

The influence of peritoneal endometriotic lesions on the generation of endometriosis-related pain and pain reduction after surgical excision

Andrea Kaiser · Andreas Kopf · Christine Gericke ·
Julia Bartley · Sylvia Mechsner

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Abstract

Purpose To investigate the influence of different kinds of endometriotic lesions, especially peritoneal endometriotic implants in pain generation and the pain reduction after surgical excision in a prospective study.

Methods Fifty-one pre-menopausal patients underwent surgical laparoscopy due to chronic pelvic pain, dysmenorrhoea and/or for ovarian cysts. In 44 patients, endometriosis was diagnosed. The pre- and post-operative pain score was determined using a standardized questionnaire with a visual analogue scale. Patients with peritoneal endometriosis were divided into two different groups depending on their pre-operative pain score: group A had a pain score of 3 or more, while group B a pain score of 2 or less. Patients without peritoneal endometriosis were classified as group C, and patients without endometriosis were classified as group D. The pre- and post-operative pelvic pain and/or dysmenorrhoea was analysed according to the different types of endometriotic lesions.

Results In groups A and C, the post-operative pain score decreased by at least 2 grades or more ($p < 0.0$). In group D, the post-operative pain score showed no significant reduction.

Conclusion The present study suggests that the surgical excision of endometriotic lesions—including peritoneal implants—is an effective treatment of endometriosis-associated pelvic pain and/or dysmenorrhoea.

Keywords Endometriosis · Pelvic pain · Dysmenorrhoea · Pain transmission · Pathophysiology of endometriosis-related pain · Surgical excision

Introduction

Endometriosis is a chronic benign oestrogen-dependent gynaecological disease affecting millions of reproductive-age women worldwide [1]. It is associated with infertility and pelvic pain, although the severity of endometriosis-associated pelvic pain does not necessarily correlate closely with the disease stage or lesion site [2–7].

The pathophysiological basis of endometriosis-associated pelvic pain is as yet; however, not fully understood. The expression of pain-associated prostaglandins and other pain-mediating substances such as histamine, kinins and interleukins by peritoneal endometriotic implants may thus be involved in pain mediation [2]. Recently, pain-conducting substance-P-positive nerve fibres were found to be directly colocalized with human peritoneal endometriotic lesions [8, 9]. These data suggest that peritoneal endometriotic implants play an important role in the aetiology of endometriosis-associated pelvic pain [8, 9].

In order to investigate the clinical relevance of peritoneal endometriotic lesions in pain transmission, we conducted a prospective study in order to evaluate the influence of surgical excision of peritoneal implants on the pre and post-operative severity of symptoms such as pelvic pain and/or dysmenorrhoea in patients undergoing surgery for endometriosis.

A. Kaiser · J. Bartley · S. Mechsner (✉)
Department of Gynaecology, Endometriosis Research Centre
Charité, Charité, Campus Benjamin Franklin,
Hindenburgdamm 30, 12200 Berlin, Germany
e-mail: sylvia.mechsner@charite.de

A. Kopf
Department for Anaesthesiology and Intensive Care,
Charité, Campus Benjamin Franklin, Berlin, Germany

C. Gericke
Institute of Biometry and Clinical Epidemiology, Charité,
Campus Mitte, Charitéplatz 1, 10117 Berlin, Germany

Materials and methods

Patients

Between March and October 2006, 51 patients underwent diagnostic laparoscopy due to chronic pelvic pain, dysmenorrhoea and/or for ovarian cysts with the presumption of endometriosis. All women were pre-menopausal with a mean age of 35 (range 21–49). 36 women had regular menstrual cycles and had received no hormonal treatment for at least two months prior to surgery. Fifteen patients were on hormonal treatment at the time of surgery (combined oral contraceptives or progesterone-only pill). The respective phases of the cycle were defined as the date of the patient's last menstrual period.

In 44 patients (86.3%), endometriosis was diagnosed and classified by surgery according to the revised classification of the American Society of Reproductive Medicine [10] (rASRM I = 11; II = 6; III = 9; IV = 18). Of these 44 patients, 16 (36.4%) had peritoneal endometriosis only (in two cases without histological confirmation), 7 (15.9%) a peritoneal and ovarian endometriotic cyst, 7 (15.9%) a peritoneal and deep infiltrating endometriosis (DIE), 1 (2.3%) a peritoneal, ovarian and DIE, 6 (13.3%) had DIE, with obliteration of the pouch of Douglas and adhesions, 3 (6.8%) a ovarian endometriotic cyst without peritoneal implants, and 4 (9.1%) an ovarian and DIE without peritoneal implants.

In all patients, the visible peritoneal implants, endometriotic cysts and deep infiltrating nodules were excised in toto. Patients with DIE in the septum rectovaginal underwent a resection of the lesion as described previously [11]. In eight (18.2%) cases, it was necessary to remove part of the rectum because of bowel infiltration and in one case a disc dissection of the anterior rectum wall was performed.

In 29 of 44 patients (65.9%) peritoneal endometriotic lesions were confirmed by histology. In seven patients with no apparent endometriosis, a peritoneal biopsy was taken. These patients suffered from adhesions ($n = 3$), hydatid ($n = 1$) and uterine fibroids ($n = 3$).

Pain evaluation

Using a standardized questionnaire with a visual analogue scale (VAS), the severity of endometriosis-associated symptoms such as pelvic pain and dysmenorrhoea was documented prior to and 3 months after surgery. The pain scale was subdivided into 10 grades. "No pain" was indicated at the left side of the scale and "the maximum pain you could imagine" at the right side of the scale. Furthermore, the presence of pain when defecating and micturating and during intercourse (dyschezia, deep dyspareunia and dysuria) was documented by entering a simple "Yes" or "No" into the questionnaire.

Patients with histologically confirmed peritoneal endometriosis ($n = 29$) were divided into two groups (A and B) depending on their pre-operative pain score for dysmenorrhoea and/or pelvic pain (Fig. 1). Group A ($n = 23$) included all patients with peritoneal endometriotic lesions who coincidentally displayed additional manifestations of endometriosis (e.g. ovarian cysts or DIE). A1, a subgroup within group A, included patients with only peritoneal endometriotic lesions and no other manifestation of endometriosis (Fig. 1). Group A and A1 had a pre-operative pain score of 3 or more (median pre-operative pain score of 7). Group B ($n = 6$) had a pre-operative pain score of 2 or less (median pre-operative pain score of 0.5). As cut-off point, a pain score of 3 (VAS) was set as this marks the border between pain requiring therapy and pain not requiring therapy [12].

Patients without peritoneal endometriosis but with other forms of endometriosis (ovarian or DIE) were defined as group C ($n = 13$) with a median pre-operative pain score of 6. All patients without endometriosis were classified as group D ($n = 7$). They had a median pre-operative pain score of 7 (Fig. 1).

The pre and post-operative pain score was compared by calculating the median of pain scores for each group. We compared the pre and post-operative pain score after surgical excision.

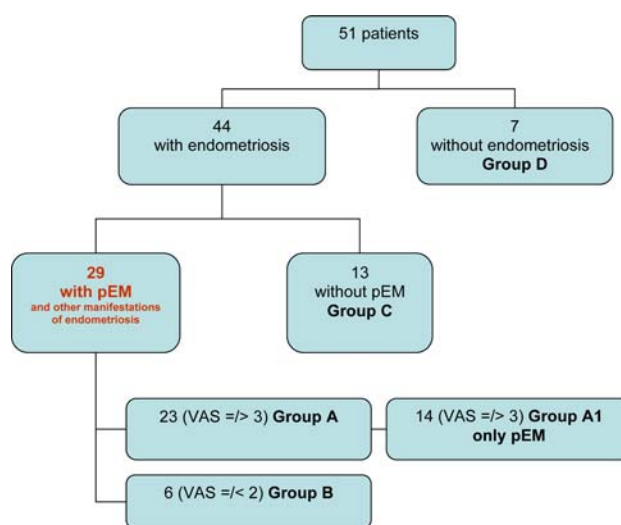


Fig. 1 Study population ($n = 51$): Patients with histologically confirmed peritoneal endometriosis (pEM) were divided into two different groups depending on their pre-operative pain score for dysmenorrhoea and/or pelvic pain: groups A, A1 and B. Group A ($n = 23$) consisted of patients with a peritoneal endometriotic lesion but who additionally displayed other manifestations of endometriosis. Group A1 is a sub population of group A having only peritoneal endometriotic lesions. Groups A and A1 had a pre-operative pain score of 3 or more. Group B ($n = 6$) had a pre-operative pain score of 2 or less. Patients with no peritoneal endometriosis but with other forms of endometriosis (ovarian or deep infiltrating endometriosis) were defined as group C ($n = 13$). All patients with no endometriosis were classified as group D ($n = 7$)

The study was approved by the Institutional Review Board (EA 4/023/05).

Statistical analysis

Statistical analysis was performed using the SPSS program statistical software (V15.0.1.1). All tests were two-sided and the level of significance was 0.05. Frequencies of occurrence were tested with the Fishers Exact Test. The paired Wilcoxon test was used for all comparisons between the pain scores (VAS).

Results

Analysis of the questionnaire

Analysis of the questionnaire showed that 43 of the 51 women (84.3%) had dysmenorrhoea and/or pelvic pain. Thirty-nine patients (76.5%) suffered from dysmenorrhoea and 27 patients (52.9%) suffered from pelvic pain. Thirty-two women (62.8%), i.e. the majority, described both dysmenorrhoea and pelvic pain. A total number of 36 patients (70.6%) suffered from dyspareunia, 28 (54.9%) women experienced dyschezia regularly, and 9 patients (17.65%) reported regular dysuria. Most of our patients ($n = 37$, 72.6%) suffered from dysmenorrhoea/pelvic pain and at least from one other additional symptom (dyspareunia, dyschezia, dysuria). A combination of dysmenorrhoea/pelvic pain and all of the other complaints was experienced by only 7 (13.7%) women (Fig. 2).

Comparison of the pre and post-operative pain score

Pelvic pain and/or dysmenorrhoea

Using the paired Wilcoxon test, significant differences in the pre and post-operative pain score were observed in groups A, A1 and C ($p < 0.05$) (Fig. 3).

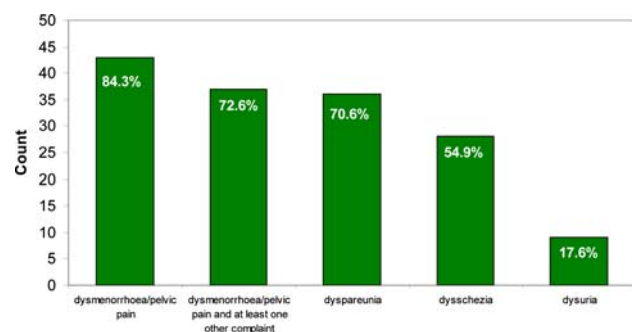


Fig. 2 Frequency of endometriosis-associated symptoms in 51 patients having dysmenorrhoea/pelvic pain and at least one other symptom, e.g. dyspareunia, dyschezia, or dysuria

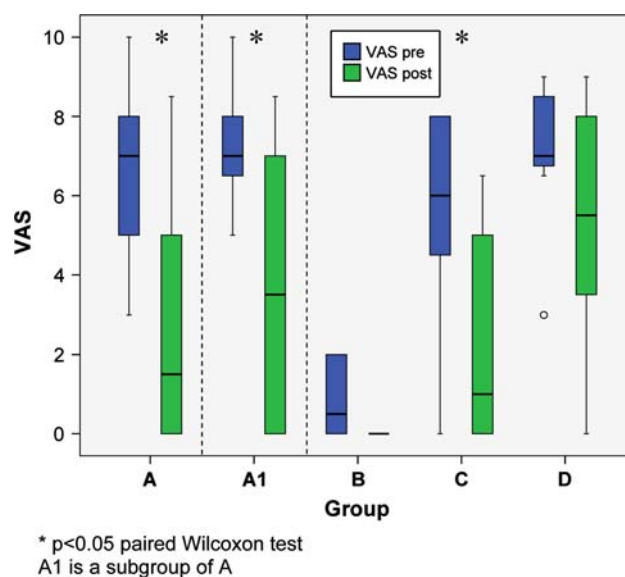


Fig. 3 The median pain score of dysmenorrhoea/pelvic pain of the different groups (A–D) before and after surgery. The correlation of the pre- versus post-operative pain score decreased significantly in group A, A1 and C (paired Wilcoxon test). The values are expressed as minimum, Q1, median, Q3 and maximum in the box plot

The median pre-operative pain score in group A was 7 (range 3–10). In 15 group A patients (65.2%), the post-operative pain score decreased by 2 grades or more, in half of them even down to zero. Six patients (26.1%) had no changes in their pain scores documented despite removal of all endometriotic lesions. The median post-operative pain score was 1.5 (range 0–8), which was significantly lower than that of the pre-operative pain ($p < 0.05$). In the sub population A1, the median pain score decreased from 7 down to 3.5 ($p < 0.05$). In group B, the median pre-operative pain score was 0.5 (range 0–2) and the post-operative pains score was reported to be zero in all patients of this group. The pre-operative pain score of group C was 6 (range 0–8) and the median post-operative pain score decreased to 1 (range 0–6.5) ($p < 0.05$). In group D, the median post-operative pain score was 5.5 and showed no significant difference in comparison to the median pre-operative pain score of 7 (Fig. 3).

Dyspareunia, dyschezia and dysuria

In groups A–C there was a reduction of other endometriosis-related symptoms such as dyspareunia, dyschezia and dysuria after laparoscopic excision of endometriotic lesions as described above. The difference was not significant via Fishers Exact Test. In group D (patients without endometriosis), no change of the intensity of these symptoms was observed (Table 1).

Table 1 Comparison of the pre and postoperative occurrence of symptoms

	Dyspareunia		Dyschezia		Dysuria	
	Pre	Post	Pre	Post	Pre	Post
All groups	36	27	28	14	9	5
A	17	12	14	6	5	2
B	1	1	2	0	0	0
C	11	7	9	5	2	2
D	7	7	3	3	2	1

No significant differences with using Fishers exact test

Frequency of dyspareunia, dyschezia and dysuria in different groups (A–D) before and after surgery. Groups A–C were tested versus group D (Fishers exact test)

Hormonal treatment

Fifteen patients developed symptoms during hormonal therapy. The distribution of patients on hormonal treatment was as follows: group A: 5 out of 23 (21.7%) (3 of these being in group A1); group B: 0 out of 6; group C: 6 out of 13 (46.2%); group D: 4 out of 7 (57.1%).

There were no significant differences regarding endometriosis-associated symptoms in regard to whether women were receiving hormonal treatment or not. The post-operative pain reduction was significant ($p = 0.05$) for both patient-groups with and without hormonal treatment, and was therefore a result of the surgical excision of the endometriotic lesions. Previous hormonal treatment did not influence pain reduction achieved by surgical excision of the lesion.

Discussion

Recently, many series of laparoscopic resection of endometriotic lesions have shown promising results in terms of the reduction of chronic pelvic pain and reduction of severe dysmenorrhoea [13]. However, the fundamental pathological mechanism underlying endometriosis-related pain seems to be unclear, particularly the role of peritoneal lesions in generating pelvic pain [14, 15].

Important data about nerval innervation of endometriosis, endometrium and myometrium have been published by different groups [8, 9, 16–20]. In this respect, the occurrence of nerve fibres in close topographical relationship to the peritoneal endometriotic lesion has been demonstrated [8, 9]. The peritoneal endometriotic lesions are able to produce several pain-mediating substances such as prostaglandins (PG) like PG E₂ and F_{2α}, histamine, kinins, NGF and interleukins, which can activate peritoneal nociceptors [2, 21–23]. However, there is no direct or indirect evidence

that peritoneal endometriosis-associated nerve fibres are involved in transmission of endometriosis-related pain.

In this prospective study, we analysed the portion of the peritoneal endometriotic lesion involved in pain generation of pelvic pain and/or dysmenorrhoea. In the present study, all patients undergoing surgery either for symptoms such as pelvic pain and/or dysmenorrhoea or the ultrasound diagnoses of ovarian cyst have been included. In order to investigate that part of peritoneal endometriotic lesion involved in pain generation, patients with peritoneal endometriotic lesions (group A), peritoneal endometriotic lesions only (group A1), and patients with other endometriotic lesions (group C) have been analysed separately. The control collective in our study underwent diagnostic laparoscopy for symptoms including pelvic pain, but no apparent endometriotic lesions were detected. However, these women suffered from fibroids and adhesions.

In order to study the clinical manifestation of symptoms in correlation with the different kinds of endometriotic lesions, we documented the severity of symptoms before surgical intervention using a questionnaire which revealed levels of endometriosis-related pain (VAS) and focused particularly on pelvic pain and dysmenorrhoea. Furthermore, the presence of dyschezia, dyspareunia and dysuria was documented (Fig. 2). The women completed the questionnaire a second time, three months after surgery.

Analysis of the questionnaire demonstrated the typical distribution of endometriosis-related pain in our study group [24]. A significant reduction of dysmenorrhoea and/or pelvic pain as expressed by VAS has been observed after laparoscopically excision in group A, A1 and C (Fig. 3). In the control-group D, there was only a slight trend towards pain reduction, without any significant change in post-operative symptoms.

Due to the complexity of the endometriosis-related symptoms, the combined occurrence of the complaints (such as dysmenorrhoea, pelvic pain, deep dyspareunia, dyschezia and dysuria) and the coincidence of different manifestation forms (endometriosis genitalis externa, adenomyosis uteri and DIE), it is very difficult to investigate one single parameter of pain transmission. Subgroup A1 had peritoneal endometriotic lesions only. Due to this, it was only pain-dependent transmission from peritoneal endometriotic lesions which could be analysed.

In group C (patients with endometriosis, but without peritoneal endometriotic lesions) we also detected a significant reduction of the post-operative pain score. This finding confirms the current knowledge that the complete excision of endometriotic lesions leads to significant improvement of endometriosis-related symptoms and quality of life [13].

Fifteen patients (5 in group A, 6 in group C and 4 in group D) under hormonal treatment, suffering from endometriosis-related symptoms were included consecutively in

this study. The patients were included depending on their symptom profile, independently of current hormonal treatment. The postoperative effect was investigated independently of previous hormone administration. Probably the patients using hormones had a higher intensity of pain before hormonal therapy and this therapy may have reduced the baseline intensity of pain symptoms thus biasing the evaluation of the potential benefit of surgery. We have, however, shown that both patients with and without hormone therapy benefit from surgery equally.

However, the pathomechanisms for the other manifestation forms still remain unclear. In DIE cases only, could it be demonstrated that perineural invasion by endometriosis was associated with hyperalgesia [18].

One possible weak point of the study is the small number of patients in the subgroups but we have already planned to extend such a study in the future.

In summary, this data confirms the evidence that endometriotic lesions correlate clinically with pain generation. It also demonstrates that the surgical excision of such lesions should be recommended as an effective treatment of endometriosis-related symptoms such as pelvic pain and/or dysmenorrhoea.

Conflict of interest statement None.

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