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Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications

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The relationship between chronic pelvic pain symptoms and endometriosis is unclear because painful symptoms are frequent in women without this pathology, and because asymptomatic forms of endometriosis exist. Our comprehensive review attempts to clarify the links between the characteristics of lesions and the semiology of chronic pelvic pain symptoms. Based on randomized trials against placebo, endometriosis appears to be responsible for chronic pelvic pain symptoms in more than half of confirmed cases. A causal association between severe dysmenorrhoea and endometriosis is very probable. This association is independent of the macroscopic type of the lesions or their anatomical locations and may be related to recurrent cyclic micro-bleeding in the implants. Endometriosis-related adhesions may also cause severe dysmenorrhoea. There are histological and physiopathological arguments for the responsibility of deeply infiltrating endometriosis (DIE) in severe chronic pelvic pain symptoms. DIE-related pain may be in relation with compression or infiltration of nerves in the sub-peritoneal pelvic space by the implants. The painful symptoms caused by DIE present particular characteristics, being specific to involvement of precise anatomical locations (severe deep dyspareunia, painful defecation) or organs (functional urinary tract signs, bowel signs). They can thus be described as *location indicating pain*. A precise semiological analysis of the chronic pelvic pain symptoms characteristics is useful for the diagnosis and therapeutic management of endometriosis in a context of pain.

Key words: chronic pelvic pain/dysmenorrhoea/dyspareunia/endometriosis/questioning

Introduction

The existence of a relationship between chronic pelvic pain symptoms and endometriosis is widely accepted by gynaecologists (Vercellini, 1997). The nature of this relationship remains poorly understood, however. Endometriosis is detected in 2–50% of cases during laparoscopy in women with no symptoms (e.g. in a context of tubal ligation) (Strathy *et al*., 1982; Kresch *et al*., 1984; Liu and Hitchcock, 1986; Moen, 1987; Kirshon *et al*., 1989; Mahmood *et al*., 1991; Rawson, 1991; Balasch *et al*., 1996; Moen and Stokstad, 2002). At the same time, various painful pelvic symptoms are frequent in the general population: a survey carried out in the USA revealed that 90% of women suffered from dysmenorrhoea, 42% from deep dyspareunia and 39% from non-menstrual pelvic pain (Jamieson and Steege, 1996). These figures are clear proof that in women with chronic pelvic pain symptoms and endometriotic lesions, endometriosis is not always the cause of their symptoms (Kresch *et al*., 1984; Stout *et al*., 1991; Hurd, 1998).

Another difficulty in establishing the relationship between pelvic pain and endometriosis is due to the polymorphism of endometriotic lesions. At microscopic level, all these lesions belong to a single entity [i.e. endometrial glands and stroma in an extra uterine location (Clement, 1990)]; however at macroscopic level, pelvic endometriosis can be subdivided into three distinct entities (Koninckx *et al*., 1994; Brosens *et al*., 1995; Nisolle and Donnez, 1997): superficial peritoneal (and ovarian) endometriosis, cystic ovarian endometriosis and deeply infiltrating endometriosis (DIE). One may hypothesize that, depending on the macroscopic type, or on other characteristics of the lesions, endometriosis will play somewhat different roles with respect to the painful symptoms. Adhesions, which are often associated with endometriosis (Clement, 1990), can themselves also play a role in painful symptoms (Kresch *et al*., 1984; Howard *et al*., 2000).

Definitive criteria to determine when the pain is actually caused by endometriosis are lacking. Some authors consequently recommend the ablation of all anomalous lesions found during laparoscopy (Hurd, 1998; Howard, 2003). However, surgical treatment of endometriosis can become difficult and risky, especially in case of DIE (Redwine and Sharpe, 1995; Koninckx *et al*., 1996; Chapron and Dubuisson, 1999; Varol *et al*., 2003). The difficulties with the surgical treatment of the most severe forms of endometriosis have

led some teams to propose limited exeresis and wide recourse to medical treatment (Gambone *et al*., 2002; Martin and O'Conner, 2003). To our mind, the best therapeutic strategy for endometriosis in a context of pain must be determined for each patient individually. It is thus essential, before considering aggressive surgery, to determine whether or not surgical or medical therapy will resolve the pain.

If the characteristics of the endometriotic lesions responsible for pain, together with the possible physiopathological mechanisms, are identified, this will permit useful criteria to be proposed for therapeutic management of endometriosis. The goal of this comprehensive review is firstly, to assess the level of evidence of the relationship between endometriosis and chronic pelvic pain symptoms and, secondly, to clarify the links between the characteristics of the endometriotic lesions and the semiology of the painful symptoms.

Methodological issues

Literature search

We undertook a Medline search using the following MESH key words: pelvic pain, dysmenorrhoea, dyspareunia, endometriosis, treatment outcome, retrospective study, prospective study and comparative study. The studies were selected by reading the title, then the abstract. The references of each study identified were also checked for other potentially relevant studies. The studies included were limited to those published after 1980. Non-comparative studies were excluded from the review.

Definition of chronic pelvic pain symptoms and potential bias related to it

There is considerable variety in the definition of chronic pelvic pain (Howard, 1993). Some authors use a restrictive definition, excluding severe dysmenorrhoea and deep dyspareunia (Howard, 1994; Kontoravdis *et al*., 1996; Mathias *et al*., 1996; Zondervan *et al*., 2001; Jones and Sutton, 2003). Like others (Rapkin, 1986; Vercellini *et al*., 1990; Carter, 1995), we recommend a broader definition that includes severe dysmenorrhoea, deep dyspareunia and all other painful symptoms located in the pelvis, for several reasons. First, some pathological conditions responsible for chronic pelvic pain symptoms (and endometriosis in particular) often associate several different painful symptoms (Fedele *et al*., 1992; Porpora *et al*., 1999; Abbott *et al*., 2004). Second, there is a good correlation between the intensity of dysmenorrhoea, of deep dyspareunia and of non-menstrual pelvic pain in the context of endometriosis (Porpora *et al*., 1999; Abbott *et al*., 2004). Third, it is likely that excluding severe dysmenorrhoea from the definition of chronic pelvic pain symptoms will affect the prevalence of endometriosis found at laparoscopy performed for this indication.

Diagnosis of endometriosis and potential bias related to it

The diagnosis of endometriosis is surgical (Buttram, 1979; Howard, 1993; The American Fertility Society, 1993), with or without histological confirmation. This may result in several indication biases.

First, because the diagnosis of endometriosis requires surgery, it will be made in three main situations: during laparoscopy for infertility, during laparoscopy for chronic pelvic pain symptoms or during surgery for ovarian cyst. In all three cases, the population selected is liable to differ considerably from the general population. For this reason, some studies have control groups based on women undergoing laparoscopy for tubal ligation (Kresch *et al*., 1984; Liu and Hitchcock, 1986; Mahmood *et al*., 1991; Balasch *et al*., 1996) or not having surgery at all (Cramer *et al*., 1986; Darrow *et al*., 1993).

Second, in most studies, the diagnosis of endometriosis is based solely on visual criteria. There is consequently a risk that depending on the indication for the laparoscopy, the surgeon will over- or under-diagnose endometriosis (Howard, 1993; Redwine, 1999). Indeed, visual diagnosis of endometriosis may fail in patients with subtle or atypical forms of peritoneal endometriosis (Nisolle *et al*., 1990; Moen and Halvorsen, 1992; Howard, 1993) or in some patients with DIE not associated with peritoneal or ovarian lesions (Chapron and Dubuisson, 1996; Bonte *et al*., 2002). Use of precise and standardized macroscopic criteria may help to make the visual diagnosis of endometriosis more reliable (Martin *et al*., 1989; Nisolle *et al*., 1990; Vercellini *et al*., 1991; Koninckx and Martin, 1994; Bonte *et al*., 2002). Such criteria were used in only four studies (Forman *et al*., 1993; Balasch *et al*., 1996; Vercellini *et al*., 1996; Chapron *et al*., 2005). Conversely, some authors recommend histological confirmation of all visible lesions (Howard, 1993; Redwine, 1999). This strategy again raises the question of the visual criteria (see below). Furthermore, obtaining histological confirmation is not always possible particularly in case of DIE (Chapron *et al*., 2003b; Chapron *et al*., 2005). In any case, in our previous studies on the correlation between painful symptoms and DIE, we obtained similar results using either visual criteria or histological criteria for the diagnosis of endometriosis (Fauconnier *et al*., 2002; Chapron *et al*., 2003a).

Several different endometriotic lesions are frequently associated in the same patient (Redwine, 1999; Chapron *et al*., 2003b) and may constitute a potential source of confusion bias. Endometriomas are very often associated with adhesions (Sampson, 1921; Vercellini *et al*., 1991; Nezhat *et al*., 1992; Brosens *et al*., 1995). Other associations are possible such as DIE lesions with endometriomas (Sampson, 1921; Schroder *et al*., 1997; Redwine, 1999; Vercellini *et al*., 2000; Chapron *et al*., 2003b) or between different anatomical locations of DIE (Fauconnier *et al*., 2002; Chapron *et al*., 2003b). When several distinct endometriotic lesions are present in the same women, it is difficult to analyse individually the source of the painful symptoms, in the absence of multivariate analysis (Fauconnier *et al*., 2002).

Classification of the studies and potential sources of bias related to this

Comparative studies can be classed basically according to four main categories: (i) prevalence studies; (ii) case–control studies; (iii) correlation studies and (iv) randomized controlled trials.

(i) Prevalence studies compare the frequency of endometriosis according to the operative indication (Table I). In these surveys, the criterion for belonging to the chronic pelvic pain group is based solely on the main operative indication and not on the actual characteristics of the painful symptoms. These studies raise the problems related to indication bias which have already been discussed.

Table I. Prevalence of endometriosis diagnosed by laparoscopy according to the operative indication (prevalence studies)

Study	Definition of CPP	Macroscopic diagnostic criteria	Histological confirmation	Control group	*N* (CPP/control)	% endometriosis in CPP group	% endometriosis in control group	Odds ratio (95% CI)
Kresh *et al.* (1984)	Including severe DM	NA	Yes	Tubal ligation	100/50	32.0	15.0	2.7 (1.1–6.4)
Koninckx *et al.* (1991)	Including severe DM and deep dyspareunia	Typical and atypical	Yes	Infertility	227/416	74.0	68.0	1.3 (0.9–1.9)
Mahmood *et al.* 1991	NA	NA	No	Tubal ligation	156/598	15.4	6.2	2.8 (1.6–4.8)
Mahmood *et al.* 1991	NA	NA	No	Infertility	156/312	15.4	34.3	0.3 (0.2–0.6)
Balasch *et al.* 1996	NA	Typical, atypical and microscopic	Yes	Tubal ligation	18/30	44.4	43.3	1.0 (0.3–3.4)
Balasch *et al.* 1996	NA	Typical, atypical and microscopic	Yes	Infertility	18/52	44.4	50.0	0.8 (0.3–2.3)

CI, confidence interval; CPP, chronic pelvic pain; DM, dysmenorrhoea; NA, not assessed.

(ii) Case–control studies (Table II) consist of comparing the characteristics (frequency, severity etc.) of chronic pelvic pain symptoms according to whether or not the women have endometriosis. The painful symptoms are assessed in standard fashion (generally by means of a questionnaire). The fact that the surgeon is generally not aware of the results of this assessment limits the risk of indication bias, provided that the case inclusion criteria are identical to those for the controls. Another way of limiting the risk of indication bias is to take as controls women who have not undergone laparoscopy (they will thus have had no operative indication) (Cramer *et al*., 1986; Darrow *et al*., 1993). These studies take the pragmatic view that the controls do not have severe endometriosis (Cramer and Missmer, 2002).

(iii) Correlation studies (Table III). These studies aim to reveal the anatomical, morphological or histological characteristics of endometriosis that are related to chronic pelvic pain symptoms. The correlation studies may provide information on the physiopathology of pain in a context of endometriosis. They do not use control groups, but make comparisons between women with endometriosis whose endometriotic lesions have different characteristics. The women with lesions not presenting the characteristic(s) studied are used as controls. Studies searching for 'dose-responsiveness' relationships between precise characteristics of the disease and the severity of the pain are also of particular interest. Indeed, if we suppose that a distinct lesion of endometriosis is responsible for a specific symptom, we would expect to find a linear trend between the degree to which the lesion extends, and the severity of the symptom (Bouyer *et al*., 1993). The extent of endometriotic lesions can be measured as a whole by the R-AFS system (The American Fertility Society, 1985), or in dissociated fashion on the basis of the individual subscores (implants or adhesions) (Chapron *et al*., 2003a). It can also be measured by other quantitative characteristics (such as the size of the implant, or its degree of sub-peritoneal infiltration, etc.). The important point is that the characteristics tested should reflect the supposed natural history of the disease (Hoeger and Guzick, 1999). The severity of the painful symptoms can be appropriately measured either by visual analogue scale (Peveler *et al*., 1996; Garry *et al*., 2000; Anaf *et al*., 2001; Abbott *et al*., 2004) or by multidimensional verbal scales (Andersch and Milsom, 1982; Jamieson and Steege, 1996).

(iv) Randomized controlled trials (Table IV) can theoretically provide evidence that endometriosis causes chronic pelvic pain symptoms by comparing the effects on pain of the destruction of lesions (medically or surgically) to therapeutic abstention.

These studies may have limited impact on the interpretation of the relationship between endometriosis and pain for several reasons.

First, the prescription of a placebo involves ethical problems for the most severe forms that generally are not included in the trials (Telimaa *et al*., 1987; Sutton *et al*., 1994). Furthermore, the use of a placebo results in large numbers of patients leaving the control groups because the pain has continued or recurred (Table IV). The rate of premature withdrawal from the trial limits the time the patients are followed up and may affect the result of the study. Indeed, in one of the studies of medical treatment (Dlugi *et al*., 1990), the rate of premature withdrawal from the placebo group was as high as 87% and affected the results beyond 3 months duration.

Second, the placebo effect needs to be taken into account. The placebo effect of laparoscopy (Baker and Symonds, 1992; Sutton *et al*., 1994; Abbott *et al*., 2004) or medical treatments (Telimaa *et al*.,

Table II. Chronic pelvic pain symptoms according to the presence or absence of endometriosis (case–control studies)

Study	Inclusion of cases	Inclusions of controls	Assessment of CPP	Macroscopic diagnosis	Histological confirmation	*N*	% with endometriosis	OR endometriosis/ DM (95% CI)	OR endometriosis/ DP (95% CI)	OR endometriosis/ NCP (95% CI)
Cramer *et al.* (1986)	Infertility	Recently delivered (same hospital)	Retrospective questionnaire	Laparoscopy or laparotomy, non-standardized	No	4062	6.6	3.14 (2.4–4.1)*	NA	NA
Liu et Hitchcock (1986)	Tubal ligation	Same as cases	Medical records	Laparoscopy, R-AFS, 1985	No	75	42.7	1.4 (0.5–4.0)†	NA	NA
Mahmood *et al.* (1991)	Infertility, CPP, tubal ligation, hysterectomy for haemorrhagia	Same as cases	Preoperative questionnaire	Laparoscopy or laparotomy, R-AFS, 1985	No	1200	16.8	2.2 (1.6–0.3)	1.7 (1.2–2.3)	1.4 (1.0–1.8)
Fedele *et al.* (1992)	Infertility	Same as cases	Preoperative questionnaire	Laparoscopy or laparotomy, R-AFS, 1985	No	124	46.0	1.2 (0.6–2.2), 70 ± 20 versus 58 ± 20‡§	3.8 (1.6–9.0)	2.5 (1.2–5.5)
Darrow *et al.* (1993)	Consecutive cases operated	Friends, controls with non-endometriosis conditions (same department)	Retrospective questionnaire	Laparoscopy, R-AFS, 1985	No	302	51.0¶, 51.5**	2.0 (1.1–3.6)*¶, 1.5 (0.8–2.6)*,**	NA	NA
Forman *et al.* (1993)	Infertility	Same as cases	Preoperative questionnaire	Laparoscopy, R-AFS, 1985	No	99	40.4	2.0 (0.9–4.5)*, 2.9 (1.1–7.4)*,††	0.9 (0.3–2.2), 0.9 (0.3–2.4)¶	1.1 (0.4–3.0), 1.2 (0.4–3.6)¶
Matorras *et al.* (1996)	Infertility	Same as cases	Preoperative standard interview	Laparoscopy, R-AFS, 1993	Yes	348	50.0	1.2 (0.8–1.9)	0.20 (1.0–0.0)	0.6 (0.2–1.9)
Muzii *et al.* (1997)	Consecutive cases operated	Infertility	Preoperative questionnaire	Laparoscopy, R-AFS, 1985	No	80	81.3	NE OR 48 ± 25 versus 35 ± 25‡,‡‡	NA	NA
Vercellini *et al.* (1997)	Infertility, CPP, cysts and other benign conditions	Same as cases	Preoperative questionnaire	Laparoscopy, R-AFS, 1985	No	315	51.7	NE OR 52 [18–74] versus 25 [0–50]‡§	NA	NA
Al-Badawi *et al.* (1999)	Infertility	Same as cases	Medical records	Laparoscopy, non-standardized	No	265	32.1	3.0 (1.4–6.2)§§	4.0 (1.3 - 11.7)††	NA

CI, confidence interval; CPP, chronic pelvic pain; DM, dysmenorrhoea; DP, dyspareunia; NA, not assessed; NCP, non-cyclic pelvic pain; NE, non-estimable; OR, odds ratio.
*Severe dysmenorrhoea versus other.
†Estimable only in the sub-population with menstrual reflux.
‡Visual analogue scale in mm.
§$P < 0.01$.
¶Cases compared with friends' controls.
**Cases compared with medical controls.
††After exclusion of women with adhesions but without endometriosis.
‡‡$P < 0.10$.
§§Relative risk because the odds ratio cannot be estimated from the numbers given in the article.

Table III. Correlation between the semiology of chronic pelvic pain symptoms and the characteristics of the endometriotic lesions (correlation studies)

Study	*N* with endom	Endom type	Histological confirmation	Characteristics studied	Evaluation pain	Multivariate analysis	Dysmenorrhoea	Dyspareunia	Non-cyclic pain
Buttram (1979)	206	All	Yes	AFS*	Medical records	No	AFS stage†	None	NA
Fedele *et al*. (1990)	160	All	No	AFS*, location	Preoperative questionnaire	No	None	None	None
Koninckx *et al*. (1991)	451	All	Yes	Histology, endom type	Medical records	Yes	Depth of sub-peritoneal infiltration	Depth of sub-peritoneal infiltration	Depth of sub-peritoneal infiltration
Marana *et al*. (1991)	206	All	No	AFS*, endom type	Preoperative questionnaire	No	None	None	None
Fedele *et al*. (1992)	57	All	No	AFS*, location, endom type	Preoperative questionnaire	No	Endometriomas, AFS stage	AFS stage	Endometriomas
Perper *et al*. (1995)	70	Not stated	No	Location, endom type, extent of adhesions, macroscopic appearance‡	Preoperative questionnaire	No	Number of implants†	NA	NA
Vercellini *et al*. (1996)	244	All	Partial	AFS*, endom type	Retrospective questionnaire	No	None	DIE vagina versus other types, Peritoneal versus ovarian only	None
Muzzi *et al*. (1997)	65	Endometriomas and superficial endometriosis	No	AFS*, endom type, macroscopic appearance‡	Preoperative questionnaire	No	Endometriomas†, adhesions†, AFS stage†	NA	NA
Porpora *et al*. (1999)	90	All	Yes	AFS*, endom type location	Preoperative questionnaire	Yes	Adhesions†	DIE USL	DIE USL, adhesions†
Gruppo Italiano per lo Studio dell'Endometriosi (2001)	469	All	No	AFS*, endom type, macroscopic appearance†	Preoperative questionnaire	No	(–) Ovarian only versus other types	Posterior DIE versus other types, atypical lesions	None
Anaf *et al*. (2000)	28	DIE vagina	Yes	Histology	Retrospective questionnaire	No	Neural and perineural infiltration	Neural and perineural infiltration	Neural and perineural infiltration
Fauconnier *et al*. (2002)	225	All DIE	Partial	Locations, endom type	Medical records	Yes	Adhesions	DIE USL (Dyspareunia) DIE vagina (painful defecation)	Bowel DIE
Chapron *et al*. (2003a)	209	Posterior DIE	Partial	AFS*, endom type degree of rectovaginal infiltration	Retrospective questionnaire	Yes	Adhesions† and degree of rectovaginal infiltration†	NA	NA

–, connotes a negative association; AFS, American Fertility Society; DIE, deeply infiltrating endometriosis; Endom, endometriosis; NA, not assessed; USL, utero sacral ligaments.
*Including the classification by Acosta and Buttram 1973, and those of AFS in 1979, 1985 and 1996.
†Connotes a linear trend between the symptom and the characteristic studied.
‡Typical versus atypical.

Table IV. Randomized clinical trials comparing medical or surgical treatment for endometriosis and placebo in the context of chronic pelvic pain

Authors, year	*N*	Treatment	Associated treatments	Follow-up duration (months)	% with premature withdrawal	R-AFS stage	Diagnostic criteria	Histological confirmation	Outcome of interest	Assessment method	Mean standardized treatment effect at 6 months*	Second-look laparoscopy
Dlugi *et al*. (1990)	63	Leuprolide acetate IM, 6 months	NS	6	10.7 (treatment), 87.1 (placebo)	All	R-AFS, 1985	No	NCP, DM and DP	Multidimensional verbal scale before-after	−25†‡	No
Bergqvist *et al*. (1998)	49	Triptorelin IM, 6 months	None	18	80.0 (treatment), 87.5 (placebo)	All	R-AFS, 1985	No	Whole pelvic pain	VAS before-after	−28	Yes, 1 month after end of treatment
Telimaa *et al*. (1987)	39	Medroxy progesterone acetate PO, 6 months	Coagulation (25.6%)	12	20.0 (treatment), 15.8 (placebo)	I or II	R-AFS, 1979	No	NCP, lower back pain, painful defecation and DP	Multidimensional verbal scale before-after	−33‡	Yes, 6 months after end of treatment
Telimaa *et al*. (1987)	39	Danazol PO, 6 months	Coagulation (23.1%)	12	10.0 (treatment), 15.8 (placebo)	I or II	R-AFS, 1979	No	NCP, lower back pain, painful defecation and DP	Multidimensional verbal scale before-after	−47‡	Yes, 6 months after end of treatment
Sutton *et al*. (1994)	74	Laser laparoscopic ablation	Adhesiolysis, section USL	6	14.9	I-III	R-AFS, 1985	No	Whole pelvic pain and number cured or improved	VAS before–after, subjective improvement	−28	No
Abbott *et al*. (2004)	39	Laparoscopic excision	Adhesiolysis	12	20.0 (treatment), 5.6 (placebo)	All	R-AFS, 1985	Yes	Whole pelvic pain Individual pain symptoms :NCP, DM, DP, painful defecation Quality of life	Subjective improvement using VAS VAS before–after EQ-5D, SF-12	−30	Yes, 6 months after the surgery

AFS, American Fertility Society; DM, dysmenorrhoea; DP, deep dyspareunia; IM, intra-muscular; NCP, non-cyclic pelvic pain; NS, not stated; PO, per os; USL, utero sacral ligaments; VAS, visual analogue scale.
*Difference in the mean decrease in the pain scale between the treatment group and the placebo group, scaled to 100.
†At 3 months because of insufficient women with follow-up at 6 months.
‡Non-cyclic pelvic pain

1987; Bergqvist *et al*., 1998) appears to be maximum during the first 6 months. Conversely, after medical (Telimaa *et al*., 1987; Bergqvist *et al*., 1998) or surgical treatment (Sutton *et al*., 1994; Anaf *et al*., 2001; Jones and Sutton, 2003), the real effect of the treatment on pain appears to be maximum after 6 months. The placebo effect is significant and may affect equally all individual painful symptoms (severe dysmenorrhoea, dyspareunia, non-cyclic pain or painful defecation) (Abbott *et al*., 2004).

Third, the possibility of recurrence or persistence of the disease may also affect the interpretation of the results. Indeed, the real impact of endometriosis on pain can only be assessed if the endometriosis has been completely treated. In the two studies concerning surgical treatment (Sutton *et al*., 1994; Abbott *et al*., 2004), it was not clearly specified whether the surgery was complete or not. In our own experience with surgery for DIE (Chapron *et al*., 2003b), as in that of other teams (Reich *et al*., 1991), incomplete surgery may sometimes occur due to difficulties for exeresis. Concerning medical treatments of endometriosis, here the question concerns the real nature of their effect on the lesions: complete destruction or inactivation? In a histological study of ovarian endometriosis after hormonal therapy, medical treatment led to an incomplete suppression of endometriotic foci (Nisolle-Pochet *et al*., 1988). Furthermore, second look laparoscopies performed after the resumption of menses have demonstrated that the disease may return with time when hormonal suppression is discontinued (Evers, 1987).

Several methodological issues raise concerns for comparison of the studies. First, because several painful symptoms may be present in the same patient, the choice of a single outcome of interest is difficult. Three studies looked at the effect of treatment on pain assessed as a whole (Sutton *et al*., 1994; Bergqvist *et al*., 1998; Abbott *et al*., 2004). The way in which this criterion was established was not clearly specified in two of these studies (Sutton *et al*., 1994; Bergqvist *et al*., 1998). In Abbott's study, which has the best methodological design, painful symptoms were assessed individually, before and after the surgical procedure, along with the assessment of the global relief of the pain after the surgery (Abbott *et al*., 2004). This latter criterion was the main outcome of interest of the study. In the two studies failing to use a single main criterion (Telimaa *et al*., 1987; Dlugi *et al*., 1990), we selected the result based on non-menstrual pelvic pain.

Second, the severity of pain was assessed by visual analogue scales in three studies (Sutton *et al*., 1994; Bergqvist *et al*., 1998; Abbott *et al*., 2004) and by multidimensional verbal scales in two (Telimaa *et al*., 1987; Dlugi *et al*., 1990). The scores were thus scaled to 100. The average effect for the treatment was estimated by taking the difference in the mean decrease in the pain scale between the treatment group and the placebo group. In Abbott's study, the average effect for the treatment was estimated by measurement of the global relief of pain after surgery (Abbott *et al*., 2004).

Finally, only two studies (Sutton *et al*., 1994; Abbott *et al*., 2004) gave the percentage of women cured or improved, making it possible to calculate odds ratios and attributable risks (Armitage and Berry, 1987). In placebo controlled studies of endometriosis treatment, the attributable risk can be interpreted as the proportion of painful symptoms that are due to endometriosis. This calculation supposes (i) that the implants were treated completely in the treatment group (ii) that the women cured or improved would have no more pain at all.

Results of the studies

Observational studies

The prevalence of endometriosis according to the operative indication is given in Table I. In the three studies comparing women operated for chronic pelvic pain with those operated for tubal ligation, the results disagree. The two oldest (Kresch *et al*., 1984; Mahmood *et al*., 1991) found endometriotic lesions more often in case of chronic pelvic pain, but exploration of the pelvis and the criteria for the visual diagnosis of endometriosis were not standardized. In the third study, the diagnosis of endometriosis was standardized, histological confirmation was required and the non-visible forms of endometriosis were also taken into account (Balasch *et al*., 1996). In this study, the frequency of endometriosis was identical in the two groups (Table I). The three studies that compared the frequency of endometriosis in women operated for chronic pelvic pain with that in women operated for infertility did not reveal any extra risk of endometriosis in relation with chronic pelvic pain (Koninckx *et al*., 1991; Mahmood *et al*., 1991; Balasch *et al*., 1996) (Table I). The fact that endometriosis also causes infertility (Adamson and Pasta, 1994; Jacobson *et al*., 2002) may explain the lack of increased incidence of endometriosis in the chronic pelvic pain group.

Concerning the results of case control studies, these generally agree with respect to dysmenorrhoea. This is more frequent in women with endometriosis than in the controls (Mahmood *et al*., 1991; Forman *et al*., 1993; Al-Badawi *et al*., 1999). In the studies that used pain scales to assess the severity of dysmenorrhoea (Fedele *et al*., 1992; Muzii *et al*., 1997), the dysmenorrhoea scores were higher for women presenting endometriosis than in the controls. Furthermore, a large epidemiological survey (Cramer *et al*., 1986) revealed a linear trend for increasing risk of endometriosis to be associated with increasing severity of the dysmenorrhoea (odds ratio for 'slight' dysmenorrhoea versus none is 1.7; odds ratio for 'moderate' dysmenorrhoea versus none is 3.4; and odds ratio for 'severe' dysmenorrhoea versus none is 6.7).

The link between dysmenorrhoea and endometriosis appears to be independent of the macroscopic type of the lesion. Thus, in a prospective study (Chapron *et al*., 2005), we found that the dysmenorrhoea scores (assessed by visual analogue scale) were equivalent in women presenting superficial endometriosis, cystic ovarian endometriosis or DIE and significantly higher than in women presenting no endometriotic lesion at all. These results are concordant with those of two other studies (Vercellini *et al*., 1996; Gruppo Italiano per lo Studio dell'Endometriosi, 2001).

Concerning the other chronic pelvic pain symptoms, the relationship with endometriosis seems less clear. Three studies found a relationship with dyspareunia (Mahmood *et al*., 1991; Fedele *et al*., 1992; Al-Badawi *et al*., 1999), and two studies a relationship with non-menstrual pelvic pain (Mahmood *et al*., 1991; Fedele *et al*., 1992). A large number of other studies did not find these relationships, however (Table II).

Correlation studies (Table III) underline the important part played by DIE in the relationship between endometriosis and pelvic pain. In one study, the depth of sub-peritoneal infiltration by endometriotic implants was measured histologically and correlated with the operative indication (Koninckx *et al*., 1991). Lesions penetrating deeply under the peritoneal surface (i.e. beyond 5 mm) were found more frequently in patients who had chronic

pelvic pain symptoms (with or without infertility) than in patients who had infertility alone (odds ratio = 3.9). Another histological study (Anaf *et al*., 2000) demonstrated that there was a relationship between the severity of the chronic pelvic pain symptoms and the infiltration of nerves in the rectovaginal space by posterior DIE lesions.

The painful symptoms that are related to DIE may have certain particular characteristics. There is a clear-cut relationship between posterior DIE and deep dyspareunia (Vercellini *et al*., 1996; Porpora *et al*., 1999; Gruppo Italiano per lo Studio dell'Endometriosi, 2001; Chapron *et al*., 2005). In a retrospective study based on women with DIE (Fauconnier *et al*., 2002), we demonstrated that the painful semiology was specific to the anatomical location or to the organ affected by the DIE implant: dyspareunia was associated with involvement of the utero-sacral ligaments, painful defecation during menses with involvement of the posterior wall of the vagina, non-cyclic pelvic pain and functional bowel signs with bowel involvement and functional urinary tract signs with involvement of the bladder (Fauconnier *et al*., 2002). In a prospective study, based on patients operated by laparoscopy for chronic pelvic pain, we demonstrated that painful defecation during menses and severe dyspareunia were specifically connected to DIE involving the posterior area compared to the other diagnoses (other macroscopic type of endometriosis or non-endometriosis diagnosis) (Chapron *et al*., 2005).

The evidence for a relation between cystic ovarian endometriosis and the painful symptoms is poor (Table III). The two studies (Fedele *et al*., 1992; Muzii *et al*., 1997) that found an association between endometriomas and chronic pelvic pain symptoms did not use multivariate analysis and thus may not be able to take into account the possible associations between endometriomas and the associated lesions. In studies using multivariate analysis, neither the presence of endometriomas nor any of their characteristics appears to be connected with the fact of having painful symptoms, (Koninckx *et al*., 1991; Porpora *et al*., 1999; Fauconnier *et al*., 2002; Chapron *et al*., 2003a) (Table III).

Several studies found a clear-cut relationship between pelvic adhesions (Douglas obliteration, or adnexal adhesions) and dysmenorrhoea (Muzii *et al*., 1997; Porpora *et al*., 1999; Fauconnier *et al*., 2002; Chapron *et al*., 2003a) (Table III). Moreover, the extent of these adhesions (measured by the R-AFS partial score) was correlated with the severity of dysmenorrhoea in three studies (Muzii *et al*., 1997; Porpora *et al*., 1999; Chapron *et al*., 2003a).

Many studies have attempted to test the relationship between the overall extent of endometriosis and the severity of painful symptoms. They were mostly based on the classifications proposed successively by the American Society for Reproductive Medicine (former American Fertility Society) (Acosta *et al*., 1973; The American Fertility Society, 1979; The American Fertility Society, 1985; The American Fertility Society, 1993; The American Society for Reproductive Medicine, 1996). Although several well-conducted studies remained negative (Fedele *et al*., 1990; Marana *et al*., 1991; Porpora *et al*., 1999; Gruppo Italiano per lo Studio dell'Endometriosi, 2001), there is overall a weak link between increasing frequency of severe dysmenorrhoea and increasing stage of the disease (Buttram, 1979; Fedele *et al*., 1992; Vercellini *et al*., 1996; Muzii *et al*., 1997) (Table III). However, none of these studies used multivariate analysis, unlike our second study based on women operated for DIE (Chapron *et al*., 2003a). Indeed, the link between the R-AFS stage and the severity of dysmenorrhoea that we found with univariate analysis, entirely disappeared after carrying out multivariate analysis. The severity of dysmenorrhoea was indeed explained by two independent factors: (i) the extent of adhesions; and (ii) the degree to which the rectovaginal space was infiltrated by DIE lesions, assessed in semiquantitative fashion by the existence of infiltration of the walls of the rectum, vagina or both organs. In another study (Perper *et al*., 1995), the severity of dysmenorrhoea appeared to be connected with the total number of implants ($r = 0.32$; $P < 0.05$).

Randomized trials using placebos

Out of five studies published, three concerned medical treatments (Telimaa *et al*., 1987; Dlugi *et al*., 1990; Bergqvist *et al*., 1998) and two surgical treatment (Sutton *et al*., 1994; Abbott *et al*., 2004) (Table IV).

Medical treatments whether with GnRH agonists (Dlugi *et al*., 1990; Bergqvist *et al*., 1998), or Danazol (Telimaa *et al*., 1987), or synthetic progestational hormones (Telimaa *et al*., 1987) have proved their efficiency against placebos for painful symptoms connected with endometriosis (Table IV). The two studies (Telimaa *et al*., 1987; Bergqvist *et al*., 1998) that included second-look laparoscopy after treatment showed that the disappearance or reduction of endometriosis is correlated with the improvement in the painful symptoms.

Analysis of the results according to the individual symptoms shows that medical treatments are efficient not only for severe dysmenorrhoea and non-cyclic chronic pelvic pain, but also for painful defecation when present (Telimaa *et al*., 1987; Dlugi *et al*., 1990; Bergqvist *et al*., 1998). The effect on deep dyspareunia seems less obvious as it was not found in two out of these three studies (Telimaa *et al*., 1987; Dlugi *et al*., 1990).

The efficiency of medical treatments seems to be temporary because secondary reappearance of the painful symptoms after treatment is halted which could affect over 50% of women treated (Vercellini *et al*., 1997; Bergqvist *et al*., 1998; Howard, 2003).

The two studies concerning surgical treatment (Sutton *et al*., 1994; Abbott *et al*., 2004) can be considered as carried out in double blind fashion, given that the patients were not informed of the type of treatment, and that the pre- and post-operative evaluation was carried out by blinded research personnel. These two studies show similar results: the improvement in pain at 6 months was greater in the group that was treated (Table IV); patients were more frequently cured or improved in the treated group than in the placebo group. Odds ratio was 5.7 [95% confidence interval (95% CI) = 1.9–17.3] in Sutton's study (Sutton *et al*., 1994) and 8.7 (95% CI = 2.0–37.4) in Abbott's study (Abbott *et al*., 2004). It can be estimated, by calculation of the attributable risk, that endometriosis was responsible for chronic pelvic pain in about half the patients included in Sutton's study (Sutton *et al*., 1994) and in about two third of the patients included in Abbott's study (Abbott *et al*., 2004).

In Abbott's study, although the decrease of overall pelvic pain was significantly more important in the group of women who had surgical treatment, the effect on individual pain symptoms, when analysed separately, was not different between the two groups (Abbott *et al*., 2004). An explanation of this paradoxical result is the study's lack of statistical power. However, the authors suggested that the efficiency of surgery should be more marked for

painful defecation and dyspareunia than for other painful symptoms (dysmenorrhoea and non-cyclic pain).

Discussion

Physiopathological explanations

Randomized clinical trials against placebos provide evidence that endometriosis generally causes chronic pelvic pain symptoms. However, they have also shown that the endometriotic lesions diagnosed in the context of a laparoscopy carried out for chronic pelvic pain are not always the culprit for the pain of which the patients complain. According to these studies, endometriosis may be responsible for the painful symptoms in more than half of women operated on. This proportion is in reality lower, as shown by the prevalence studies. When all types of endometriosis are taken into account, these studies tend to show that endometriosis is no more frequent in women operated on for pain, than in women operated on for other indications (infertility or tubal ligation). The differences between prevalence studies and clinical trials may be explained by the fact that the women included in the latter present more serious forms of endometriosis (Cramer and Missmer, 2002). Rather than the presence of endometriosis itself, it is the characteristics of the lesions and their extent that would explain the chronic pelvic pain symptoms.

To attribute chronic pelvic pain symptoms to endometriosis, both the semiology of the painful symptoms and the characteristics of the endometriotic lesions can serve as a basis. Case–control and correlation studies clearly indicate an association between severe dysmenorrhoea and endometriosis. The causal nature of this association is suggested by the fact that dose-responsiveness relationships have been found: (i) the existence of a linear trend for increasing frequency of endometriosis diagnosed to be associated with increasing intensity of dysmenorrhoea; (ii) the existence of a linear trend for increasing extent of the disease (as measured by the R-AFS stage) to be associated with increasing intensity of dysmenorrhoea. The association between severe dysmenorrhoea and endometriosis is not specific to any particular macroscopic type of endometriosis nor any particular location. This undiscriminating aspect of dysmenorrhoea should be considered in parallel with the ubiquitous character of the histological lesion (endometrial gland and stroma).

Several physiopathological mechanisms might explain the relationship between endometriosis and severe dysmenorrhoea. Dysmenorrhoea could be due to cyclic recurrent micro-bleeding within the lesions and the consequent inflammation (Brosens, 1997; Vercellini, 1997). The fact that cyclic recurrent micro-bleeding occurs as a common feature in all three macroscopic entities of endometriosis (Brosens, 1997) may explain the fact that severe dysmenorrhoea is related to endometriosis but not to a specific macroscopic form of the disease. Furthermore, the hypothesis of cyclic recurrent micro-bleeding may also explain the fact that women with DIE infiltrating very deeply into the rectovaginal space (i. e. involving vaginal or rectal wall) had the most severe dysmenorrhoea (Chapron *et al*., 2003a). Indeed, in DIE not all implants may harbour evidence of micro-bleeding. Micro-bleeding within the DIE lesions is related with the presence of microendometriomas, which may be present in certain locations, particularly when the submucosal layer of the vagina or rectum are involved (Brosens, 1997).

Adhesions appear also to play an independent role in the genesis of dysmenorrhoea (see results of the study section and Table III). Given that a large proportion of women with endometriosis also have adhesions, it may be that the relationship between endometriosis and dysmenorrhoea is partly due to them.

The last hypothesis concerning dysmenorrhoea and endometriosis questions the direction of the causal association between them: severe dysmenorrhoea could indeed be due to the cause of the endometriosis, rather than a consequence of existing lesions. This hypothesis has arisen from epidemiological studies addressing the aetiological aspect (Cramer and Missmer, 2002). Endometriosis is indeed encouraged by the existence of obstructive pathologies affecting the genital tract (Te Linde and Scott, 1950; Huffman, 1981) or by retrograde menstruation (Liu and Hitchcock, 1986) both of which are known to cause severe dysmenorrhoea.

Concerning the characteristics of endometriotic lesions, DIE is the only macroscopic type of lesion for which the relationship with chronic pelvic pain symptoms appears to be well understood. Conviction concerning the causal nature of the association is based essentially on histological correlation studies: (i) One study proves unambiguously that, in a population of women with different endometriosis lesions, those diagnosed with DIE suffered from the most severe painful symptoms (Koninckx *et al*., 1991); (ii) the relationship between DIE and pain may be explained by compression or infiltration of the sub-peritoneal nerve fibres by DIE implants (Anaf *et al*., 2000). DIE is a distinct entity and its lesions present particular morphological and histological characteristics (Cornillie *et al*., 1990; Donnez *et al*., 1996b) that may explain this ability to infiltrate neighbouring tissues.

Painful symptoms connected with DIE present particular semiological characteristics which distinguish them from painful symptoms of other origins (i.e. connected with other types of endometriosis or other pathologies responsible for chronic pelvic pain) (Chapron *et al*., 2005). These symptoms are related to the involvement of specific anatomical locations (severe dyspareunia and painful defecation during menses) or specific organs (functional urinary tract signs and bowel signs) by the DIE implants (Fauconnier *et al*., 2002). Infiltration of the pelvic nerves by the lesions (Anaf *et al*., 2000) explains the parallel between the anatomical location of the lesions and the pain semiology. These painful symptoms can thus be described as *location indicating pain.* In most cases the pain is of the mechanical and provoked type: mobilization of the organs affected by the DIE lesions triggers or aggravates the pain.

The relationship between chronic pelvic pain symptoms and cystic ovarian endometriosis is a subject of debate. Taking non-controlled studies as a basis, treatment of the endometriomas (and associated adhesions) results in the painful symptoms being cured in a large proportion of cases (Sutton *et al*., 1997; Jones and Sutton, 2003). However, correlation studies have shown no particular relationship between the pain and the endometriomas. One of the hypotheses that we make, along with other authors (Koninckx *et al*., 1991; Vercellini, 1997), is that apart from severe dysmenorrhoea, the existence of painful symptoms in a woman with an endometrioma may be caused by associated DIE lesions which should be sought for and treated. These associations between cystic ovarian endometriosis and DIE are frequently found and can involve two particularly serious forms: bowel endometriosis (Schroder *et al*., 1997; Redwine, 1999) and ureteral endometriosis

(Vercellini *et al*., 2000). Another hypothesis concerns the role of the associated adhesions. Ovarian endometriomas are adherent to the surrounding pelvic structures in more than 90% of the case (Sampson, 1921; Vercellini *et al*., 1991; Nezhat *et al*., 1992). One histological study on structural features of adhesions in women with endometriosis has shown that periovarian adhesions contain endometrial and inflammatory cells which may generate painful symptoms (Jirasek *et al*., 1998).

Implications

(i) Analysis of the painful symptoms may be useful for the preoperative diagnosis of endometriosis. Severe dysmenorrhoea deserves to be tested as a screening tool for endometriosis, for example in women consulting for infertility or presenting an ovarian cyst. In the context of infertility, the presence of this symptom could encourage laparoscopic investigation (Forman *et al*., 1993). Conversely, fine analysis of dysmenorrhoea has not proved to be of any diagnostic value for preoperative diagnosis of DIE (Chapron *et al*., 2005), which could be due to the fact this symptom is rather independent relative to the macroscopic form of the disease. Nonetheless, in the same study, we demonstrated that two signs could be useful for the preoperative diagnosis of posterior DIE: severe dyspareunia and painful defecation during menstruation (Chapron *et al*., 2005).

(ii) The facts that dysmenorrhoea is associated with endometriosis, whatever the macroscopic form of the disease, and that it appears to be correlated with various elements indicating the extent of the disease, mean that this symptom could be used as an overall prognostic factor for the disease (like the duration of infertility in the context of infertility). A prognostic criterion may be very useful for establishing and validating new classifications (Hoeger and Guzick, 1999) or to test new treatments in the context of endometriosis-related pain.

(iii) Semiological analysis of the chronic pelvic pain symptoms can also help in the definition of the surgical strategy. In the context of DIE, treatment may require extensive surgery (Redwine, 1992; Garry *et al*., 2000), which may include utero-sacral ligament resection (Chapron *et al*., 1999), partial colpectomy (Martin, 1988; Donnez and Nisolle, 1995), resection of rectal endometriosis (Bailey *et al*., 1994; Thomassin *et al*., 2004), and partial cystectomy (Chapron and Dubuisson, 1999). However, although these treatments give good results, their efficiency for alleviating pain is far from being guaranteed (Bailey *et al*., 1994; Tran *et al*., 1996; Chapron *et al*., 1999; Chapron and Dubuisson, 1999; Chapron *et al*., 2001; Kavallaris *et al*., 2003; Thomassin *et al*., 2004). In addition, the risk of serious complications inherent to this type of surgery has been estimated at between 4 and 6% of cases (Koninckx *et al*., 1996; Varol *et al*., 2003). The essential point to be taken into account in the operative indication is whether the pain is indeed due to the lesions diagnosed. In our opinion, the existence of *location indicating pain* matching the DIE implants observed justifies comprehensive exeresis of the lesions.

(iv) Medical hormonal treatments seem generally efficient for alleviating the painful symptoms related with endometriosis whatever its macroscopic type. This is due to the fact that endometriotic lesions are hormone dependent (Brosens, 1994). However, the effect of medical treatment on the most serious lesions is nevertheless questionable. In our experience of DIE (Chapron *et al*., 2003b), like in that of other teams (Koninckx and Martin, 1994; Vercellini *et al*., 1998; Thomassin *et al*., 2004), after an initial phase of spectacular improvement, the painful symptoms (particularly when *location indicating pain* symptoms are present) may subsequently reappear under medical treatment. The evolution of active and glandular lesions towards fibrous lesions (Cornillie *et al*., 1990; Brosens *et al*., 1994) under the influence of medical treatment could explain these failures. Indeed, the efficiency of hormonal treatments for lesions with not very active glandular tissue and dense fibrous lesions, instead, is weak (Shaw, 1992). In DIE, apart from glandular tissue, fibrosis can also affect the nerves in the sub-peritoneal pelvic space and thus may play an important role in the genesis of the pain (Anaf *et al*., 2000). Furthermore, it has been suggested, on the basis of a histological study, that some posterior DIE implants (those involving the vagina or the rectum) may not be hormonally driven and do not respond to hormonal suppression by GnRH agonists in the way that peritoneal lesions do (Donnez *et al*., 1996a). For all these reasons, it is important to set up studies to assess specifically the efficacy of medical hormonal treatments on DIE-related symptoms, together with their influence on the histology of the lesions.

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