Human Reproduction vol.11 no.2 pp.387–391, 1996

Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study

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In 100 consecutive patients who were undergoing laparoscopy for infertility (group 1, $n = 52$), chronic pelvic pain (group 2, $n = 18$) or tubal sterilization (group 3, $n = 30$, asymptomatic fertile women), peritoneal biopsies were taken from areas of visually normal peritoneum of uterosacral ligaments. Twenty-six patients in group 1 (50%), eight patients in group 2 (44.4%) and 13 patients in group 3 (43.3%), were found to have laparoscopic evidence of endometriosis elsewhere in the pelvis. The majority of women (80.7% in group 1, 87.5% in group 2, and 100% in group 3) had stage I disease. The incidence of the distinctive appearances of the lesions was similar in the three groups of patients and 7% of all women or 15% (7/47) of those patients having endometriosis at laparoscopy had only subtle (non-'typical') endometriotic peritoneal lesions. Uterosacral biopsies showed the presence of endometriotic tissue in three cases (5.7%), two cases (11%) and three cases (10%) in groups 1, 2, and 3 respectively. One of the two patients in group 2 and two of the three patients in group 3 had no evidence of endometriosis at laparoscopy; thus histological study revealed the presence of endometriosis in normal peritoneum in 11% (5/47) of patients having macroscopic endometriosis and in 6% (3/53) of patients without endometriosis at laparoscopy. Previous oral contraceptive users were significantly higher among women having macroscopic and/or microscopic endometriosis than among women without the condition. In conclusion, our prospective study shows a high prevalence (45–50%) of endometriosis (including microscopic forms) in both patients with chronic pelvic pain and asymptomatic women (fertile and infertile), thus supporting the modern concept that in many women endometriosis may be a paraphysiological condition while probably only in some patients small amounts of endometriosis are an 'annoyance' with implications to their reproductive health and may produce symptoms (e.g. pelvic pain) and therefore should be defined as a 'dis-ease'. Previous use of oral contraceptives may increase the risk of developing endometriosis.

Key words: endometriosis/fertile women/infertility/oral contraceptive use/pelvic pain

Introduction

The term endometriosis is defined pathologically by the presence of tissue outside the uterus that is histologically similar to endometrium. Studies in both Europe and the United States argue for a true increase in the number of cases reported (Houston *et al.*, 1988; Martin *et al.*, 1989; Koninckx *et al.*, 1994), but the estimates of the prevalence of mild forms of endometriosis may be unreliable because most of the published studies were retrospective and misdiagnosis of subtle endometriosis cannot be excluded. Endometriosis is very accurately diagnosed by visual inspection of the pelvis, and histological confirmation is not mandatory for clinical decision making; thus, the gold standard for the definitive diagnosis of endometriosis is laparoscopy (Muse, 1988; Barlow and Kennedy, 1990; Donnez *et al.*, 1990; Pittaway, 1992; Olive and Schwartz, 1993; Brosens *et al.*, 1994). It is now well established that the typical presentation of endometriosis is protean. Black, yellow, white and red lesions; yellow-brown patches; sub-ovarian adhesions; glandular excrescences; vesicular lesions; areas of peritoneal hypervascularization or petechial peritoneum; and circular peritoneal defects, are all distinctive appearances of pigmented or non-pigmented endometriotic peritoneal lesions with histological confirmation rates ranging from 22 to 98% (Luciano and Manzi, 1992; Pittaway, 1992; Brosens *et al.*, 1994; Nisolle *et al.*, 1994). Moreover, both light microscopy and scanning electron microscopy have been used by several authors to document microscopic implants of endometriosis in normal-appearing peritoneum of infertile patients with or without other areas of endometriosis (Murphy *et al.*, 1986; Nisolle *et al.*, 1990; Nehzat *et al.*, 1991). However, the study by Redwine (1988) failed to uphold the concept of invisible, microscopic endometriosis in patients with chronic pelvic pain.

The present study was performed in three groups of patients: infertile patients, patients with chronic pelvic pain and asymptomatic fertile women requesting tubal sterilization. On the basis of the above discussed data, the specific aims of this study were firstly, to investigate prospectively the prevalence of endometriosis at laparoscopy in the three groups of patients and secondly, to evaluate histologically biopsies of visually normal peritoneum taken from all these women. Available data on the issue of oral contraceptives and endometriosis are scanty and controversial (Vercellini *et al.*, 1993) and any study of endometriosis is potentially biased because operative intervention (laparoscopy or laparotomy) is necessary to diagnose the condition, and selective factors may determine who has surgery (Vessey *et al.*, 1993). Also, it is possible that treatment of clinical symptoms of endometriosis may *per se* lead to increased contraceptive use. Thus, a third objective of

our prospective study was to investigate the relation between oral contraception and the risk of pelvic endometriosis in those three well-defined groups of patients.

Materials and methods

In 100 consecutive patients who were undergoing laparoscopy for infertility (group 1, $n = 52$), chronic pelvic pain (group 2, $n = 18$) or tubal sterilization (group 3, $n = 30$), peritoneal biopsies were taken from areas of visually normal peritoneum of uterosacral ligaments. The mean age was similar in the three groups studied (32.1 ± 3.9, 32.6 ± 4.9, and 33.8 ± 4.8 years respectively). The mean parity for patients in groups 2 and 3 was 1.5 (range 0–6) and 2.4 (range 1–13) respectively. Eleven of the infertile patients (21%) had secondary infertility, seven had one child, while the remaining four patients had had one spontaneous first-trimester abortion. All patients in group 2 consistently reported non-cyclic pelvic pain in the same location for a minimum of 6 months which was unrelated to menses and/or sexual intercourse (Kresch *et al.*, 1984; Reiter, 1990). All fertile women were asymptomatic. No patient had been pregnant in the previous year or had been treated with hormonal therapy for endometriosis. Seven patients undergoing tubal sterilization were taking oral contraceptives at the time of laparoscopy. Forty-nine (53%) of the remaining 93 patients had taken the pill for ≥12 months but had stopped taking it for over 1 year before laparoscopy.

A systematic laparoscopic evaluation of all pelvic peritoneal surfaces was carried out in all patients. Endometriosis was staged according to the revised American Fertility Society (1985) scoring. Apart from intra-ovarian cysts, superficial ovarian and peritoneal endometriosis was classified as recently suggested by Brosens *et al.* (1993) as follows: red lesion (flame-like lesion, or a haemorrhagic vesicle or a vascularized polypoidal or papular lesion); black lesion: a puckered, black lesion; white lesion: scarred tissue with or without some pigmentation. In addition to systematic biopsy of visually normal peritoneum overlying the uterosacral ligaments, biopsies of suspicious lesions were taken when the visual diagnosis of endometriosis was in doubt (19 cases). Biopsies were taken with a 5-mm Wolf punch biopsy forceps (8384.13; Richard Wolf Medical Instruments, Knittlingen, Germany). Uterosacral ligaments biopsy resulted in two specimens (from the right and left ligaments) 3–4 mm in maximum dimension, which were immediately placed in formalin and processed in the routine fashion for light microscopy as previously reported by others (Redwine, 1988; Martin *et al.*, 1989). All biopsy specimens were evaluated by the same expert gynaecological pathologist who was unaware of diagnostic groups. Several step sections (one every 100–150 μm) were made of each specimen. Standard haematoxylin and eosin stains were performed on all specimens. Endometriosis was diagnosed by the presence of both endometrial glands and stroma. Intra-mesothelial endometriosis (surface endometrial epithelium without stroma and glands) as reported by Vasquez *et al.* (1984) was not considered in the present study.

Uterosacral ligaments were studied because the posterior pelvic peritoneum is the area of the pelvis most commonly involved by disease in all age groups, and it was surmised that microscopic foci of invisible endometriosis should be most prevalent on the peritoneum of the cul-de-sac and uterosacral ligaments (Redwine, 1987, 1988; Gruppo italiano per lo studio dell'endometriosi, 1994; Nisolle *et al.*, 1994). As previously suggested, the laparoscope was placed 4–5 cm from the peritoneum to evaluate its surface; thereafter, the laparoscope was placed close to the peritoneum to achieve some magnification (Redwine, 1988; Nisolle *et al.*, 1990). Peritoneum eligible for study had to have a perfectly smooth surface with no fibrosis or abnormal vascular patterns, and transparency with no associated colour or suggestion of sub-peritoneal cystic structures.

Statistical comparisons were performed by χ^2 analysis or Kruskal–Wallis test as appropriate.

Table I. Prevalence by AFS stage and laparoscopic appearances of endometriosis in the three groups studied

Endometriosis	Groups of patients		
	1. Infertile ($n = 52$)	2. Pelvic pain ($n = 18$)	3. Fertile ($n = 30$)
No. of patients[a]	26 (50%)	8 (44.4%)	13 (43.3%)
AFS stage[b]			
I	21 (80.7%)	7 (87.5%)	13 (100%)
II	4 (15.4%)	1 (12.5%)	0
III	1 (3.9%)	0	0
IV	0	0	0
Laparoscopic appearance[c]			
Red lesion	8 (30%)	1 (12.5%)	3 (23%)
Black lesion	24 (92%)	6 (75%)	9 (69%)
White lesion	13 (50%)	2 (25%)	5 (38%)
Intra-ovarian cysts	2 (7.7%)	2 (25%)	0

[a]$P = 0.77$.
[b]$P = 0.67$.
[c]$P = 0.51$.

Table II. Results of peritoneal biopsies in the three groups studied

Diagnosis	Groups of patients			
	1. Infertile ($n = 52$)	2. Pelvic pain ($n = 18$)	3. Fertile ($n = 30$)	Total
Laparoscopy +[a]/Histology –	23 (44.2%)	7 (38.9%)	12 (40%)	42
Laparoscopy +/Histology +[b]	3 (5.7%)	1 (5.5%)	1 (3.3%)	5
Laparoscopy –/Histology –	26 (50%)	9 (50%)	15 (50%)	50
Laparoscopy –/Histology +	0 (–)	1 (5.5%)	2 (6.6%)	3
Total				100

[a]Laparoscopy + : evidence of endometriosis at laparoscopy.
[b]Histology + : histologic evidence of endometriosis in biopsies from normal uterosacral ligaments.

Results

Table I shows the prevalence of endometriosis by revised American Fertility Society (1985) classification and the diagnosis of appearances of the condition in the three study groups. Twenty-six patients in group 1 (50%), eight patients in group 2 (44.4%) and 13 patients in group 3 (43.3%), were found to have laparoscopic evidence of endometriosis elsewhere in the pelvis. These figures were not statistically different. The majority of women (80.7% in group 1, 87.5% in group 2, and 100% in group 3) had stage I according to the revised American Fertility Society (1985) classification of endometriosis. The incidence of the distinctive appearances of the lesions was similar in the three groups of patients (Table I) and 7% of all women or 15% (7/47) of those patients having endometriosis at laparoscopy had only subtle (non-'typical') endometriotic peritoneal lesions. Biopsy of the endoscopically suspected endometriosis in 19 patients revealed the presence of endometrial glands and stroma in 17 cases (89.5%), while the two other biopsies showed fibrosis with haemosiderin-laden macrophages and endometrium-like stroma alone respectively.

Table III. Relation between oral contraceptive use and the risk of endometriosis

	Groups of patients				
	1. Infertile (n = 52)	2. Pelvic pain (n = 18)	3. Fertile (n = 30)	Endometriosis (n = 50)	No endometriosis (n = 50)
Age*[a]	32.1 ± 3.9	32.6 ± 4.9	33.8 ± 4.8	33.3 ± 4.1	32.9 ± 4.8
Oral contraceptive use[b]					
Never users	21 (40.3%)	11 (61.1%)	12 (40%)	15 (30%)	29 (58%)
Ever users	31 (59.6%)	7 (38.9%)	18 (60%)	35 (70%)	21 (42%)
current users	0	0	7 (23.3%)	4 (8%)	3 (6%)
ex users	31 (59.6%)	7 (38.9%)	11 (36.7%)	31 (62%)	18 (36%)
Duration of use (years)*[c]	3.9 ± 3.6	8.2 ± 6.4	3.7 ± 3.6	4.5 ± 3.58	6.22 ± 6.47
Time since last use (years)*[d]	7.4 ± 3.1	3.1 ± 3.7	4.9 ± 4.2	5.92 ± 3.98	6.59 ± 4.19
Time since first use (years)*[e]	9.9 ± 4.0	10.5 ± 6.4	8.3 ± 5.8	10.68 ± 5.24	9.43 ± 4.85

*Data are mean ± SD.
[a]No significant differences between groups 1, 2 and 3 nor between patients with and without endometriosis.
[b]No significant differences between groups 1, 2 and 3 except for current users (significantly higher in group 3, $P < 0.001$). All indicators of oral contraceptive use (except current users) significantly higher in the endometriosis group ($P < 0.01$).
[c]Duration of oral contraceptive use significantly higher in group 3 ($P < 0.01$). No significant differences between patients with and without endometriosis.
[d]Recency of oral contraceptive use significantly higher in group 1 ($P < 0.01$). No significant differences between patients with and without endometriosis.
[e]Latency of oral contraceptive use similar for groups 1, 2 and 3 and for patients with and without endometriosis.

The latter two cases were considered as negative for endometriosis.

Results of normal peritoneum biopsy in patients with and without laparoscopically diagnosed endometriosis in the three groups studied are summarized in Table II. Biopsy specimens from both uterosacral ligaments were available for all but one of the 100 patients; one left uterosacral specimen was lost in a fertile woman who had no endometriosis at laparoscopy. Biopsies showed the presence of endometriotic tissue in three cases (5.7%), two cases (11%) and three cases (10%) in groups 1, 2, and 3 respectively. One additional specimen showing mesothelial cell proliferation alone was considered as negative for endometriosis. The size of endometriotic lesions found in normal appearing peritoneum was 460 ± 225 μm (range 129–813). One of the two patients in group 2 and two of the three patients in group 3 had no evidence of endometriosis at laparoscopy. This means that histological study revealed the presence of endometriosis in normal peritoneum in 11% (5/47) of patients having macroscopic endometriosis and in 6% (3/53) of patients without endometriosis at laparoscopy. Interestingly, the patient with chronic pelvic pain who had negative laparoscopy/positive histology had undergone tubal sterilization 10 years previously with no suspicion of endometriosis at laparoscopy.

The relation between oral contraceptive use and the risk of endometriosis is considered in Table III. As expected, the number of current users and duration of oral contraceptive use at the time of laparoscopy were significantly higher in group 3 and time since last use significantly higher in group 1, but there were no significant differences regarding the remaining indicators of oral contraceptive use between groups 1, 2 and 3. In contrast, the frequency of endometriosis was significantly increased in subjects who had ever used oral contraceptives. The use of oral contraception was significantly higher in the whole group of patients with endometriosis. Endometriosis was diagnosed in four of the seven current users of oral contraceptives at the time of laparoscopy. Among the 93 remaining patients, 46 had macroscopic and/or microscopic endometriosis. Mean age and duration, recency and latency of oral contraceptive use were similar in patients with and without endometriosis but 31 of 46 women (67.4%) having the condition reported previous oral contraceptive use, a figure which is significantly higher ($P < 0.005$) than that (18/47 patients or 38.3%) found in patients having no endometriosis.

Discussion

The most important observation of the present study is the high frequency of minimal forms of endometriosis according to the revised American Fertility Society (1985) classification in women of reproductive age independently from infertility, parity and pain symptoms. This is in agreement with previous studies showing that endometriosis is being increasingly diagnosed among women of premenopausal age, mainly infertile women and patients with pelvic pain (Mahmood and Templeton, 1990; Vercellini and Crosignani, 1993; Gruppo italiano per lo studio dell'endometriosi, 1994; Koninckx *et al.*, 1994; Thomas, 1994). The 43.3% incidence of endometriosis found in our prospective study of asymptomatic fertile women, all of them having stage I, is clearly in agreement with Rawson's recent prospective laparoscopic study (1991) in women of reproductive age without the symptoms typical of the condition showing minimal or mild endometriosis in 44% of the subjects. This is remarkable considering that to establish the prevalence of mild forms of endometriosis the least biased population to study prospectively consists of multiparous women without pelvic pain desiring tubal sterilization (Vercellini and Crosignani, 1993). Subtle endometriosis was noted as an isolated finding in 15% of cases of endometriosis in our series which is in agreement with the 11% and 13% reported by Martin *et al.* (1989) and Stripling *et al.* (1988), respectively.

The use of the revised American Fertility Society (1985) classification, however, has been recently criticized on the basis that the activity of the disease is not evaluated. Thus, it has been suggested that the classification could be improved by including the type of active lesion in the staging of

peritoneal endometriosis (Brosens *et al.*, 1993; Donnez *et al.*, 1993). The fresh red lesions would represent the most early active peritoneal lesion and dominate in early years of reproductive life (Wiegerinck *et al.*, 1993; Brosens *et al.*, 1994). Inflammatory reactions, pigmentation with haemosiderin and progressive fibrosis result in these lesions persisting as typical and finally as healed, white peritoneal lesions. Thus, typical dark black and white lesions are considered as older and/or burnt out endometriosis (Koninckx *et al.*, 1991). In our study the mean age was similar in the three groups studied but the percentage of patients with endometriosis having red lesions was higher in the infertile group (30%) than among fertile women (23%) or patients with pelvic pain (12.5%) (Table I). Although these figures were not statistically different, a type II error cannot be excluded because of the limited number of patients in groups 2 and 3. The low incidence of active (red) lesions in group 2 is in agreement with the report by Koninckx *et al.* (1991) showing that subtle and active endometriosis was not associated with pelvic pain. Further studies are needed to establish the incidence of these lesions in infertile patients and fertile women and their pathophysiological implications.

Another valuable finding of our study was the histological demonstration of microscopic endometriosis in visually normal peritoneum overlying the uterosacral ligaments in a limited percentage of women, independently from the study group and laparoscopic diagnosis of endometriosis at other sites. Conflicting results have been reported regarding the incidence and even the existence of microscopic endometriosis in infertile patients and women with chronic pelvic pain having macroscopic endometriosis or not (Murphy *et al.*, 1986; Redwine, 1988; Nisolle *et al.*, 1990; Nezhat *et al.*, 1991). Identification of endometriosis in 25% of biopsy specimens from visually normal anterior or posterior cul-de-sac peritoneum in patients undergoing conservative surgery for endometriosis was reported by Murphy *et al.* (1986). However, none of the normal posterior pelvic peritoneum biopsy specimens taken from 33 patients having chronic pelvic pain (all women) and/or endometriosis (24 patients) was found to be positive for endometriosis in the study by Redwine (1988). Nezhat *et al.* (1991) found that only one out of 76 patients (1.3%) with laparoscopically proven endometriosis demonstrated microscopic endometriosis in normal appearing peritoneum. In contrast, Nisolle *et al.* (1990) reported that histology proved the presence of endometriosis in normal peritoneum (uterosacral ligaments) from infertile women with endometriosis in 13% (7/52) of cases and from infertile women without endometriosis in 6% (2/32) of cases. The difference between the two groups was not significant. Thus, these figures are similar to the 5–6% positive biopsy rates found by us among infertile patients having endometriosis at laparoscopy and women undergoing laparoscopy for tubal sterilization or chronic pelvic pain but having no macroscopic endometriosis. To our knowledge, unsuspected endometriosis documented by histological study of visually normal peritoneum in fertile women has not been previously reported. As previously emphasized by Nisolle *et al.* (1990), the size of endometriotic lesions in normal appearing peritoneum (313 ± 185 μm in their study and similar to our findings) probably explains why the peritoneum had a normal aspect and why the lesion was not visible even though a meticulous inspection was made to identify small lesions.

We found a significant association between endometriosis and use of oral contraception. Epidemiological studies on endometriosis have often yielded discordant results but of the multiple risk factors proposed, menstrual pattern is one of the few to have achieved general acceptance in the literature (Vercellini *et al.*, 1993). Since oral contraceptives reduce the amount of menstrual flow, an effect on the risk of development of endometriosis in women utilizing the pill could be expected. Although the subject is controversial (Vercellini *et al.*, 1993), two very recent reports (Vessey *et al.*, 1993; Parazzini *et al.*, 1994) suggest that endometriosis is suppressed during current and recent pill use but the risk of the disease is higher after the pill is stopped. In the study by Parazzini *et al.* (1994), the relation between oral contraceptive use and risk of endometriosis was analysed separately in cases with infertility, pelvic pain and in women having a previous pregnancy or not. There was no significant interaction between oral contraception use and any of these covariates. This is in agreement with our results but it should be noted that four of the seven current users of oral contraceptives at the time of laparoscopy had macroscopic endometriosis in the present study.

In conclusion, our prospective study shows a high prevalence (45–50%) of endometriosis (including microscopic forms) in both patients with chronic pelvic pain and asymptomatic women (fertile and infertile), thus supporting the modern concept that in many women with patent Fallopian tubes, endometriosis, rather than a 'disease', may be a normal consequence of uninterrupted menstrual periods. In such women, significant amounts of endometriosis may be present without producing any symptoms. In some patients, however, small amounts of endometriosis are an 'annoyance', with implications for their reproductive health, and may produce symptoms (e.g. pelvic pain) and therefore should be defined as a 'dis-ease' (Rawson, 1991; Vercellini and Crosignani, 1993; Thomas, 1994). Previous use of oral contraceptives may increase the risk of developing endometriosis.

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Received on December 22, 1994 ; accepted on October 18, 1995