Deeply infiltrating endometriosis: pathogenetic implications of the anatomical distribution

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BACKGROUND: To investigate whether knowledge of the anatomical distribution of histologically proven deeply infiltrating endometriosis (DIE) lesions contributes to understanding the pathogenesis. METHODS: Observational study between June 1992 and December 2004 (retrospective study between 1992 and 2000; prospective study between 2001 and 2004). Continuous series of 426 patients suffering from pelvic pain who underwent complete surgical excision of DIE. DIE lesions were classified according to four different possibilities: (i) Firstly, DIE lesions were classified as located in the anterior or posterior pelvic compartment. (ii) Secondly, DIE were classified as left, median and right. (iii) Thirdly, DIE lesions were classified as pelvic or abdominal. (iv) Fourthly, DIE lesions that could present in a right and/or left location were classified as unilateral or bilateral. RESULTS: These 426 patients presented 759 histologically proven DIE lesions: bladder (48 lesions; 6.3%); uterosacral (USL) (400 lesions; 52.7%); vagina (123 lesions; 16.2%); ureter (16 lesions; 2.1%) and intestine (172, 22.7%). DIE lesions are significantly more often located in the pelvis \(n = 730\) lesions than in the abdomen \(n = 29\) lesions \(P < 0.0001\). Pelvic DIE lesions are significantly more often located in the posterior compartment of the pelvis \(682\) DIE lesions (93.4%) versus 48 DIE lesions (6.6%); \(P < 0.0001\). Pelvic DIE lesions are significantly more frequently located on the left side. For patients with unilateral pelvic DIE lesions, the anatomical distribution is significantly different in the three groups: left (172 lesions; 32.0%), median (284 lesions; 52.8%) and right (82 lesions; 15.2%) \(P < 0.0001\). For patients with lateral lesions, left DIE lesions (172 lesions; 67.8%) were found significantly more frequently than right DIE lesions (82 lesions; 32.2%) \(P < 0.0001\). A similar predisposition was observed when we included patients with bilateral pelvic DIE lesions \(P = 0.0031\). The same significantly asymmetric distribution is observed for total (pelvic and abdominal) DIE lesions. CONCLUSIONS: Our results demonstrate that distribution of DIE lesions is asymmetric. It is possible that this is related to the anatomical difference between the left and right hemipelvis and to the flow of peritoneal fluid. These findings support the hypothesis that retrograde menstruation of regurgitated endometrial cells is implicated in the pathogenesis of DIE.

Key words: anatomical distribution/deeply infiltrating endometriosis/implantation/pathogenesis/retrograde menstruation

Introduction

Endometriosis is a very controversial and enigmatic disease (Garry, 2004), and many theories regarding the pathogenesis have been advanced. Two physiopathological hypotheses are the most often proposed to explain the pathogenesis of endometriosis. The first theory is that of retrograde menstruation in which the lesions would be secondary to implantation and proliferation of regurgitated endometrial cells in an ectopic situation (Sampson, 1927). The second theory is that of metaplasia (Meyer, 1919), either of the celomic metaplasia (Gruenwald, 1942) or Mullerian remnants metaplasia (Donnez et al., 1995).

There are three types of endometriosis: superficial endometriosis, ovarian endometrioma and deeply infiltrating endometriosis (DIE). DIE is a specific entity (Cornillie et al., 1990) histologically defined in arbitrary manner when endometriotic lesions extend more than 5 mm underneath the peritoneum (Köninxck et al., 1991). DIE is responsible for painful symptoms (Fauconnier and Chapron, 2005) whose severity is strongly correlated with the depth of the DIE lesions (Köninxck et al., 1991; Porpora et al., 1999; Chapron et al., 2003a).

If retrograde menstruation participates in the physiopathology of endometriosis, it is logical to consider that the anatomical pattern of endometriotic lesions would be determined by
factors (gravidity, proximity to the site of abdominal entry, anatomical considerations, etc.) influencing the distribution and implantation of endometrial cells in the abdominal cavity. Concerning superficial endometriosis, several works have shown that lesions were most often located in the posterior compartment of the pelvis (Dmowski and Radwanska, 1984; Jenkins et al., 1986; Ishimaru and Masuzaki, 1991; dell’endometriosi, 1994) and on the left side (Al-Fozan and Tulandi, 2003; Parazzini, 2003). Unlike non-endometriotic benign ovarian cysts (Vercellini et al., 2000), ovarian endometriomas are significantly more frequent on the left ovary (Vercellini et al., 1998; Al-Fozan and Tulandi, 2003; Szurkowski and Emerich, 2005). Recurrent ovarian endometriomas are more frequent on the left ovary (Vercellini et al., 2002), and the overall rate of endometriosis recurrence was found to be significantly higher when the left ovary was involved (Ghezzi et al., 2001).

Very little work has been devoted to the analysis of the location of DIE lesions. Recently, a surgical DIE classification was proposed based on anatomical distribution of the lesions with a recommended surgical management for each DIE location (Chapron et al., 2003b). The sole aim of this publication was to specify the methods of surgical treatment for patients presenting DIE. To our knowledge, only two other authors (Vercellini et al., 2000b, 2004; Chapron et al., 2001a) have studied the distribution of DIE lesions with the aim of attempting to understand the pathogenesis better. These studies conclude that uterosacral ligament (USL) lesions (Chapron et al., 2001a), intestinal lesions (Vercellini et al., 2004) and ureteral lesions (Vercellini et al., 2000b) are more often observed on the left side.

The goal of our work, which is based on a continuous series with a very large number of patients presenting histologically proven DIE, is to establish whether the study of the anatomical distribution of abdomino-pelvic DIE lesions (USL, vagina, bladder, ureter and intestine) can provide a greater understanding of the pathogenesis.

Materials and methods
Between June 1992 and December 2004, a continuous series of 426 patients suffering from pelvic pain underwent complete surgical management (operative laparoscopy or laparotomy) for DIE. The diagnosis of DIE was histologically proven for each patient. Between June 1992 and December 2000, medical, operative and pathological reports of each patient were re-examined retrospectively in blinded fashion by two authors. Disagreements were resolved by discussion with a third gynaecologist author. The same analysis was performed prospectively for patients operated between January 2001 and December 2004. DIE lesions were classified according to five locations: (i) bladder, when lesions infiltrate the bladder muscularis propria (Chapron and Dubuisson, 1999); (ii) USL, when lesions infiltrate only the USL(s) (Chapron and Dubuisson, 1996); (iii) vaginal, when lesions infiltrate the anterior rectovaginal pouch, posterior vaginal fornix and retroperitoneal area between the anterior rectovaginal pouch and posterior vaginal fornix (Chapron et al., 2001b; Martin and Batt, 2001); (iv) ureteral when DIE lesions infiltrate the ureteral wall (intrinsic ureteral endometriosis) or when external ureteral compression by DIE lesions is responsible for a ureteral obstruction (extrinsic ureteral endometriosis) (Clement, 1994) and (v) intestinal, when lesions involve the muscularis propria of the bowel. When a patient presented multiple DIE locations, we classified her in the stage corresponding to the worst one (Chapron et al., 2003b). According to the definition, we classified lesions in the following order from least to worst: USL, vagina, bladder and ureter. We studied the DIE location(s) for each patient according to the above criteria, i.e.: bladder, USL, vagina, ureter and intestine. Concerning the intestinal DIE lesions, the different locations were the following: rectum, recto-sigmoid junction, sigmoid colon, descending colon, transverse colon, ascending colon, appendix, ileocecal junction, small intestine and omentum. DIE lesions were classified according to four different possibilities. Firstly, DIE lesions were classified as located in the anterior or posterior pelvic compartment. By definition (Jenkins et al., 1986), anterior DIE was defined as bladder DIE and posterior DIE included the other pelvic DIE locations: USL, vagina, ureter and intestine. Secondly, DIE were classified as left, median and right. By definition, we classified as left DIE lesions the following: left USL, left ureter, sigmoid colon and descending colon; as median DIE lesions the following: bladder, vagina, rectum, recto-sigmoid junction, transverse colon, small intestine and omentum; and as right DIE lesions the following: right USL, right ureter, ascending colon, appendix and ileocecal junction. Thirdly, DIE lesions were classified as pelvic or abdominal. We classified as abdominal DIE lesions the following: descending colon, transverse colon, ascending colon, appendix, ileocecal junction, small intestine and omentum. All the other DIE locations (bladder, USL, vagina, ureter, rectum, rectosigmoid junction and sigmoid colon) were considered as pelvic DIE lesions. Fourthly, DIE lesions that could present on either side (right versus left) were classified as unilateral or bilateral.

For each patient, general data were noted (age, parity, gravidity, height, weight and BMI) together with the existence of pelvic pain (dysmenorrhoea, deep dyspareunia and chronic pelvic pain), history of medical and/or surgical treatment for endometriosis, stage of the disease according to the revised American Fertility Society classification (rAFS) (Society, 1985) and mean rAFS scores (total, implants and adhesions) according to the same classification (Society, 1985).

Statistical tests
The proportion of histologically proved DIE lesions was analysed using the χ² test. The odds ratio (OR) of the observed frequencies of left- and right-sided lesions were also computed. The 95% confidence interval (95% CI) was computed using the normal approximation. The differences are considered to be statistically significant if P ≤ 0.05. All analyses were performed with StatView 5.0 software (SAS Institute Inc.).

Results
Patient characteristics are summarized in Table I. Patient distribution, according to the DIE lesion classification, was as follows: bladder (37 patients; 8.7%); USL (222 patients; 52.1%); vagina (61 patients; 14.3%); ureter (15 patients; 3.5%) and intestine (91 patients; 21.4%) (Table II). These 426 patients presented 759 histologically proven DIE lesions: bladder (48 lesions; 6.3%); USL (400 lesions; 52.7%); vagina (123 lesions; 16.2%); ureter (16 lesions; 2.1%) and intestine (172; 22.7%). Details of intestinal DIE lesions are the following: rectum and rectosigmoid junction (113 lesions; 65.7%); sigmoid colon (30 lesions; 17.4%); caecum and ileocaecal junction (7 lesions; 4.1%); appendix (11 lesions; 6.4%); small bowel (8 lesions; 4.7%) and omentum (3 lesions; 1.7%) (Figure 1). We observed no intestinal DIE lesions on the transverse colon or descending colon. The mean number of DIE lesions per patient was 1.8 ± 1.25 (range 1–7). One hundred and seventy-four patients (n = 174; 40.8%)
presented multiple DIE lesions. For patients with multiple DIE lesions ($n = 252; 59.2\%$), the mean number of DIE lesions per patient was $2.9 \pm 1.3$ (range 2–7).

Among these 426 patients, 18 patients presented abdominal DIE lesions. For one of these 18 patients, the abdominal DIE lesion (appendix) was the only DIE lesion without any associated pelvic DIE lesions. The 17 other patients with abdominal DIE lesions presented associated pelvic DIE lesions. Among the 425 patients with pelvic DIE, 408 (96.0\%) patients presented no associated abdominal DIE lesions. DIE lesions are significantly more often located in the pelvis ($n = 730$ lesions) than in the abdomen ($n = 29$ lesions) ($P < 0.0001; OR = 25.17; 95\% CI = 18.43–34.38$).

Pelvic DIE lesions ($n = 425$ patients; 730 pelvic DIE lesions) are significantly more often located in the posterior compartment of the pelvis ($682$ DIE lesions (93.4\%) versus 48 DIE lesions (6.6\%); $P < 0.0001; OR = 14.21; 95\% CI = 10.71–18.84$). Pelvic DIE lesions are significantly more often found on the left side. For patients with median and unilateral pelvic DIE lesions ($n = 330$ patients; 538 DIE lesions), the anatomical distribution of these lesions between the three groups differs significantly: left (172 lesions; 32.0\%), median (284 lesions; 52.8\%) and right (82 lesions; 15.2\%) ($P < 0.0001$). For patients with lateral lesions, left DIE lesions (172 lesions; 67.8\%) were found significantly more frequently than right DIE lesions (82 lesions; 32.2\%). This is significantly different from the expected proportion of 50\% ($P < 0.0001; OR = 2.1; 95\% CI = 1.47–3.00$) (Table III). A similar pattern was observed when we included patients ($n = 425$) with bilateral pelvic DIE lesions ($P = 0.0031; OR = 1.51; 95\% CI = 1.16–1.96$) (Table III).

Abdominal DIE lesions ($n = 29$) are more frequently located on the right side (appendix and ileocecal junction). For patients with abdominal DIE lesions, the anatomical distribution of DIE lesions between the three groups differs significantly: left (0 lesions; 0\%); median (11 lesions; 37.9\%) and right (18 lesions; 62.1\%) ($P < 0.0001$).

Total (pelvic and abdominal) DIE lesions are significantly more frequently located on the left side. For patients with median and unilateral total DIE lesions ($n = 331$ patients; 567 DIE lesions), the anatomical distribution of DIE lesions differs significantly between the three groups: left (172 lesions;
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Discussion

These data suggest that the anatomical distribution of pelvic DIE lesions presents a double asymmetry. Pelvic DIE lesions are more frequently observed in the posterior pelvic compartment and are most often located on the left side. Furthermore, abdominal DIE lesions are far less frequent than pelvic DIE lesions, and unlike these, they are most often located in the right side of the abdominal cavity (appendix and ileocaecum junction).

All these observations plead in favour of the theory of regurgitation and the importance of peritoneal flow patterns in DIE pathogenesis. Other studies have shown that the posterior pelvic compartment is the most frequent site of DIE lesions (Dmowski and Radwanska, 1984; Jenkins et al., 1986; Cornillie et al., 1990; Ishimaru and Masuzaki, 1991; dell’endometriosi, 1994; Chapron et al., 2003b; Redwine, 1999; Bazot et al., 2004a). With the patient standing erect, under the effect of gravity, menstrual blood reflux accumulates in the bottom of the Pouch of Douglas, which is the most dependent portion of
the abdomino-pelvic cavity. The effect of gravity also explains why pelvic DIE lesions are more frequently observed than abdominal DIE lesions and why intestinal DIE lesions are preferentially located on the rectum and the recto-sigmoid junction (113 lesions; 65.7% in our experience) (Figure 1). The far lower frequency of deep bladder endometriosis compared with USL, vaginal and rectal DIE can be explained by the anatomy, because the lower limit of the vesico-uterine pouch is located well above the lower limit of the Pouch of Douglas, which lies opposite the middle third of the posterior vaginal wall (Kuhn and Hollyock, 1982; Baessler and Schuessler, 2000). The more the uterus is retroverted, which makes it easier for the peritoneal liquid to flow from the anterior compartment towards the posterior compartment, the more the DIE lesions will be found posteriorly (Jenkins et al., 1986).

The anatomical differences between left and right hemipelvis, because of the presence of the sigmoid colon on the left, could explain why pelvic DIE lesions are observed more frequently on the left pelvic side wall. The close anatomical relationship between the sigmoid colon and the left adnexa forms a barrier to pelvic diffusion of menstrual blood reflux, resulting in an anatomical situation that could encourage adhesions and growth of regurgitated endometrial cells on the left pelvic side wall. This anatomical configuration could also explain why endometriomas are more often seen on the left side (Vercellini et al., 1998; Al-Fozan and Tulandi, 2003; Parazzini, 2003; Sznurkowski and Emerich, 2005) and why two-thirds of patients with sciatic nerve endometriosis had right-side lesions (Vercellini et al., 2003). The sigmoid colon could constitute an obstacle between regurgitated endometrial cells implanted on the left posterolateral pelvic peritoneum and the left lumbosacral plexus, thus protecting the left sciatic nerve (Vercellini et al., 2003).

Results of research into the flow of peritoneal fluid support the hypothesis that peritoneal liquid plays a part, together with regurgitated endometrial cells, in DIE pathogenesis. Meyers (1973) demonstrated that intraperitoneal fluid continually follows a circulation through the abdomen. These currents are caused by changes in hydrostatic pressure because of movement of the diaphragm and peristalsis of the bowel. In the erect position, the pressure in the lower abdomen is three times higher than in the upper abdomen (Drye, 1948). The digestive structures and their mesenteric attachments channel the intraperitoneal fluid flow, and variations in intraperitoneal pressure direct this flow clockwise (Foster et al., 1981). Four predominant sites have been identified for the preferential, repeated or arrested flow of peritoneal fluid: (i) the pelvic cavity and especially the Pouch of Douglas; (ii) the right lower quadrant at the termination of the small bowel mesentery (caecum and ileocaecum junction); (iii) the superior aspect of the sigmoid mesocolon; and (iv) the right paracolic gutter (Meyers, 1973). Just as for superficial lesions (Jenkins et al., 1986) (Table V), the anatomical distribution of DIE lesions correlates with the pathways for the peritoneal fluid flow. A similar observation was made concerning the distribution of intraperitoneal malignant seeding (Meyers, 1973) and acute effusions (Meyers, 1970). Consequently, it cannot be excluded that menstrual regurgitation with deposition and implantation of regurgitated endometrial cells in the abdomino-pelvic cavity could be dependant upon intraperitoneal pressure and the natural flow of fluid in the peritoneal recesses.

These observations would explain the considerably higher frequency of DIE lesions in the pelvis than in the abdomen, together with the fact that these lesions are more often located to the left in the pelvis and the right in the abdomen. This theory helps to explain not only the anatomical distribution of the various types of endometriosis (superficial, endometriomas and DIE) but also that of certain particular endometriotic locations (Table V).

Four other observations plead in favour of regurgitation playing a role for the different types of endometriotic lesions. Firstly, unlike those patients presenting endometriosis without deep lesions, those with DIE have a significantly reduced Douglas pouch depth (Vercellini et al., 2000a). This obliteration of the Pouch of Douglas is secondary to the inflammatory...
process subsequent to peritoneal implantation of regurgitated endometrial cells, which gives the false impression that deep lesions are of retroperitoneal origin. Magnetic resonance imaging clearly shows that DIE originates from the retrocervical area and not from the rectovaginal septum (Chapron et al., 2002). Firstly, the term 'rectovaginal septum endometriosis' is incorrect in the anatomical sense (Chapron et al., 2004), as DIE lesions are initially located above the upper border of the rectovaginal septum. Secondly, no peritoneal and/or ovarian endometriotic lesions are seen after tubal ligation (Rock et al., 1981), and the rate of endometriosis recurrence at 24 months is significantly less important when endometrial ablation is associated with laparoscopic treatment of endometriosis (Bulletti et al., 2001). Thirdly, peritoneal fluid represents a specific microenvironment that could play a role in the pathogenesis of endometriosis (Ramey and Archer, 1993; Koninckx et al., 1999). Several studies have shown that ovulation is more frequent on the left side (Potashnik et al., 1987; Jarvela et al., 2000; Fukuda et al., 2001). Greater exposure to progesterone in the right hemipelvis could contribute in this part of the pelvis to set up an inappropriate microenvironment for implantation of endometriotic cells and for developing DIE. Fourthly, the asymmetric nature of pelvic vascularization, because of the entrance of the left ovarian vein into the homolateral renal vein rather than into the vena cava, explains why varicocele occurs more frequently on the left side (Giacchetta et al., 1989). This venous stasis on the left side could give rise to local variation in blood stream factors that would affect the development of DIE, which is more dependent on plasma levels than the influence of the peritoneal liquid (Koninckx et al., 1999).

In conclusion, our results, together with the vast body of evidence available in the literature, strongly support the implantation theory in DIE pathogenesis and that the role of the peritoneal liquid is essential for understanding the anatomical distribution of DIE lesions.

References

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