Association rate between deep peritoneal endometriosis and other forms of the disease: pathogenetic implications

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BACKGROUND: It has been suggested recently that deep endometriosis and the other forms of the disease do not share a common pathogenetic mechanism. In this study, we hypothesize that, if this is true, deep peritoneal endometriosis and the other forms should not be significantly associated. METHODS: Clinical and surgical records of all women who were referred to the Department of Obstetrics and Gynecology, Clinica ‘L.Mangiagalli’ between January 1995 and June 2002 and who were diagnosed with deep peritoneal pelvic endometriosis at the time of surgery were retrieved. The concomitant presence of superficial endometriotic implants, endometriomas and pelvic adhesions was evaluated. A binomial probability distribution model was used to calculate the 95% confidence interval (95% CI) of the association rates. RESULTS: Ninety-three women with deep peritoneal endometriosis were identified. The presence of superficial endometriotic implants, endometriomas and pelvic adhesions was documented in 61.3% (95% CI 51.4–71.2%), 50.5% (95% CI 40.3–60.7%) and 74.2% (95% CI 65.3–83.1%) of patients with deep endometriotic nodules, respectively. Overall, deep peritoneal endometriosis was the only form of the disease in only 6.5% (95% CI 2.8–12.3%) of cases. No relevant differences regarding these associations were observed according to the location and the size of the deep endometriotic nodules. CONCLUSIONS: Results from this study do not support the hypothesis that deep endometriosis should be considered as a distinct entity of the disease.

Key words: adhesion/deep endometriosis/endometriosis/pathogenesis/superficial endometriosis

Introduction

Deep infiltrating peritoneal endometriosis is a particular form of the disease that is strongly associated with pelvic pain symptoms such as dysmenorrhea, deep dyspareunia, chronic pelvic pain and painful defecation (Fauconnier et al., 2002). The intensity of these symptoms seems to be correlated with the depth of infiltration, the location, and the tendency of some of these lesions to invade neuronal structures (Koninckx et al., 1991; Anaf et al., 2000a, 2002). The most frequent locations of deep endometriosis are the uterosacral ligaments, the Douglas cul-de-sac, the rectum, the rectovaginal septum and the bladder (Cornillie et al., 1990). In recent years, the pathogenesis of this form of the disease has become debated. Indeed, whereas Sampson’s theory stating that endometriosis arises from menstrual endometrium regurgitated into the pelvis through the fallopian tubes during menstruation is widely accepted to explain the origin of non-deep peritoneal forms of the disease, the importance of retrograde menstruation in determining the development of deep endometriosis has been questioned recently. Specifically, it was proposed that at least some forms of deep endometriotic lesions should be considered as adenomyotic nodules whose histopathogenesis is related to the metaplasia of Müllerian remnants (Nisolle and Donnez, 1997). The most important argument to support this theory is that, on descriptive grounds, deep endometriosis strongly resembles adenomyosis. Indeed, this form of the disease is presented as a nodular lesion which is histologically characterized by dense tissue composed of fibrous and smooth muscle cells with islands or strands of glands and stroma. Thus, the major component of the nodular lesion is not endometrial tissue but fibromuscular tissue with sparse finger-like extensions of glandular and stromal tissue. This pathogenetic metaplastic model has been hypothesized to explain in particular the origin of deep nodules of the rectovaginal septum and of the bladder (Nisolle and Donnez, 1997). A similar mechanism cannot be excluded also for deep lesions localized in other sites of the pelvis as a high content of smooth muscle cells has been documented for all deep nodules regardless of their localization (Anaf et al., 2000b).

In this study, we have hypothesized that if deep endometriosis and the other forms of the disease do not share a common pathogenetic mechanism, they should not be signifi-
cantly associated. In other words, if a different and peculiar pathogenetic mechanism leading to deep nodules exists, the frequency of the presence of other forms of endometriosis in patients with deep endometriosis should be similar to that observed in the general population. Therefore, to gain insights into this debated topic, we have evaluated the frequency of non-deep forms of the disease such as superficial implants, endometriotic ovarian cysts and pelvic adhesions among patients affected by deep endometriosis.

Materials and methods

We have retrieved the clinical records of all women who were referred to the Department of Obstetrics and Gynecology, Clinica ‘L. Mangiagalli’ between January 1995 and June 2002 and who were diagnosed with deep peritoneal pelvic endometriosis at the time of surgery. Institutional review board approval was not requested because this was a retrospective study.

Deep endometriosis was defined as the presence of histologically confirmed peritoneal endometriosis infiltrating to a depth of at least 5 mm beneath the peritoneal surface (Cornillie et al., 1990). Description of surgery was always performed by one of five different surgeons (M.B., M.C., M.I., M.V. and E.S.) who have been actively engaged for a long time in endometriosis clinics and research. Information regarding clinical and surgical data was extracted from detailed patients’ charts. According to the protocol used in our Department, descriptions of the anatomical pelvic situation and surgical procedures are extremely detailed. Specifically, the following items always have to be described: abdominal situation, uterus, right ovary, right tube, left ovary, left tube, Douglas cul-de-sac, vesico-uterus cul-de-sac, other peritoneal locations, tube patency assessed by salpingo-cromo-scopy and other remarks. Moreover, in our unit, a sketch of the anatomical situation is systematically drawn. Cases were discarded if written and graphic description did not coincide and/or if an infective origin of adhesions was suspected. Adhesions were considered of endometriotic nature if not attributable to another cause. The diameter of deep endometriotic nodules was recorded at the time of histological examination or at the time of surgery when lesions could not be entirely surgically removed. Endometriotic cysts were always entirely or partially excised and sent for microscopic evaluation to confirm the diagnosis. Superficial endometriotic implants were excised and histologically evaluated only if there were doubts regarding the endometriotic nature of the lesions. Otherwise, they were electro-coagulated at the time of surgery.

Ninety-five patients were recruited. Two cases were discarded since the written and graphic descriptions were found to be discordant, leaving 93 patients for data analysis. The median (range) diameter of deep endometriotic nodules was 1.5 (0.5–4.0) cm. Eighteen (19.3%) patients were found to have more than one nodule. The mean ± SD (range) age of patients was 30.7 ± 4.8 (19–41) years. Pain symptoms were distributed as follows: 77.4% reported moderate to severe dysmenorrhea, 46.2% deep dyspareunia, 51.6% chronic pelvic pain and 7.5% painful defecation. Fourteen percent did not report relevant pain symptoms at all. A total of 64.5% reported more than one pain symptom. Other complaints included lower urinary tract symptoms (5.4%) and gastrointestinal symptoms (11.8%). Infertility, defined as failure to achieve a pregnancy within 12 months, was reported by 37.6% of women. The median (range) duration of infertility was 36 (12–120) months. A proportion of 15.1% women had previously delivered. Twenty-six patients had previously undergone pelvic surgery. For 21 of them, the main indication for prior intervention was endometriosis. The vast majority of patients were operated on using laparoscopic techniques. Laparotomy was required in 7.5% of cases. According to the ASRM classification (ASRM, 1997), 18.3% were stage I, 19.4% stage II, 38.7% stage III and 23.7% stage IV. Concomitant gynaecological pathological findings were observed in 13 cases; specifically, myomas were documented in seven cases, non-endometriotic ovarian cysts in three cases, uterine septum in two cases and endometrial polyps in one case.

A binomial probability distribution model was used to calculate the 95% confidence interval (95% CI) of the frequency of the presence of non-deep peritoneal forms of the disease (Pearson and Hartley, 1970).

Results

The association rates between deep endometriosis and other forms of the disease are shown in Table I. Deep peritoneal implants were the only observed form of the disease in only six women (6.5%). The localization of the lesions in these six women was as follows: rectovaginal septum (one case), Douglas cul-de-sac (two cases), uterosacral ligaments (two cases), and uterosacral ligament and bladder (one case). All of them reported at least two different pain symptoms. Since it might be hypothesized that inclusion of patients who previously had undergone pelvic surgery may influence the results, the analysis was repeated including only the 67 patients who had not been operated on in the past. This analysis led to similar results. Specifically, the presence of superficial peritoneal implants, endometriotic ovarian cysts and pelvic adhesions was observed in 65.7% (95% CI 54.3–77.1%), 53.7% (95% CI 41.8–65.6%) and 70.1% (95% CI 59.1–81.1%) of women, respectively. The presence of at least one of these forms of endometriosis was documented in 92.5% (95% CI 84.9–97.0%) of patients.

No relevant differences regarding the association between deep endometriosis and other forms of endometriosis were observed according to the location and the size of the nodules (Table II). Finally, data were also evaluated considering separately women who were found to have large nodules (diameter ≥2 cm) of the rectovaginal septum and/or of the bladder since these lesions may represent a distinct entity (Nisolle and Donnez, 1997). Twenty cases were identified: 11 cases had endometriosis of the rectovaginal septum, eight cases had deep bladder nodules and one case had both types of lesions. The overall presence of other forms of endometriosis in these women was 95.0% (95% CI 78.4–99.8%). Specifically, the presence of superficial peritoneal implants, endometriotic ovarian cysts and pelvic adhesions was observed in 45.0%
Discussion

In this study, we have documented a strong association between the presence of deep peritoneal endometriotic nodules and other forms of the disease in a large series of women with deep peritoneal endometriosis. Overall, superficial implants and/or endometriotic ovarian cysts and/or pelvic adhesions were observed in 93.5% of cases. In only a small minority of women (six out of 93; 6.5%) were deep peritoneal implants the only observed form of the disease. Considering that some authors have hypothesized a different pathogenetic origin in particular for deep large endometriotic nodules of the rectovaginal septum and/or of the bladder, we have repeated the analysis in this subgroup of patients (Nisolle and Donnez, 1997). High rates of association with other forms of the disease could also be observed in this specific group of women.

There are at least three major concerns regarding our study design. First, we did not include controls. In this regard, given both the aims of our study and the impossibility of adequately detecting the presence of endometriosis without a direct visualization of the pelvis, only a surgical control group would have been accepted. A population-based group is thus advisable but also unrealizable due to the ethical concerns related to the necessity of an invasive diagnosis (Zondervan et al., 2002). On the other hand, considering the strong association observed in this study, a pure matter of chance appears extremely unlikely. Indeed, it is currently estimated that there is a 10% prevalence of endometriosis in the general population (Eskenazi and Warner, 1997). This rate appears significantly lower when compared with the rates observed in our study (the 95% CI of the rate of association between deep endometriosis and other forms of endometriosis varied between 87.7 and 97.2%). A second concern with this study is related to its retrospective design. In this regard, it should be emphasized that a rigid and complete protocol for both clinical data recording and anatomical surgical description is system-atically followed in our Department. The availability of both a written and graphic description of the anatomical situation allowed us both to control the accuracy of data and to define precisely the localization of the lesions. It is of note that only two cases had to be discarded due to discrepancies between the written and graphic description. Therefore, we believe that, despite the retrospective design of our study, available data should be considered accurate, thus supporting the reliability of our observations. Finally, it has to be noted that the presence of an association, although highly suggestive, does not definitively demonstrate that deep endometriotic nodules should not be considered a different form of endometriosis. Indeed, it cannot be totally excluded that deep endometriosis and the other forms of the disease are two distinct entities that only share some common risk factors. In our opinion, this interpretation is unlikely, however, considering the extremely high degree of association observed.

Although the present study supports a common pathogenetic mechanism for the different forms of endometriosis, it does not clarify why, from a histological point of view, deep endometriotic nodules but not the other forms of the disease resemble adenomyosis. In this regard, it has to be noted that Anaf et al. (2000b), using immunochemical techniques with a monoclonal antibody against muscle-specific actin, recently have demonstrated that a smooth muscle component is in fact present in all types of endometriotic lesions. On the other hand, they failed to observe this component in disease-free peritoneum. These authors thus hypothesize that the smooth muscle component may result from the totipotential capacity of the pelvic and lower abdomen mesothelium to differentiate. In other words, the implanted endometrium may cause a metaplastic response in the underlying tissue. This metaplastic response might differ from one location to the other, thus explaining histological differences among the different forms of endometriosis. In light of these findings, the definition of distinct endometriotic entities based on the difference in the tissue composition of the lesions (endometriotic lesions versus adenomyotic nodules) appears inconsistent. Furthermore, in refutation of the metaplasia theory, patients with deep endometriosis of the rectovaginal septum have about a one-third reduction in the depth of the Douglas pouch, an observation that would not be expected if the lesions have an extraperitoneal origin (Vercellini et al., 2000). Finally, it also cannot be ruled out that the same disease may originate from several different pathogenetic mechanisms. In this context, it is interesting to note that Fedele et al. (1998) reported four cases of bladder endometriosis resulting from the extension of adenomyosis lesions of the anterior uterine wall to the bladder. However, albeit that this may be possible, this extremely particular pathogenetic mechanism cannot explain the large majority of cases of bladder endometriosis (Chapron et al., 2002).

In conclusion, results from the present investigation and from current available studies do not support the idea that deep endometriosis should be considered as external adenomyosis arising from metaplasia of Müllerian remnants.

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Table II. Frequency of other forms of endometriosis in 93 patients with deep peritoneal endometriosis according to location and dimension of the nodules

<table>
<thead>
<tr>
<th>Forms of the disease</th>
<th>Total no. of cases</th>
<th>n</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectovaginal septum</td>
<td>16</td>
<td>15</td>
<td>93.8</td>
<td>73.6–99.7%</td>
</tr>
<tr>
<td>Douglas cul-de-sac</td>
<td>17</td>
<td>15</td>
<td>88.2</td>
<td>67.4–97.9%</td>
</tr>
<tr>
<td>Uterosacral ligaments</td>
<td>46</td>
<td>43</td>
<td>93.5</td>
<td>84.0–98.2%</td>
</tr>
<tr>
<td>Bladder</td>
<td>16</td>
<td>15</td>
<td>93.8</td>
<td>73.6–99.7%</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
<td>12</td>
<td>100</td>
<td>87.9–100%</td>
</tr>
<tr>
<td>Diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 cm</td>
<td>44</td>
<td>40</td>
<td>90.9</td>
<td>80.4–96.8%</td>
</tr>
<tr>
<td>&gt;1 cm and ≤2 cm</td>
<td>31</td>
<td>30</td>
<td>96.8</td>
<td>85.6–99.8%</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>18</td>
<td>17</td>
<td>94.4</td>
<td>76.3–99.7%</td>
</tr>
</tbody>
</table>

*The total number of cases is >93 since 14 (15.1%) patients had deep nodules in more than one site.

*If more than one nodule was present in a single patient, the biggest one was used for the analysis.

(95% CI 25.9–65.3%), 30.0% (95% CI 14.0–50.8%) and 85.0% (95% CI 65.6–95.8%) of women, respectively. Results were similar when considering patients with bladder and rectovaginal nodules separately (data not shown).
References


Submitted on April 17, 2003; resubmitted on June 23, 2003; accepted on September 16, 2003