelandic Population, 1981–2000

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Total Locations</th>
<th>Visually Confirmed Locations</th>
<th>Histologically Verified Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Ovarian</td>
<td>723</td>
<td>143</td>
<td>580</td>
</tr>
<tr>
<td>Deep pelvisb</td>
<td>195</td>
<td>140</td>
<td>55</td>
</tr>
<tr>
<td>Appendagesc</td>
<td>78</td>
<td>20</td>
<td>58</td>
</tr>
<tr>
<td>Central pelvisd</td>
<td>104</td>
<td>39</td>
<td>65</td>
</tr>
<tr>
<td>Vesicouterinea</td>
<td>47</td>
<td>29</td>
<td>18</td>
</tr>
</tbody>
</table>

aN = 1,089 women; more than one main location possible in some cases.
bRectovaginal septum, pouch of Douglas, and uterosacral ligaments.
cBroad and ovarian ligaments, tubes, and mesosalpinx.
dPelvis peritoneal walls and posteriorly on the uterus, inside peritoneal tissues.
eaBladder peritoneum, peritoneum anteriorly on the uterus.
In conclusion, we found that the crude annual incidence of endometriosis in Iceland was 0.1%, which is in accordance with recent findings from other studies. The age-standardized incidence of histologically verified endometriosis was unchanged throughout the study period in spite of advances in laparoscopic techniques.

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