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Pelvic peritoneal endometriosis is linked to the endometrial inflammatory profile: a prospective cohort study

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Abstract

Background Pelvic endometriosis is an estrogen-driven inflammatory syndrome of unknown origin that alters the peritoneal microenvironment and likely impairs endometrial receptivity, adversely affecting fertility. Chronic endometritis (CE) may be a potential contributing factor to reduced endometrial receptivity in endometriosis. The aim of the study was to analyze the correlation between pelvic endometriosis and CE.

Methods The study included women undergoing laparoscopy for suspected pelvic endometriosis, and each underwent endometrial aspiration biopsy for CE. The stage of endometriosis was assessed intraoperatively, and CE activity was evaluated histopathologically and immunohistochemically. The associations between selected clinical characteristics of the disease and the density of endometrial plasma cells, immunohistochemical status, and histopathological profile of the endometrium were analyzed.

Results Stage III endometriosis reduced the risk of the inflammatory immunohistochemical profile by 80% (OR = 0.18, $p = 0.037$) when compared to Stage I. Peritoneal endometriosis was associated with a 3.429-fold increase in the risk of the immunohistochemical endometrial inflammatory profile (OR = 3.429, $p = 0.038$). No significant associations were found between the clinical features of the disease and plasma cell density or the histopathological profile of the endometrium (all p values > 0.05). No significant differences were observed in IVF use ($p = 0.67$), pregnancy rates ($p = 1$), or live birth rates ($p = 0.41$) between infertile women with and without CE.

Conclusions Should peritoneal endometriosis be diagnosed during a laparoscopy conducted for the treatment of infertility, it is advisable to obtain an endometrial biopsy for CE evaluation, as this may enhance the efficacy of the therapeutic approach. The hypothetical link between pelvic endometriosis-related inflammation, its clinical manifestations, and CE requires further investigation. The lack of a noninvasive marker for endometriosis and its grade limits the study results due to reliance on surgical cases, highlighting the need for advanced research in the field of noninvasive diagnostic tools.

Trial registration NCT05824507 (registered April 20, 2023).

Keywords Pelvic endometriosis, Idiopathic infertility, Chronic endometritis, Obstetric outcomes

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Background

Pelvic endometriosis is acknowledged as a complex estrogen-responsive inflammatory disorder, distinguished by extrauterine growth of endometrial-like tissue [1]. This condition, characterized by chronic lower abdominal pain in diverse manifestations and decreased fertility, significantly contributes to the deterioration of the quality of life of affected women [2]. The etiology of endometriosis remains largely unknown, though factors such as genetic predisposition, immune system dysregulation, retrograde menstruation, and environmental factors have been proposed [3–5]. The failure to identify the etiological factor leads to an inability to develop effective treatment, which is currently limited to symptomatic management. Several factors have been identified through which endometriosis adversely influences the obstetric outcomes in suffering women compared to those in the general population. These factors include the disruption of the anatomical relationships of the pelvic organs attributable to the presence of peritoneal adhesions, hormonal imbalances that impede ovulation, diminished ovarian reserve, dysfunction of the local immune response, and compromised transport of reproductive cells resulting from localized inflammation [6, 7]. It has been investigated that the peritoneal microenvironment in endometriosis undergoes pro-inflammatory changes that negatively impact a range of physiological processes, particularly those associated with fertilization and implantation [8]. Certain studies have indicated that the disruption of inflammatory balance is not confined to the peritoneal cavity but also extends to the uterine cavity, potentially interfering with the processes related to embryo implantation [9]. Chronic endometritis (CE) is a condition that may potentially compromise endometrial receptivity in the course of endometriosis [10, 11]. It is associated with symptoms such as abnormal uterine bleeding and infertility [12]. Given that both pelvic endometriosis and CE impact reproductive outcomes, understanding their correlation could significantly enhance our insight into the reproductive challenges experienced by women with endometriosis and facilitate the formulation of more targeted treatment strategies. It was thus determined to verify the hypothesis that a relationship existed between pelvic endometriosis and CE. The objective of the study was to investigate the relationship between pelvic endometriosis and CE, thereby elucidating the potential interactions between these conditions and their impact on obstetric outcomes.

Methods

The prospective cohort study comprised women undergoing laparoscopy for abdominal pain or infertility associated with pelvic endometriosis. The investigation was conducted at the Clinical Department of Gynecological Endocrinology and Gynecology at the University Hospital in Krakow between June 2021 and June 2022, having received prior approval from the Bioethics Committee of Jagiellonian University (no. 1072.6120.76.2021). The study was registered in the online database ClinicalTrials.gov under the reference number NCT05824507 (registered April 20, 2023). All participants provided their written informed consent to participate in the research and to publish the results containing their anonymized data. The study was conducted in accordance with the Declaration of Helsinki. The dataset collected during the study has been made publicly accessible in the Harvard Dataverse Repository at https://doi.org/https://doi.org/10.7910/DVN/IRIEUQ [13]. Women qualified for surgical treatment due to the failure of conservative management of pelvic pain associated with endometriosis, the presence of a significantly sized endometriotic cyst exceeding 4 cm in diameter that posed a risk of adnexal torsion, or idiopathic infertility accompanied by symptoms suggestive of potential coexisting intraperitoneal endometriosis [14]. The inclusion criterion used was an age range of 18 to 45 years. The exclusion criteria were as follows: i) abdominal surgeries performed within the six months prior to hospitalization, ii) history of surgical treatment for reproductive organ pathology iii) developmental defects of the reproductive organs, iv) treatment with antibiotics or probiotics within the preceding six months, and v) active infections of the genital tract. Women enrolled in the study underwent a routine gynecological evaluation, which included a comprehensive collection of medical history and verification of cervical cytology results, a physical examination, and specifically, a vaginal speculum examination, a bimanual examination, and an ultrasound assessment of the reproductive organs. Pelvic and abdominal ultrasound examinations were conducted using a Samsung WS80A with Elite device (Samsung Electronics, Suwon, South Korea), employing both a transvaginal volume transducer (EV2-10A) and a transabdominal volume transducer (V4-8). The painful conditions that necessitated surgical intervention included primary or secondary dysmenorrhea unresponsive to conservative treatment, chronic pelvic pain unrelated to the menstrual cycle phase, as well as lower abdominal pain accompanied by symptoms suggestive of gastrointestinal disorders [15]. Dysmenorrhea was diagnosed when the intensity of menstrual pain exceeded a threshold of 5 on a 10-point Numeric Rating Scale [16]. Idiopathic infertility was diagnosed when no abnormalities were identified concerning ovulation, ovarian reserve, tubal patency, uterine cavity, and semen analysis [17]. A prerequisite for proceeding with the surgical intervention was the presentation of a normal cervical

cytology result. The only additional procedure performed for scientific purposes was the endometrial aspiration biopsy, which was conducted concurrently with the surgical intervention. Endometrial tissue was aspirated in a volume of 2 ml using negative pressure generated by a catheter connected to a syringe specifically designed for endometrial aspiration biopsy (BiopsGyn, Amed, Poland). The collected endometrial sample was sent for histopathological and immunohistochemical examination for CE. The laparoscopic interventions were conducted using a Karl Storz laparoscope (Karl Storz, Tuttlingen, Germany) fitted with optics that provided a 30-degree viewing angle. The objective of surgical intervention for pain-related indications was the excision of endometriotic lesions. In instances of infertility, the aim was to conduct a thorough inspection of the abdominal cavity for foci of endometriosis, to excise these lesions and to restore the proper anatomical relations of the pelvic organs through the removal of peritoneal adhesions. The procedure was completed by determining the stage of the disease and was followed by subsequent counseling aimed at achieving pregnancy. The stage of endometriosis was determined according to revised American Society for Reproductive Medicine classification [18].

The excised lesions were subsequently subjected to histopathological examination to confirm the diagnosis. Tissue specimens collected during the procedures were immediately preserved in 10% neutrally buffered formalin and then sent for histopathological analysis, where they were subjected to additional processing and preservation in liquid paraffin. Tissue specimens from endometrial aspiration biopsies, as well as small samples suspected of endometriosis, were submitted in their entirety for histological examination. In contrast, larger endometriotic lesions were evaluated macroscopically by a pathologist, who subsequently selected representative sections for detailed analysis. The formalin-fixed paraffin-embedded tissue sections were stained with hematoxylin and eosin for diagnostic evaluation. The diagnosis of endometriosis was confirmed when both endometrial glands and stroma were identified in samples collected from locations outside the uterine cavity. The diagnosis of CE was determined through histopathological and immunohistochemical evaluations. The diagnosis of CE in histopathology was established through the identification of a significant inflammatory infiltrate, primarily composed of lymphocytes, plasma cells and macrophages, along with associated changes in the endometrial stroma and glands. The CD138/syndecan-1 (B-A38) mouse monoclonal antibody (Cell Marque-Sigma Aldrich, Merck KGaA, Darmstadt, Germany), a specific marker for the selective identification of plasma cells, was utilized for immunostaining. Three-micrometer paraffin sections were cut and stained utilizing standardized automated techniques including on-instrument deparaffinization, antigen retrieval, peroxidase blocking, incubation with primary and secondary antibodies, detection, and counterstaining with hematoxylin. The following assay was performed with an ultraView DAB Detection Kit (Ventana Medical Systems, Inc., Tucson, Arizona, USA) using the validated Roche protocol (deparaffinization in 72℃, conditioning in Ventana ULTRA CC1 Solution for 36 min in 95 ℃, Cell Marque CD138 clone B-A38 incubation for 28 min, counterstaining with Roche Hematoxylin II for 32 min and Bluing Reagent for 4 min) for the Benchmark Ultra slide staining system (F. Hoffmann-La Roche Ltd, Basel, Switzerland). The diagnosis of CE by immunochemistry was made by identifying at least one plasma cell in a single high-power field [19]. The pathologist was not aware of the detailed clinical data of the study participants or its assumptions. In order to achieve the objectives of the study, demographic data, data on the course of surgical treatment, data on the characteristics of the disease and data from pathology reports were collected. Women diagnosed with CE were administered empirical antibiotic therapy, consisting of oral ofloxacin at a daily dose of 400 mg for 10 days, in addition to vaginal metronidazole at a daily dosage of 500 mg for 10 days. The eligible women were followed for 24 months following surgery to collect obstetric data.

Statistical analysis

The analysis of quantitative variables was performed by calculating descriptive statistics such as mean, standard deviation, median, quartiles, and minimum and maximum values. The analysis of qualitative variables involved calculating absolute and percentage frequencies of all possible values that these variables could assume. Correlations between quantitative variables were analyzed using Spearman's correlation coefficient. The comparison of quantitative variable values between two groups was conducted using the Mann–Whitney U test. For comparisons of quantitative variables across three or more groups, the Kruskal–Wallis test was employed, followed by Dunn's post-hoc test in the presence of statistically significant differences among groups. A univariate analysis of the impact of potential predictors on a dichotomous variable was conducted using logistic regression. The results were presented as odds ratios (OR) along with 95% confidence intervals. A significance level of 0.05 was adopted for the analysis, thus all p-values below 0.05 were interpreted as indicative of significant associations. The analysis was conducted using R software, version 4.4.1 [20]. Assuming an estimated fraction size of 50%, a significance level of 0.05, a total population size

of 74 individuals, and an acceptable error margin of 5%, the estimated minimum sample size obtained was 63 individuals.

Results

The recruitment process for the study was presented in the flow diagram (Fig. 1). The study included 64 women undergoing laparoscopy due to suspected endometriosis in the course of pelvic pain syndrome and/or infertility, among whom 24 were assessed for infertility and 40 were treated for pelvic pain. The characteristics of the studied population concerning selected variables obtained from medical interviews, the protocols of the laparoscopic procedures, and the histopathological and immunohistochemical reports were presented in Table 1.

The associations between the individual clinical characteristics of the disease and plasma cell density were presented in Table 2. No significant associations were found between the studied characteristics of the disease and plasma cell density in the endometrium (all

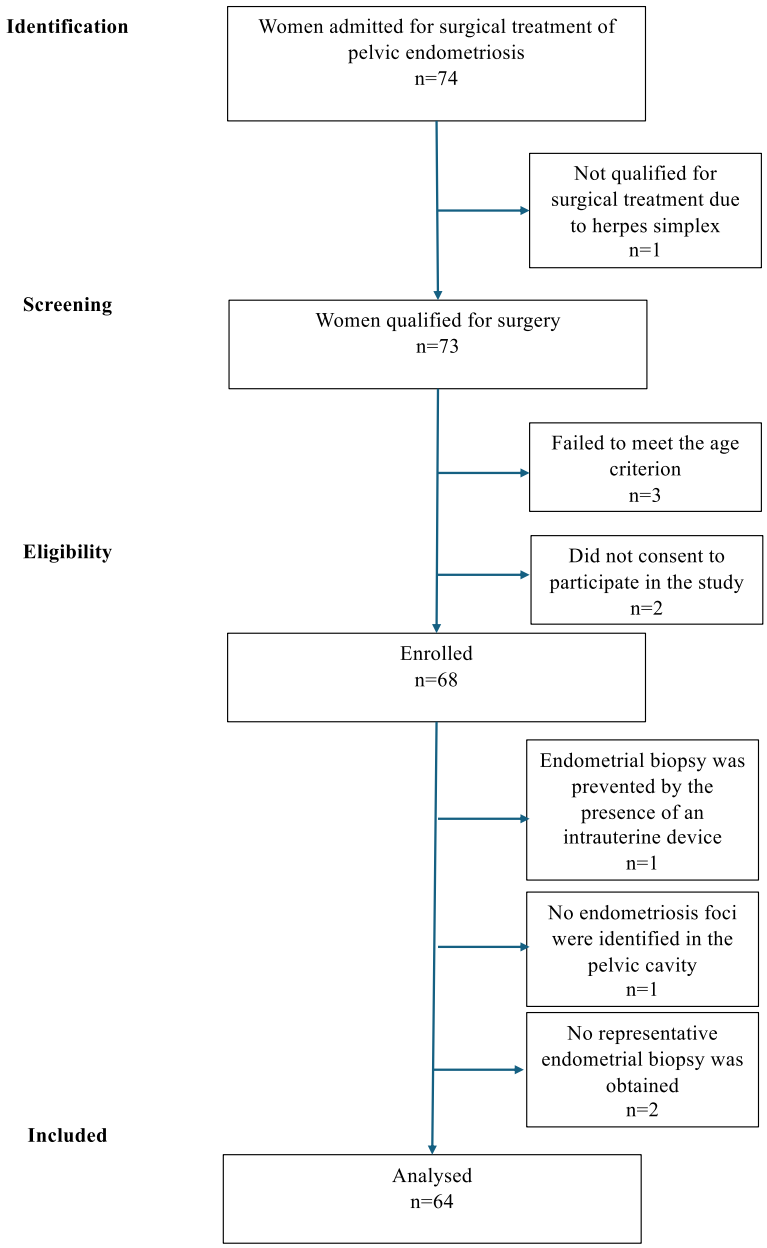

Fig. 1 Flow diagram illustrating the participant recruitment process for the study

Table 1 The characteristics of the population in terms of data from medical history, intraperitoneal lesions, interventions performed, grade and histopathological features of the disease

Parameter		Total ($N=64$)
Medical interview data		
Age [years]	Mean (SD)	33.09 (5.78)
	Median (quartiles)	33 (28–38)
	Range	22–45
	n	64
Infertility	No	40 (62.50%)
	Primary	18 (28.12%)
	Secondary	6 (9.38%)
Pelvic Pain Syndrome	No	26 (40.62%)
	Yes	38 (59.38%)
Dysmenorrhea	No	20 (31.25%)
	Yes	44 (68.75%)
Abnormal uterine bleeding	No	50 (78.12%)
	Yes	14 (21.88%)
Pregnancies	Mean (SD)	0.62 (1.06)
	Median (quartiles)	0 (0–1)
	Range	0–5
	n	64
Deliveries	Mean (SD)	0.55 (0.85)
	Median (quartiles)	0 (0–1)
	Range	0–3
	n	64
Disease-related lesions		
Right ovary endometrioma [mm]	Mean (SD)	23.2 (27.49)
	Median (quartiles)	10 (0–42.5)
	Range	0–80
	n	64
Left ovary endometrioma [mm]	Mean (SD)	24.7 (24.97)
	Median (quartiles)	20 (0–50)
	Range	0–80
	n	64
Peritoneal endometriosis	No	25 (39.06%)
	Yes	39 (60.94%)
Endometrioma	No	14 (21.88%)
	Yes	50 (78.12%)
Surgical intervention		
Excision	No	22 (34.38%)
	Yes	42 (65.62%)
Fenestration	No	52 (81.25%)
	Yes	12 (18.75%)
Coagulation	No	46 (71.88%)
	Yes	18 (28.12%)
Adhesions	No	16 (25.00%)
	Yes	48 (75.00%)
Disease characteristics		
Grade	I	8 (12.50%)
	II	3 (4.69%)
	III	39 (60.94%)
	IV	14 (21.88%)
Plasmocytes	Mean (SD)	5.31 (13.57)
	Median (quartiles)	1 (0–4.25)
	Range	0–95
	n	64
Immunostaining	Negative	41 (64.06%)
	Positive	23 (35.94%)
Histopathology	Negative	48 (75.00%)
	Positive	16 (25.00%)

p-values were above 0.05). Additionally, no significant correlations were found between ovarian endometrioma diameter and the density of endometrial plasma cells (for the right ovary, $r=-0.161$, $p=0.204$; for the left ovary, $r=-0.109$, $p=0.391$).

The relationships between specific qualitative clinical features of the disease and the immunohistochemical status of the endometrium were presented in Table 3. Logistic regression models, conducted separately for each of the examined variables, indicated that grade III reduced the risk of an inflammatory immunohistochemical profile by 82.0% (OR = 0.18, $p=0.037$) in comparison to grade I. Peritoneal endometriosis increased the risk of an inflammatory immunohistochemical profile 3.429 times (OR = 3.429, $p=0.038$).

The relationships between specific qualitative clinical characteristics of the disease and the histopathological profile of the endometrium were presented in Table 4. Logistic regression analyses, conducted individually for each of the variables under consideration, revealed that none of the examined characteristics served as significant predictors of the probability of an inflammatory histopathological profile (all p-values were above 0.05).

In a subpopulation of infertile women ($n=24$, 24/64, 37.5%), 15 individuals (15/24, 62.5%) were found to have CE. Among the infertile women, 7 (7/24, 29.17%) attempted to conceive through in vitro fertilization (IVF), 10 (10/24, 41.67%) achieved pregnancy, and 8 (8/24, 33.33%) attained live birth within 24 months following the surgical intervention. No significant differences were found between infertile women with CE and those without CE with regard to the use of IVF (5/15, 33.3% vs. 2/9, 22.2%, $p=0.67$), the percentage of pregnancies achieved (6/15, 40.0% vs. 4/9, 44.4%, $p=1$), or the rates of live births (4/15, 26.67% vs. 4/9, 44.44%, $p=0.41$).

Table 2 Evaluation of the relationships between specific qualitative clinical characteristics of the disease and plasma cell density

Parameter	Trait	Plasmocytes [n/HPF]							*p*
		Mean	SD	Median	Min	Max	Q1	Q3	
Grade	I (*N* = 8)	6.00	6.50	5.0	0	20	1.0	7.50	*p* = 0.079
	II (*N* = 3)	2.00	2.65	1.0	0	5	0.5	3.00	
	III (*N* = 39)	4.59	15.74	0.0	0	95	0.0	2.00	
	IV (*N* = 14)	7.64	11.61	3.0	0	40	0.0	7.75	
Endometrioma	No (*N* = 14)	4.14	5.40	2.0	0	20	1.0	5.75	*p* = 0.165
	Yes (*N* = 50)	5.64	15.12	1.0	0	95	0.0	4.00	
Peritoneal endometriosis	No (*N* = 25)	1.88	3.88	1.0	0	18	0.0	1.00	*p* = 0.1
	Yes (*N* = 39)	7.51	16.83	1.0	0	95	0.0	6.50	
Infertility	No (*N* = 40)	5.15	15.55	1.0	0	95	0.0	4.00	*p* = 0.455
	Primary (*N* = 18)	6.78	10.87	1.5	0	40	0.0	5.75	
	Secondary (*N* = 6)	2.00	3.52	0.5	0	9	0.0	1.75	
Pelvic Pain Syndrome	No (*N* = 26)	6.62	18.74	1.0	0	95	0.0	5.00	*p* = 0.994
	Yes (*N* = 38)	4.42	8.62	1.0	0	40	0.0	3.75	
Dysmenorrhea	No (*N* = 20)	7.10	20.91	1.0	0	95	0.0	5.25	*p* = 0.768
	Yes (*N* = 44)	4.50	8.64	1.0	0	40	0.0	4.00	
Abnormal uterine bleeding	No (*N* = 50)	4.94	14.19	1.0	0	95	0.0	4.00	*p* = 0.477
	Yes (*N* = 14)	6.64	11.45	1.0	0	40	0.0	7.25	

2 groups comparison: p—Mann–Whitney test; grade > 2 groups comparison: Kruskal–Wallis test + post-hoc analysis (Dunn test)

Table 3 Evaluation of the relationships between specific qualitative clinical characteristics of the disease and the immunohistochemical status of the endometrium

Trait		N	Immunostaining +	OR	95%CI		p
Grade	I	8	5	1	ref		
	II	3	1	0.3	0.018	4.908	0.398
	III	39	9	0.18	0.036	0.904	0.037 *
	IV	14	8	0.8	0.135	4.745	0.806
Endometrioma	No	14	7	1	ref		
	Yes	50	16	0.471	0.141	1.569	0.22
Right ovary lesion [mm]		-	-	0.988	0.968	1.008	0.224
Left ovary lesion [mm]		-	-	0.995	0.975	1.016	0.65
Peritoneal endometriosis	No	25	5	1	ref		
	Yes	39	18	3.429	1.07	10.989	0.038 *
Infertility	No	40	13	1	ref		
	Primary	18	9	2.077	0.667	6.471	0.207
	Secondary	6	1	0.415	0.044	3.928	0.443
Pelvic Pain Syndrome	No	26	10	1	ref		
	Yes	38	13	0.832	0.295	2.345	0.728
Dysmenorrhea	No	20	8	1	ref		
	Yes	44	15	0.776	0.261	2.308	0.648
Abnormal uterine bleeding	No	50	18	1	ref		
	Yes	14	5	0.988	0.287	3.401	0.984

p-univariate logistic regressions

* statistically significant ($p < 0.05$)

Table 4 Evaluation of the relationships between specific qualitative clinical characteristics of the disease and the histopathological profile of the endometrium

Trait		N	Histopathology +	OR	95%CI		*p*
Grade	I	8	3	1	ref		
	II	3	1	0.833	0.051	13.633	0.898
	III	39	8	0.43	0.084	2.193	0.31
	IV	14	4	0.667	0.106	4.206	0.666
Endometrioma	No	14	4	1	ref		
	Yes	50	12	0.789	0.209	2.981	0.727
Right ovary lesion [mm]		-	-	0.993	0.972	1.015	0.553
Left ovary lesion [mm]		-	-	0.993	0.97	1.017	0.559
Peritoneal endometriosis	No	25	5	1	ref		
	Yes	39	11	1.571	0.472	5.232	0.461
Infertility	No	40	9	1	ref		
	Primary	18	5	1.325	0.372	4.72	0.664
	Secondary	6	2	1.722	0.27	10.981	0.565
Pelvic Pain Syndrome	No	26	9	1	ref		
	Yes	38	7	0.427	0.135	1.349	0.147
Dysmenorrhea	No	20	7	1	ref		
	Yes	44	9	0.478	0.147	1.547	0.218
Abnormal uterine bleeding	No	50	11	1	ref		
	Yes	14	5	1.97	0.547	7.097	0.3

P-univariate logistic regressions

Discussion

The negative impact of endometriosis on fertility is widely recognized; however the biological mechanism underlying this interaction, particularly with respect to whether and how it modulates the microenvironment of the uterine cavity, has yet to be elucidated. Likewise, the role of CE in the diagnostic process and therapeutic approaches to infertility remains to be determined. These uncertainties has prompted further research into the impact of these two conditions on reproductive health, aiming to improve our mechanistic insights and clinical understanding. Recent studies investigating the inflammatory, immunological, and infectious factors related to endometriosis have highlighted common features with CE, indicating that the prevalence of CE among women with endometriosis ranged from 3 to 53%, depending on the diagnostic criteria and detection methods employed [21]. Importantly, the overall prevalence of CE has been reported to be significantly higher in women with endometriosis at 29.41% compared to 5.4% in those without the condition [22], while a study utilizing Pipelle endometrial sampling for tissue collection – similar to the approach used in this study – found the prevalence to be 13% [23]. Based on findings from prior studies indicating a potential correlation between endometriosis and CE [10, 22], an investigation was conducted to explore the relationship between the stage and specific clinical manifestations of pelvic endometriosis and the activity of CE. Identifying such a relationship could contribute not only to a better understanding of the etiology of symptoms associated with endometriosis but also facilitate the development of appropriate strategies for managing the accompanying disorders. As for the relationship between the intensity of CE and the stage of endometriosis, our study did not demonstrate such a correlation, which aligned with previous research findings [22, 24].

Considering the unexplained etiopathogenesis of the disease and the variety of theories surrounding its development, this result can be interpreted by acknowledging that the mechanisms underlying individual manifestations of the disease may differ [25]. The results of our study indicated that peritoneal endometriosis was associated with an over threefold increase in the risk of an inflammatory endometrial profile, as determined by immunohistochemical analysis. A potential explanation for this phenomenon may lie in the recently proposed hypothesis regarding the impact of bacterial contamination on the development of endometriosis [26]. According to its authors, fibronectin and laminin induced by bacterial lipopolysaccharide may support the adhesion of endometrial cells – shed during menstruation and retrogradely translocated to the peritoneal cavity – to the peritoneal mesothelium after binding to their respective receptors. Furthermore, the previously described

significantly higher macrophage infiltration of eutopic and ectopic endometrium in women with stage I and II endometriosis than in women with stage III and IV would support this hypothesis [27]. The observations made in the cited study [27] led to the conclusion that early and active red endometriotic lesions and the adjacent peritoneum are abundantly infiltrated by clusters of macrophages, which may contribute to disease progression, which was not observed in scarred, black or inactive, fibrous, whitish lesions [28]. Considering the clinical aspect of this phenomenon, the introduction of broad-spectrum antibiotic therapy [24] at this stage could stop the fueling of inflammation and theoretically the progression of endometriosis, leading to the resolution or prevention of disease symptoms. It should be noted that in clinical practice, identifying this moment could pose a considerable challenge, which is why a thorough examination and a carefully collected medical history are so important. Moreover, this hypothesis obviously requires verification not only in future research, but also in clinical practice.

The literature has indicated that the pathogenesis of deep endometriosis might differ, involving retrograde uterine bleeding in newborns followed by the invasion of implanted epithelial progenitor cells, or through genetic or epigenetic modifications of ectopic endometrial cells resembling the formation of benign tumors [25]. Indeed, grade III decreased the risk of an endometrial inflammatory profile as assessed by immunohistochemistry by 82% when compared to grade I. Taking into account this observation and the results of previous studies referenced above, it appears that endometrial biopsy with the intention of treating CE with antibiotics to improve disease symptom control or obstetric outcomes in more advanced stages of endometriosis is inappropriate.

The lack of a requirement for visual confirmation of endometriosis through laparoscopy or histopathological examination prior to symptomatic treatment significantly impairs the differentiation between individual presentations of the disease and its grades. Additionally, no clinically useful biological marker specific to any manifestation or grade of the disease has been identified. The absence of specific biomarkers poses a significant challenge in the diagnostics of endometriosis, highlighting the need for non-invasive diagnostic tools. One potential approach is the analysis of the intestinal microbiota, where an endometriotic phenotype has been characterized by an increase in the genera Prevotella, Blautia, and Bifidobacterium, alongside a decrease in Paraprevotella, Ruminococcus, and Lachnospira [29]. Recent studies have also proposed extracellular vesicles (EVs) as promising candidates for this purpose. EVs, carrying disease-specific molecular cargo, are abundant in various body fluids and have been isolated from multiple sources in patients with endometriosis, including blood, peritoneal fluid, and the uterine cavity. Notably, variations in EVs expression levels have been observed in women with endometriosis compared to those without, including individuals with submucosal fibroids or other benign non-endometrial lesions [30]. Moreover, micro ribonucleic acids (miRNAs) analyzed in specimens obtained through endometrial sampling may serve as indirect indicators of the cellular microenvironment contributing to the development of endometriotic implants. This approach holds the potential to detect endometriosis at a molecular level, enabling interception before macroscopic lesions become identifiable through ultrasound imaging [31].

It is important to note that certain prospective studies have not demonstrated statistically significant differences in the prevalence of CE between women with and without endometriosis, nor across different stages of endometriosis [24]. When analyzing scientific data, it is essential to recognize that studies on the relationship between endometriosis and CE often focus solely on women with advanced-stage IV endometriosis [10], or unconfirmed suspected cases, frequently failing to differentiate between stages [21]. Moreover, these studies are hindered by small sample sizes [10, 22, 24, 32], variable cut-off points for plasma cell density defining CE [21], lack of causal assessments [10], and ultimately inconsistent conclusions. Likewise, our study is constrained by a small sample size and an uneven distribution of women with varying stages of endometriosis, potentially affecting the statistical power of certain calculations. The small sample size, particularly in stages I and II, can be attributed to the practice of avoiding unnecessary surgeries for managing disease symptoms, such as pain and infertility, which can often be treated conservatively or through assisted reproductive techniques. Furthermore, histopathological confirmation of the disease is not required prior to the commencement of treatment, further reducing the recruitment pool. The exclusive analysis of surgical cases may have introduced selection bias, potentially limiting the generalizability of the findings to the broader population of women with endometriosis, including those diagnosed through non-surgical methods. Our study did not include an analysis of molecular or genetic factors that could have provided deeper insights into the potential link between the inflammatory processes in CE and pelvic endometriosis. The strengths of our study include the confirmation of endometriosis stage through laparoscopic evaluation for each participant, and the inclusion of women with mild disease, which enriches the diversity and applicability of our findings. By identifying a significant association between peritoneal endometriosis and

an inflammatory immunohistochemical endometrial profile, the study highlights a specific subset of individuals with endometriosis who may benefit from targeted diagnostic and therapeutic interventions. Our study contributes to ongoing efforts to identify noninvasive diagnostic tools that may not only assist in the diagnostics and treatment of infertility associated with endometriosis but also facilitate the identification of specific manifestations of the disease. Subsequent research pursuits should involve investigations into the biological mechanisms linking both chronic inflammatory conditions and the molecular mechanisms of the disease, leading to the identification of a biological marker facilitating noninvasive diagnosis.

Conclusions

If peritoneal endometriosis is diagnosed during a laparoscopy conducted for the treatment of infertility, it is recommended to obtain an endometrial sample for CE evaluation, as this may increase the effectiveness of the therapeutic intervention.

The unconfirmed association between pelvic endometriosis and CE does not justify routine endometrial diagnostics in search of the cause of decreased fertility in women with endometriosis.

The hypothetical relationship between the two inflammatory conditions studied, pelvic peritoneal endometriosis and CE, requires further investigation.

Abbreviations

CE Chronic endometritis
OR Odds ratio

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Authors' contributions

I.G. designed the study concept and protocol, performed the surgical procedures, collected and analyzed clinical data, and was a major contributor in writing and editing the manuscript K.D. performed the surgical procedures, collected and analyzed clinical data, performed statistical analysis R.J. performed the surgical procedures, wrote and edited the manuscript D.T. performed the surgical procedures, wrote and edited the manuscript K.M-C. performed the pathology, wrote and edited the manuscript M.P. performed the surgical procedures, analyzed clinical data, and was a major contributor in writing and editing the manuscript.

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Data availability

The dataset collected during the study has been made publicly accessible in the Harvard Dataverse Repository at https://doi.org/10.7910/DVN/IRIEUQ.

Declarations

Ethics approval and consent to participate

The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Bioethics Committee of the Jagiellonian University (no. 1072.6120.76.2021). Informed written consent was obtained from all individual participants included in the study.

Consent for publication

Written consent to publish anonymized data was secured from each study participant using an institutional form approved by the Bioethics Committee of Jagiellonian University.

Competing interests

The authors declare no competing interests.

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