

## Epidemiology of endometriosis

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Endometriosis is a cause of acquired dysmenorrhoea, dyspareunia, intermenstrual bleeding and menorrhagia, infertility, and pelvic pain of varying severity and location.<sup>1</sup> The disease is seen as one with obscure determinants, with little known about its distribution in the population, and with poor response to treatment. This review evaluates the current knowledge on the epidemiology of endometriosis.

### Disease description

Endometriosis was recognised as a pathological entity only in the 1860s, and as a recognisable clinical problem in the 1920s.<sup>2</sup> It is a condition in which tissue with the histological structure and physiological responses of uterine mucosa occurs in sites other than the uterus; commonly within the pelvis.<sup>2</sup> The implants produce vesicles or haemorrhages that are seen as blue, brown, or black nodules on peritoneal surfaces of the pelvis. If severe, the implants may go on to produce fibrosis and adhesions.<sup>3</sup> It is not known why implants that do not cause physical distortion are associated with infertility or cause disproportionate pelvic discomfort.<sup>4</sup> Little is known about the natural history of endometriosis.<sup>5-7</sup> Because the physical findings are non-specific, clinical findings can be confused with those of pelvic inflammatory disease, benign or malignant ovarian disease, fibroids, and gastrointestinal or urinary problems.

Since the 1970s, diagnostic confirmation has been possible by directly visualising the pelvis using a laparoscope. Before this, laparotomy was the only confirmatory method possible.

### Burden of disease

Endometriosis is not life threatening, but it is an important cause of morbidity in women. In England and Wales there are few routine data on its contribution to the burden of ill health in the population. The disease did not have a separate code in the national Morbidity Studies from General Practice<sup>8</sup> or in Hospital In-Patient Enquiry data.<sup>9</sup> Routine data from the United States (USA) for 1980 showed that the hospital admission rate for endometriosis was twice the rate for ectopic pregnancy in 15-44 year old women and accounted for half a million bed days per year.<sup>10</sup> A population based study undertaken in Rochester, USA in 1979 suggested that the prevalence of endometriosis was 3.3%.<sup>11</sup>

For the individual, the disease can cause chronic pain or infertility that may require hospi-

tal admission, surgery, or long periods of treatment which may have unpleasant side effects. Treatment is often unsatisfactory, although it can result in resolution of the symptoms.<sup>12</sup> Radical suppression of ovarian function by treatment with drugs such as danazol and gonadotrophin releasing factors may still not achieve permanent cure.<sup>13-15</sup> For extensive disease, surgical castration may be the only definitive treatment.<sup>12</sup> An understanding of the aetiology of endometriosis is needed in order to reduce the burden of morbidity in women. Little is presently known about its causes because of the problem of case definition and methodological flaws in study design.

### Case definition

Standardised objective criteria for the reliable diagnosis of endometriosis are difficult to establish as it has a variable, non-specific clinical presentation and natural history. Confirmation of the diagnosis requires laparoscopy. There are, however, few data on the repeatability of laparoscopic findings. Validity may also be less than thought as atypical lesions and microscopic changes can occur.<sup>16</sup>

There are criteria to stage the severity of disease at laparoscopy based on morphology.<sup>17</sup> Criteria for establishing whether a case is one of sickness, prognostic of infertility, or amenable to treatment would be useful but such systematic investigation has only just begun.<sup>3 5 18 19</sup>

More simple tests such as the serum ovarian tumour marker CA-125 are being investigated. CA-125, however, may have a low specificity and sensitivity. In one survey of infertile women it was raised in just over 50% of those with endometriosis but it was also high in women with other pelvic disorders including pelvic inflammatory disease.<sup>20</sup> In another study of women with both infertility and pelvic symptoms, the sensitivity was only 16% (10 of 60) although the specificity was 98% (85 of 87).<sup>21</sup>

Immunological markers of endometriosis, such as anti-endometriosis antibody, have been found. Using an immunohistochemical method to detect the antibody, the sensitivity was 77.5% (31 of 40) and the specificity 42.5% (17 of 40).<sup>22</sup> In another study using passive haemagglutination, the sensitivity was 74% (17 of 23) and the specificity 100% (28 of 28).<sup>23</sup> The control samples in both studies, however, were either from men or from cord blood. Further work on larger numbers of women is needed to determine the usefulness of these tests.

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Accepted for publication  
November 1992

At present the clinical and epidemiological case definition for endometriosis requires laparoscopy, which has to be undertaken in a hospital. Cases identified in this way may be unrepresentative of cases in the general population because of variation in the presenting symptoms, in the health seeking behaviour of patients, the referral process, diagnostic practice, and differential access to diagnostic facilities. Studies which use cases found when laparoscopy is performed for other reasons also suffer from this considerable ascertainment bias.

It may be possible to avoid ascertainment bias in some hospital settings. For instance, sampling women with endometriosis who had presented with a pelvic mass or acute abdomen. All women with these presenting conditions, although uncommon,<sup>24</sup> would have had direct visualisation of the abdomen or pelvis. To generalise the results to all women with endometriosis, however, would require greater knowledge of the natural history of the disease.

One study tried to reduce some of the ascertainment bias in the use of hospital cases by constructing operational definitions based on levels of diagnostic certainty.<sup>11</sup> These were defined as follows:

- (1) Histologically proved endometriosis only.
- (2) Histologically proved or surgically visualised disease.
- (3) The above and those with clinically probable endometriosis.

Bias was reduced in the last definition by including women who had not yet undergone selection for laparoscopy. The sensitivity and specificity of these operational definitions, however, have still to be determined.

### Descriptive epidemiology

#### INCIDENCE AND PREVALENCE

Routinely collected data from the USA showed that in 1980 there were 18.4 hospital admissions for endometriosis per 100 000 women aged 15–44 years.<sup>10</sup> The data cannot, however, reflect the true incidence of disease. Repeat admissions would have been counted as separate episodes. Women seen as outpatients, or who had not come to the attention of medical services, or who were asymptomatic would not have been included.

Only one study has measured disease incidence, defined as newly diagnosed cases of endometriosis.<sup>11</sup> All these cases in women aged 15 to 49 years in the population of Rochester, USA in 1979, were able to be traced as only one medical

facility existed for the study population. The at risk population, 17 000 women in that age group, was obtained from the decennial census. Interobserver reliability of case ascertainment was near 100% when checked by a repeat survey of the records. The incidence rates per 100 000 women years at risk for decreasing levels of certainty of diagnosis were as follows:

- (1) Histologically proved endometriosis only—108.8.
- (2) Histologically proved or surgically visualised disease—160.4.
- (3) The above, and those with clinically probable endometriosis—237.4.

The incidence of diagnosed endometriosis was about 0.3% in white 15 to 49 year old women each year. In assuming a 10 year duration of disease on average, the authors estimated that the period prevalence would have been between 2.5–3.3%. As population studies are otherwise absent, there are no accurate data on time trends or geographical distribution of disease.

The only other data are from cross sectional prevalence surveys of case-groups from hospital settings. As can be seen in table I the prevalence varies considerably both within and between the case-group categories. True variations in prevalence, however, cannot be distinguished from chance effects, distortions caused by ascertainment bias or confounding. Geographical differences in prevalence would have been affected by changes in diagnostic habits and differences in access to health care between countries. Studies that are able to identify, measure, and investigate incident cases in a defined population would, of course, be of greater use.

#### AGE DISTRIBUTION

The risk of endometriosis may not increase linearly with age. In Houston's study the incidence rate of clinically probable cases rose sharply with age up to 35 years and then fell rapidly only after age 44.<sup>11</sup> Other incidence studies that measure age specific rates would be useful to confirm these findings.

#### SOCIOECONOMIC STATUS

It is often stated that endometriosis is seen more frequently in higher socioeconomic groups.<sup>25 26</sup> The evidence comes historically from case group studies. For instance, a higher prevalence was seen in a study of white private gynaecology patients compared with white or black non-private patients.<sup>27</sup> Differential access to health care by socioeconomic group was, however, likely.

Two recent case-control studies also suggested an association with higher socioeconomic status.<sup>28 29</sup> In the former study differential access by cases compared with controls may also have been operating; the cases having a mostly chronic condition and the controls coming from a hospital group requiring laparoscopies for a variety of often acute conditions. The latter study, conducted in the USA using population based controls, showed a positive socioeconomic association only in those presenting with infertility, not in those with pelvic symptoms.<sup>29</sup> It is possible that in the USA, access to infertility services is more

Prevalence of endometriosis in studies of case-groups

Clinical case-group investigated	Authors and year of study	Study region	Prevalence % (no)
Laparoscopic sterilisations	Liu and Hitchcock, (1986) <sup>30</sup>	Nottingham	43 (108)
	Moen, (1987) <sup>48</sup>	Norway	51 (75)
	Kirshon and Poindexter, (1988) <sup>49</sup>	USA	7 (566)
Infertility	Cates <i>et al</i> (1983) <sup>54</sup>	<i>WHO multicentre study:</i>	
		Africa	1 (842)
		Asia	10 (1992)
		Latin America	3 (1228)
		East Mediterranean	1 (432)
		West Europe, North America, and Australia	6 (3904)
		Hasson, (1976) <sup>31</sup>	USA
Strathy, (1982) <sup>55</sup>	USA	21 (100)	
Chronic pelvic pain	Hasson, (1976) <sup>31</sup>	USA	15 (212)

influenced by socioeconomic status than investigations for pelvic symptoms.

#### ETHNICITY

An association with ethnicity has also been suggested in case-group studies in the USA. In the 1930s it was taught that endometriosis was rare in black people.<sup>2</sup> Prevalence was noted to be lower in black compared with white non-private patients.<sup>27-30</sup> This was also remarked upon more recently, but it was also suggested that the highest prevalence occurred in South-East Asian patients.<sup>31</sup> However, little account was taken of likely confounding factors such as socioeconomic status.<sup>32</sup> In a study of private white and black gynaecological surgery patients there was no difference.<sup>33</sup>

A high prevalence of endometriosis in Japanese women has been suggested.<sup>34</sup> The evidence is based on one cross sectional survey of gynaecological admissions to hospitals in Hawaii in 1974 in which fewer than four cases with endometriosis were Japanese.<sup>35</sup> Thus little data of sufficient rigor exist to show socioeconomic or ethnic differences in disease risk.

#### Aetiology

##### MENSTRUAL IRREGULARITIES, EXERCISE, AND SMOKING

Retrograde menstruation is a well recognised<sup>34</sup> and plausible pathogenetic explanation of how viable endometrial cells are seeded in the abdominal cavity. This has been documented in 57 of 75 (76%) of women who underwent laparoscopic sterilisation while menstruating. Fifty per cent of those with retrograde menstruation had endometriosis compared with 5% of those without retrograde flow.<sup>36</sup>

Two case-control studies have investigated risk factors for endometriosis mediated via retrograde menstruation. In one, using women on delivery wards as control subjects, an increased risk was associated with increased duration of bleeding and with dysmenorrhoea. These may, however, have merely been symptoms of disease. This study also suggested that exercise of more than two hours per week was protective (odds ratio (OR) 0.6, 95% confidence interval (CI) 0.4, 0.8). The types of exercise most strongly related to decreased risk were conditioning exercises, including jogging or calisthenics. Smoking more than one packet of cigarettes per day from the age of 17 years was also protective (OR 0.5, 95% CI 0.3, 0.9).<sup>37</sup>

The other case-control study of endometriosis used population based control subjects. The study population was analysed as two separate groups, those cases with infertility and those with pelvic symptoms, because various factors including socioeconomic status, race, age, and marital status were found to be very different between the two groups. An association was found between endometriosis and dysmenorrhoea but not with duration of bleeding in both cases with infertility and cases with pelvic symptoms. As with the previous study, the case-control design did not allow separation of risk factors from what were likely to be symptoms of disease. Exercise was not associated with disease in the infertility group but was

significantly protective in the pelvic symptoms group even after adjustment for educational level, dysmenorrhoea, age at menarche, body mass index, and smoking (relative risk (RR) in the infertility group 1.35, 95% CI 0.84, 2.16, RR in the pelvic symptom group 0.36, 95% CI 0.19, 0.69). A protective effect of smoking was found after adjustment for the level of education, age at menarche, dysmenorrhoea, body mass index, exercise, and oral contraceptive use. The protective effect was greatest in those with primary infertility (OR 0.18, CI 0.07, 0.47), followed by those with pelvic symptoms (OR 0.53, 95% CI 0.24, 1.19) and least in those with secondary infertility (OR 0.73, CI 0.27, 1.98).<sup>29</sup> The reasons for this gradient are unclear.

There is a suggestion that smoking and exercise are associated with oestrogen deficiency<sup>38</sup> and, if endometriosis is oestrogen sensitive, findings of smoking or exercise protecting against endometriosis may be plausible.

##### UNOPPOSED OVARIAN FUNCTION

Unopposed cyclic ovarian hormone secretion has long been thought to encourage proliferation of endometrial tissue.<sup>19-34</sup> It is well known that removal of the ovaries reduces risk of disease<sup>39</sup> and that disease risk falls with the onset of the menopause. Oestrogen receptors have been detected in endometriosis tissue but at lower levels than in endometrial tissue.<sup>40-41</sup> In a trial of maintenance of endometrial implants placed in the peritoneal cavities of monkeys, only oestrogen prolonged growth of the ectopic tissue compared with progesterone or placebo.<sup>42</sup> The idea that women may be protected against endometriosis when ovulation is interrupted by pregnancy or use of combined oral contraception<sup>25-43-44</sup> is therefore plausible. Evidence to confirm this hypothesis is, however, scarce.

Histological regression of endometriotic deposits has not been seen consistently in pregnancy.<sup>45</sup> In a follow up study, 19 of 50 (38%) women with endometriosis who became pregnant re-attended with symptoms of the disease within 5 years.<sup>46</sup> Anovulation in over 10% of a case-series of women with endometriosis has also been reported.<sup>47</sup> Prospective data would be useful to confirm that anovulation preceded the onset of endometriosis. If this were shown it would suggest that the presence of oestrogen may not be essential for disease to occur, though such results would not exclude its role as a predisposing factor.

The relationship of combined oral contraception and endometriosis was studied in a case-group of women undergoing laparoscopic sterilisation.<sup>48</sup> Nineteen of 98 (19%) were found to have endometriosis on laparoscopy. No difference was seen between those with or without disease in their age, their age at menarche, age at first pregnancy, number of deliveries, and type of contraception used. There was, however, a significant difference between cases and controls in the mean time of unopposed ovulation (cases 11.2 years, controls 8.4 years ( $p < 0.02$ )). The duration of combined oral contraceptive use may have explained this finding but the data were not presented. A similar larger study of 566 patients (42 of whom had endometriosis) compared the

proportions with or without disease in combined oral contraceptive users and in users of barrier methods or of no contraception. No association with any one type of contraception was seen.<sup>49</sup> Apart from sampling error selection bias may have resulted in an underestimate of the effect of ovarian suppression on disease risk. Cases and controls obtained from women having laparoscopic sterilisations under-represented infertile women, who have a higher prevalence of endometriosis.

The effect of increasing age and higher socioeconomic status on the risk of disease has been thought to be mediated by delaying pregnancy and having fewer children.<sup>25</sup> There is, however, poor evidence of an association between pregnancy, socioeconomic status, and endometriosis. A detailed hospital based case-control study did not show this even in the late 1940s.<sup>30</sup> A total of 646 women with histologically proved endometriosis were compared with 600 women admitted to hospital with pneumonia. Fertility rates in both private and non-private cases were similar within the strata of time since marriage and age at marriage. The same was seen in the control patients. Fertility rates were lower in the cases than in the control subjects, suggesting only that endometriosis reduces fertility.

#### IMMUNOLOGICAL FINDINGS

Research into the immunology of endometriosis may be useful in delineating further the pathogenesis of the disease. In one case-control study, a twofold increased risk (95% CI, 0.6, 6.8) of endometriosis was found in patients with systemic lupus erythematosus.<sup>50</sup> Newly diagnosed cases of systemic lupus erythematosus discharged from hospital were compared with controls randomly selected from hospital discharges other than from obstetric and gynaecology specialities. The sample size was, however, too small to exclude chance given the wide confidence interval.

Raised non-specific IgG antibodies have been found in significantly more women with endometriosis compared with female blood donors<sup>51</sup> and, as mentioned earlier, raised antiendometrial antibody levels were found in significantly more cases compared with control male or cord blood samples ( $p < 0.001$ ).<sup>22 23</sup>

#### GENETIC PREDISPOSITION

It has been suggested that a genetic predisposition for endometriosis may exist.<sup>12 26</sup> An association with a positive family history was found in two studies. Design flaws exist, however, in both studies and may have introduced bias producing an overestimate of the magnitude of the association. In one of the studies, 6.9% of cases compared with 0.9% of controls were found to have affected relatives. The controls used were the patients' husbands. Recall bias by women with disease was possible and the husband controls may have been less able or motivated to know about ill health in their own families. Interviewer bias was also possible as the family history in both groups was obtained by an interviewer not blind to the diagnosis.<sup>52</sup>

The second study found cases from the mailing list of an endometriosis support group who had

volunteered a positive family history on the application form. The study used 'best friends' as controls. Because of the method of selection of cases, it is inappropriate to make a case-control comparison. However, of the 43 women with endometriosis who reported other family members with the disease, most involved the maternal line.<sup>53</sup>

#### Conclusions

Thus far, the data on the distribution and determinants of endometriosis in the population are limited. The disease occurs in reproductive age groups but a linear increase with age has not been shown and the quoted socioeconomic and ethnic differences in disease prevalence are not well founded. Knowledge of time trends and geographical differences in disease risk is lacking.

Menstrual regurgitation may be a pathogenic factor, and risk factors that increase the likelihood of regurgitation into the pelvic cavity need to be investigated further. There may be an increased risk with unopposed ovarian function but it is not yet adequately documented to properly give preventive advice such as encouraging pregnancy or the use of combined oral contraception. Other tentative findings that might be followed up are the role of smoking and exercise on disease risk.

Until a simple test that may be safely applied at a population level becomes available, care with study design is needed to reduce ascertainment bias. For instance, Houston used an operational epidemiological definition for all clinically probable symptomatic endometriosis presenting to medical services in a defined population.<sup>11</sup> It avoided a part of the ascertainment bias in hospital based studies by including probable cases who had not yet undergone selection for laparoscopy. The study was also able to measure incidence rather than prevalence. In some studies the selection of the control groups may have introduced bias. Population based or hospital control subjects other than obstetric or gynaecology patients maybe more appropriate than women known to be fertile. If attention is also given to confounding and power based calculations of sample size, it should be possible to test more accurately the aetiological hypotheses suggested so far.

We thank George Davey-Smith for helpful comments and Evelyn Middleton for typing help. Punam Mangtani is a Medical Research Council Fellow in Health Services Research and Margaret Booth is funded by a Medical Research Council Programme Grant.

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