Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2025.26980

Turk J Obstet Gynecol 2025;22(3):186-93

Non-invasive diagnosis of endometrioma through cervical swabs using Fourier transform infrared spectroscopy

Endometriomanın servikal sürüntü üzerinden Fourier dönüşümlü kızılötesi spektroskopi ile non-invaziv tanısı

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Abstract

Objective: This study aimed to investigate whether Fourier transform infrared (FTIR) spectroscopy applied to cervical swab samples could detect meaningful biochemical differences between women diagnosed with endometriomas and healthy controls, thereby assessing its potential as a non-invasive diagnostic tool.

Materials and Methods: A total of 104 cervical swab samples-52 from women with endometriomas diagnosed via transvaginal ultrasonography and 52 from healthy controls—were initially collected and processed. Following an optimization process and quality control of spectral data, 24 endometrioma and 20 control samples were included in the final analysis. FTIR spectra were obtained in the 4000-600 cm^{-1} range, and the primary outcomes included comparative peak intensities and areas under specific wavenumbers reflecting various bio-organic molecules.

Results: Statistically significant differences were observed at 2350 cm^{-1} and 1050 cm^{-1}, indicative of alterations in carbon dioxide and carbohydrate metabolism, respectively, in the endometrioma group compared with healthy controls ($p<0.05$). No significant differences were detected in other spectral regions associated with lipids (2950, 1460, 1400 cm^{-1}) and proteins (e.g., amid-I and amid-II regions), suggesting that endometrioma may primarily affect carbohydrate metabolism and carbon dioxide balance rather than lipid and protein pathways. Both groups were comparable in demographic and hormonal characteristics, thus bolstering the validity of the findings.

Conclusion: FTIR spectroscopy of cervical swab samples revealed distinctive biochemical profiles in women with endometriomas, particularly related to carbon dioxide and carbohydrate metabolism. These data suggest that FTIR analysis, which is rapid and minimally invasive, holds promise for the future development of non-invasive diagnostic strategies for endometrioma. However, larger multicenter studies that include surgical confirmation and disease staging are needed to establish its clinical utility definitively.

Keywords: Endometrioma, cervix, spectroscopy, carbohydrates, diagnostic techniques

Öz

Amaç: Bu çalışma, servikal sürüntü örnekleri üzerinde Fourier transform infrared (FTIR) spektroskopisi kullanılarak, endometrioma tanısı almış kadınlarla sağlıklı kadınlar arasında anlamlı biyokimyasal farklılıkların saptanıp saptanamayacağını araştırmayı amaçlamıştır. Böylece FTIR spektroskopisinin non-invaziv bir tanı yöntemi olarak kullanılabilirliği değerlendirilmektedir.

PRECIS: Fourier transform infrared spectroscopy of cervical swabs revealed distinct carbohydrate and carbon dioxide metabolism alterations in endometrioma, suggesting its potential use as a non-invasive diagnostic tool for this disease.

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Received/Geliş Tarihi: 27.05.2025 **Accepted/Kabul Tarihi:** 17.08.2025 **Epub:** 02.09.2025 **Publication Date/Yayınlanma Tarihi:** 05.09.2025

Cite this article as: Karakaşlı A, Görkem Ü, Toğrul C, Yıldırım E, Köse DA, Yurdakul Ö. Non-invasive diagnosis of endometrioma through cervical swabs using Fourier transform infrared spectroscopy. Turk J Obstet Gynecol. 2025;22(3):186-93

Gereç ve Yöntemler: Araştırma kapsamında, transvajinal ultrasonografi ile endometrioma tanısı konulan 52 kadın ve 52 sağlıklı bireyden toplam 104 servikal sürüntü örneği toplanmıştır. Spektral veri optimizasyonu ve kalite kontrol sonrasında, analiz için endometrioma grubundan 24 ve kontrol grubundan 20 örnek seçildi. FTIR spektroskopik ölçümler 4000-600 cm^{-1} dalga sayısı aralığında gerçekleştirilerek, spesifik dalga sayılarında pik yoğunlukları ve alanları karşılaştırıldı.

Bulgular: Çalışmanın bulgularına göre endometrioma grubunda sağlıklı kontrollere göre karbonhidrat metabolizmasını yansıtan 1050 cm^{-1} ve karbondioksiti yansıtan 2350 cm^{-1} bölgelerinde istatistiksel olarak anlamlı farklılıklar saptandı (p<0,05). Lipit ve proteinlerle ilişkili diğer spektral bölgelerde gruplar arasında anlamlı bir farklılık bulunmadı.

Sonuç: Sonuç olarak, FTIR spektroskopisi ile servikal sürüntü örneklerinin analizi, endometrioma tanısı açısından umut vadeden ve invaziv olmayan yöntem olarak öne çıkmaktadır. Özellikle karbonhidrat ve gaz değişimlerine ait biyokimyasal sinyallerin yakalanabilmesi, bu yöntemin hastalığın erken saptanmasında ve invaziv tanı yöntemlerine alternatif olarak kullanılmasında potansiyel taşıdığını göstermektedir. Ancak yöntemin klinik pratikte kullanılabilirliği için, cerrahi doğrulama ve hastalık evrelemesini içeren daha büyük ve çok merkezli çalışmaların yapılması gerekmektedir.

Anahtar Kelimeler: Endometrioma, serviks, spektroskopi, karbonhidratlar, tanı teknikleri

Introduction

Endometriosis is a common chronic disease in women of reproductive age, characterized by symptoms such as pelvic pain, dysmenorrhea, and infertility. The form of this disease that produces cystic lesions in the ovaries is termed “endometrioma”. Endometriosis most frequently localizes in the pelvis, especially in the ovaries. However, due to its non-specific symptoms, it is often confused with other causes of chronic pelvic pain, leading to difficulties in diagnosis. The gold-standard diagnostic method, involving surgery and histopathological examination, is associated with a typical delay of 8-12 years in diagnosis[1,2]. This delay adversely affects not only the diagnostic process but also timely access to treatment, causing a substantial decrease in quality of life.

Potential biomarkers found in the biological fluids of women with endometriosis may play an important role not only in diagnosis, but also in evaluating treatment efficacy. Advanced technologies such as proteomics, metabolomics, and genomics have emerged as promising tools for the detection of these biomarkers. Proteomic studies have shown significant changes in the levels of various proteins and peptides in the serum, urine, and cervicovaginal fluids of women with endometriosis[3-6]. Cervicovaginal fluid, in particular, allows for the identification of more specific biomarkers in the diagnosis of gynecological diseases due to its direct exposure to the uterine environment.

In recent years, Fourier transform infrared (FTIR) spectroscopy has attracted attention as a sensitive and rapid technology for analyzing the molecular structure of biological materials. This technology has demonstrated high potential in distinguishing diseased tissues from normal tissues. Successful applications of FTIR spectroscopy have been reported in the existing literature for the diagnosis of breast cancer, prostate cancer, and various gynecological conditions[7-10]. However, evidence of sufficient quality for the routine use of this technology in diagnosing complex diseases such as endometriosis is not yet available[11]. Advantages of FTIR spectroscopy include its rapid and cost-effective nature, the feasibility of non-invasive sampling from biological fluids, and the ability to provide sensitive results at the molecular level. In particular, the use of FTIR technology in samples such as cervicovaginal fluid may allow the detection of more specific biomarkers due to the benefits conferred by exposure to the uterine environment.

This study aimed to evaluate whether FTIR spectroscopy findings in cervical swab samples from women with endometriomas differ from those of healthy controls. In this context, the goal is to investigate changes in band structure and intensity in the FTIR spectra obtained from endometriotic and healthy tissues, which may serve an alternative diagnostic method for endometriosis and introduce an innovative perspective to current diagnostic approaches.

Materials and Methods

This cross-sectional prospective study was conducted between December 17, 2019, and November 17, 2021, in the Infertility and Gynecology Outpatient Clinics, of Hitit University Training and Research Hospital. The study included patients who presented to the infertility clinic and were diagnosed with endometrioma, as well as healthy women without any gynecological diseases attending solely for routine cervical swab screening. Written informed consent was obtained from all participants before enrollment. The data obtained have not been published elsewhere. This study was approved by the Hitit University Faculty of Medicine Research Ethics Committee with approval number 115, dated 11.12.2019.

Inclusion criteria for the endometrioma group were being between 18 and 45 years of age, having had unprotected intercourse for at least one year without achieving pregnancy, and exhibiting transvaginal ultrasonography findings, consistent with the typical endometrioma definition of the American College of Radiology’s O-RADS Ultrasound Risk Stratification System[12]. In the healthy control group, inclusion criteria comprising being between 18 and 45 years of age and having no gynecological complaints or diseases. Exclusion criteria included abnormal cervical swab findings, premalignant or malignant findings, evidence of bleeding or vaginitis, a history of active or chronic vaginitis, intravaginal medication use, use of an intrauterine device, history of chronic disease or long-term medication use. As a result, a total of 104 women participated in the study and were divided into two main groups: (i) 52 patients diagnosed with endometrioma and (ii) 52 healthy controls.

Cervical swab samples were collected from the cervical os following Pap smear sampling. The collected samples were placed in 0.09% sodium chloride solution for 10 minutes and then stored at -20 °C. All samples were preserved under these conditions until the day of analysis. After the optimization process for the cervical swab technique, relatively fewer samples remained for analysis. The spectral data obtained were visually examined for morphological features, and samples with spectra showing similar wave patterns were selected for statistical analysis. The spectra from 24 participants in the endometrioma group and 20 participants in the control group were included in the statistical analyses. Spectra excluded due to differences in wavelength patterns, which may have resulted from variations in biochemical composition, technical factors, biological differences between individuals, or environmental factors.

Spectroscopic analyses were carried out using a Thermo Nicolet 6700 FTIR Spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). The infrared spectrum was measured based on vibrations in polar covalent bonds of molecules, a method used to analyze the unique "fingerprint" structure of organic compounds. In this study, the attenuated total reflectance technique was employed to record spectra in the range of 4000-600 cm^{-1}. The 0.09% sodium chloride solution, used to obtain the background spectrum, was subtracted from the measurements.

Statistical Analysis

All data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 26.0 software. The Kolmogorov-Smirnov test was applied to assess the normality of data distribution. Descriptive statistics for continuous variables were presented as mean, standard deviation, median, minimum, and maximum values. Data with normal distribution were analyzed by the Independent Samples t-test, and the Mann-Whitney U test was used for data not following a normal distribution. A p-value <0.05 was considered statistically significant for all analyses.

Results

A total of 104 samples-52 from the endometrioma group and 52 from the control group-were analyzed via FTIR spectroscopy. After the optimization process for the cervical swab technique, fewer samples remained; the obtained spectra were examined visually for morphological features. Samples with spectra exhibiting similar wave patterns were selected for statistical analysis. Consequently, the spectra of 24 participants in the endometrioma group and 20 participants in the control group were included in the statistical analyses.

The findings regarding the comparison of demographic and hormonal parameters between the control and endometriosis groups are presented in Table 1. There were no statistically significant differences between the groups in age (p=0.787), body mass index (p=0.368), follicle stimulating hormone (p=0.605), estradiol (p=0.418), or anti-Müllerian hormone (p=0.082). These results indicate that the two groups were largely similar in terms of demographic and hormonal characteristics (p>0.05 all).

FTIR spectra were obtained for all samples in the wavenumber range of 4000-600 cm^{-1}. However, due to strong overlapping peaks arising from the sodium chloride solution, the 3800-3000 cm^{-1} region was excluded from the analysis. In line with existing literature, nine peaks were detected in the cervical swab samples, reflecting various bio-organic molecules such as proteins, lipids, nucleic acids, and carbohydrates. These peaks, their wavenumbers, and the corresponding organic components identified in the literature are listed in Table 2.

As shown in Figures 1 and 2, differences in the quantitative properties of the peaks were observed between the two study groups. Upon analysis, the peak area reflecting carbon dioxide (CO_2) at 2350 cm^{-1} and the peak area corresponding to oligosaccharides and polysaccharides at 1050 cm^{-1} were found to be significantly higher in the endometrioma group than in the healthy control group (U=151.0, p<0.05, and U=154.0, p<0.05, respectively). These findings are summarized in Table 3.

Furthermore, the peak area at 1250 cm^{-1} was higher in the endometrioma group compared to the control group (mean ranks: 25.46 vs. 18.95); however, this difference was borderline in terms of statistical significance (p=0.094). No statistically significant differences were observed at other wavenumbers (e.g., 2950 cm^{-1} and 1650 cm^{-1}), suggesting a similar distribution of

Table 1. Comparison of demographic and hormonal parameters between control and endometriosis groups

Variable	Control group		Endometriosis group		t-value	df	p-value	95% CI lower	95% CI upper
	Mean	SD	Mean	SD					
Age	29.83	2.98	30.00	3.28	-0.27	102.00	0.787	-1.38	1.05
BMI	24.47	2.13	24.07	2.33	0.90	102.00	0.368	-0.47	1.27
FSH	7.78	1.19	7.65	1.19	0.52	102.00	0.605	-0.34	0.58
E2	60.26	14.20	58.19	11.70	0.81	102.00	0.418	-2.98	7.11
AMH	3.36	0.59	3.57	0.58	-1.76	102.00	0.082	-0.43	0.03

Mean values, standard deviations (SD), t-values, degrees of freedom (df), p-values, and 95% confidence intervals (CI) are provided, BMI: Body mass index, FSH: Follicle stimulating hormone, E2: Estradiol, AMH: Anti-Müllerian hormone bio-organic molecules between the two groups in those regions. Overall, the FTIR analysis demonstrated distinct differences at 2350 cm^{-1} and 1050 cm^{-1} in the endometrioma group, whereas other wavenumbers showed a relatively stable distribution.

Discussion

This study aimed to compare the FTIR spectroscopic findings of cervical swab samples from women with endometriomas to those from healthy controls, and in doing so identify potential biochemical alterations that could be used for diagnostic purposes. Our results indicate that the peak areas under 2350 cm^{-1}, corresponding to carbon dioxide, and 1050 cm^{-1}, reflecting oligosaccharide and polysaccharide content, was significantly higher in the endometrioma group compared to the control group. Conversely, no statistically significant difference was detected between the groups at other wavenumbers known to represent lipids, proteins, phospholipids, and nucleic acids.

The increased peak area at 2350 cm^{-1} in the endometrioma group suggests a specific change in CO_2 metabolism. CO_2 is a major byproduct of cellular metabolism and may accumulate in states of inflammation, hypoxia, or heightened metabolic activity. Schultz et al.[13] demonstrated that the CO_2 peak observed in

Table 2. Characteristics of the selected peak wavenumbers for the study

Peak wavenumber (cm^{-1})	Description	Organic component
Peak1 (2950 cm^{-1})	CH_3 asymmetric stretching	Lipids
Peak2 (2350 cm^{-1})	CO_2; cellular metabolic rate, atmospheric carbon dioxide	-
Peak3 (1650 cm^{-1})	Amide I; 80% C=O stretching, 10% N-H bending, 10% C-N stretching	Proteins
Peak4 (1560 cm^{-1})	Amide II; N-H stretching	Proteins
Peak5 (1540 cm^{-1})	Amide II; 60% N-H bending, 40% C-N stretching	Proteins
Peak6 (1460 cm^{-1})	CH_3 bending	Lipids
Peak7 (1400 cm^{-1})	COO- symmetric stretching	Fatty acids
Peak8 (1250 cm^{-1})	PO_2- asymmetric stretching (without hydrogen bonding)	Nucleic acids, phosphoproteins, and phospholipids
Peak9 (1050 cm^{-1})	C-O stretching accompanied by C-O bending of carbohydrate C-OH groups	Oligosaccharides and polysaccharides

The table includes peak wavenumbers (cm^{-1}), their corresponding descriptions, and the associated organic components

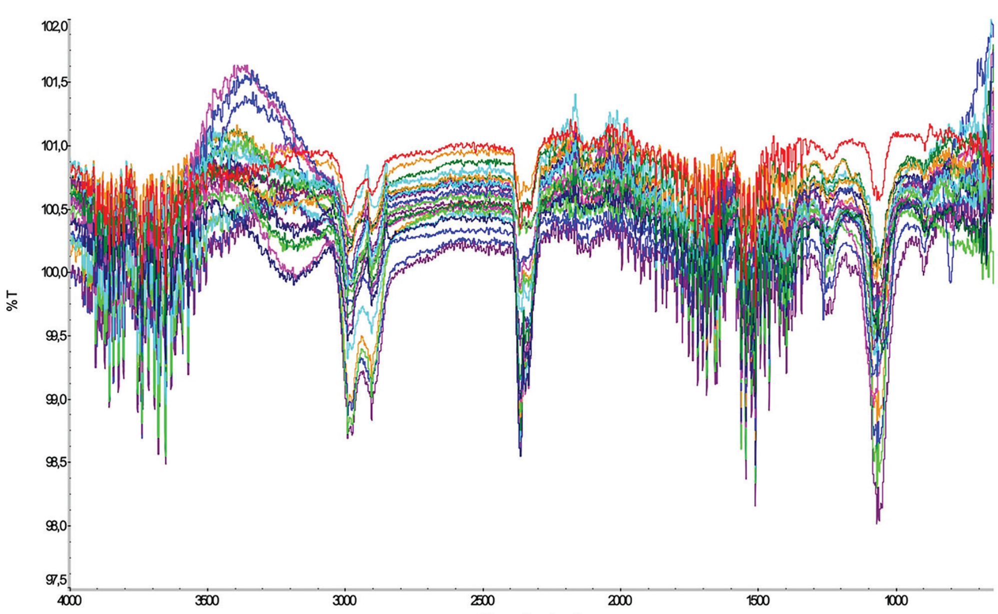

Figure 1. FTIR spectra of the endometriosis group, showing the characteristic peaks of biomolecular components

FTIR: Fourier transform infrared

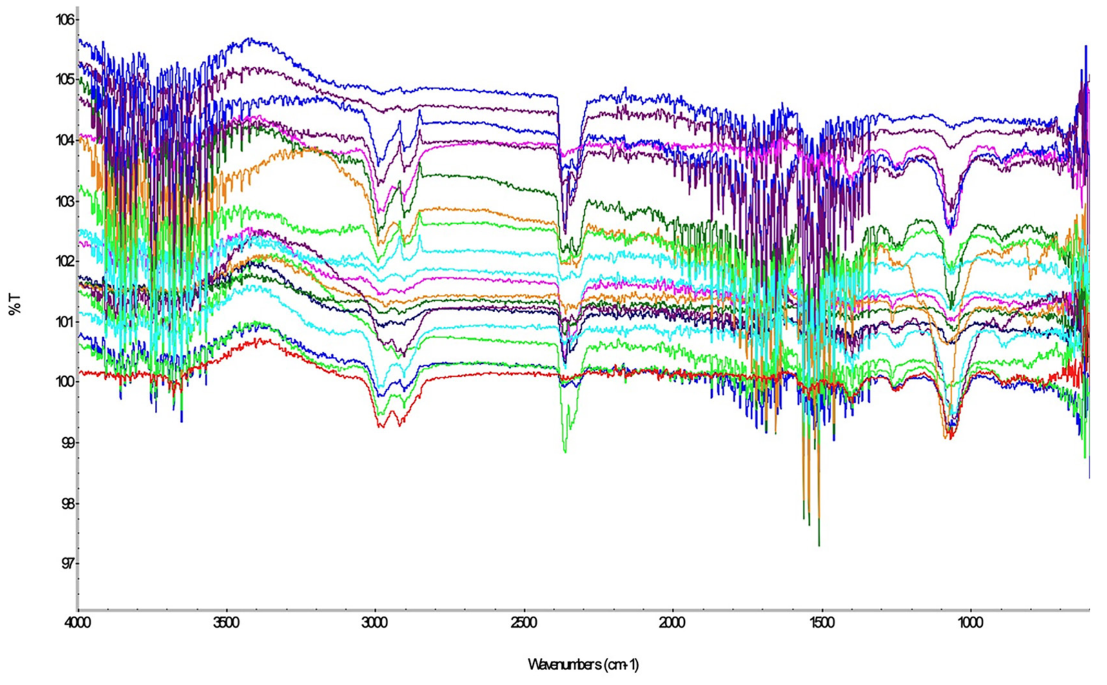

Figure 2. FTIR spectra of the control group, displaying the spectral differences compared to the endometriosis group
FTIR: Fourier transform infrared

Table 3. Comparison of the areas under the peaks between groups using the Mann-Whitney U test

Peak	Group	Mean rank	Sum of ranks	U	Z-score	p
Peak1 (2950 cm^{-1})	Endometrioma	25.17	604.00	176.0	-1.508	0.131
	Control	19.30	386.00			
Peak2 (2350 cm^{-1})	Endometrioma	26.21	629.00	151.0	-2.098	0.036*
	Control	18.05	361.00			
Peak3 (1650 cm^{-1})	Endometrioma	22.42	538.00	238.0	-0.047	0.962
	Control	22.60	452.00			
Peak4 (1560 cm^{-1})	Endometrioma	23.81	571.50	208.5	-0.743	0.458
	Control	20.93	418.50			
Peak5 (1540 cm^{-1})	Endometrioma	21.96	527.00	227.0	-0.306	0.759
	Control	23.15	463.00			
Peak6 (1460 cm^{-1})	Endometrioma	22.29	535.00	235.0	-0.118	0.906
	Control	22.75	455.00			
Peak7 (1400 cm^{-1})	Endometrioma	22.44	538.50	238.5	-0.035	0.972
	Control	22.58	451.50			
Peak8 (1250 cm^{-1})	Endometrioma	25.46	611.00	169.0	-1.673	0.094
	Control	18.95	379.00			
Peak9 (1050 cm^{-1})	Endometrioma	26.08	626.00	154.0	-2.027	0.043*
	Control	18.20	364.00			

*: P<0.05 values are considered statistically significant. The table presents mean ranks, sum of ranks, U-values, Z-scores, and p-values for each peak

biological materials could be attributed to the intracellular CO_2 produced through glucose metabolism. However, it has also been reported that atmospheric CO_2 may introduce measurement errors. A study by Kokot et al.(14) investigating serum samples showed that increases in CO_2 peaks among individuals with endometriosis were associated with inflammatory processes. This observation aligns with our findings of elevated signal intensity around 2350 cm^{-1}, suggesting that this region may serve as both a diagnostic and a prognostic biomarker.

Our investigation revealed that peak areas at 1050 cm^{-1} were significantly higher in the endometrioma group than in the control group. This wavenumber is associated with bending and stretching vibrations of the C-O bond in the C-OH groups of carbohydrates, thereby reflecting oligosaccharides and polysaccharides. In the literature, it has been proposed that this wavenumber could be indicative of molecular alterations linked to endometriosis. In a study by Cheung et al.(15), wavenumbers corresponding to carbohydrate peaks played a pivotal role in distinguishing between eutopic endometrium and ectopic endometriotic tissues. Bozdağ et al.(16) found that in cervical swab samples, carbohydrate bond vibrations at 1153 cm^{-1} and 1035 cm^{-1} were elevated in early-stage endometriosis, but decreased in advanced-stage disease. Moreover, Nsugbe(17), using Raman spectroscopy, reported that wavenumbers reflecting carbohydrate metabolism are key determinants in differentiating between healthy and endometriotic individuals, and that the analysis of Raman data via machine learning algorithms further supports the clinical utility of these wavenumbers. In contrast, Notarstefano et al.(18) found that in granulosa cells, the carbohydrate content at 1053 cm^{-1} was lower in the endometrioma group than in healthy controls.

These discrepancies may stem from factors such as endometriosis stage, lesion site, and the disease's biochemical microenvironment. For example, an increase in carbohydrate metabolism has been associated with early-stage endometriosis, whereas this alteration appears less pronounced in advanced stages. Although our study did not include staging of the endometrioma cases, the elevated carbohydrate peaks observed in the patient group may indicate the predominance of earlier-stage disease. Overall, our findings suggest that endometrioma may affect glycosylation patterns and carbohydrate metabolism, and that spectroscopy offers a powerful method for detecting such molecular changes.

In our study, no significant differences were observed between the groups at 2950, 1460, and 1400 cm^{-1}, which represent lipid components. Nonetheless, the literature indicates that endometriosis can influence lipid metabolism. Notarstefano et al.(18) reported a decline in the degree of saturation for lipid alkyl chains and an increase in peroxidized lipid content in endometrioma cases. Furthermore, Bozdağ et al.(16) noted that in advanced endometriosis, lipid-protein vibrations at 1450 cm^{-1} were higher than in controls.

Regarding protein components, Cheung et al.(15) identified the amid-I and amid-II vibrational regions in FTIR spectra of endometriotic tissues as key spectral features associated with endometrial pathologies. Notarstefano et al.(18) observed a decrease in properly folded proteins and an increase in unfolded proteins in granulosa cells. In a serum-based study, Kokot et al.(14) reported that inflammation-related protein levels were significantly elevated in individuals with endometriosis, a finding that could explain why protein peaks showed no differences in our study, given that cervical swab and serum samples reflect different biochemical properties. Taken together, these results imply that endometrioma may influence protein metabolism and secondary protein structures.

However, in our study, no statistically significant difference was detected between the groups in the Amide I and Amide II regions of the FTIR spectra, which reflect proteins. Although changes in protein structure have been reported in samples such as serum or granulosa cells in the literature, cervical swab samples may not fully capture these alterations. This may be explained by two main reasons: (i) FTIR spectroscopy can primarily detect prominent structural changes in complex biological matrices, as it has limited sensitivity to subtle conformational variations; (ii) the cervix is anatomically distant from the peritoneal or ovarian microenvironment where endometriotic foci reside, and thus may not fully reflect local inflammatory protein alterations. Indeed, while increases in peaks originating from lipids and some proteins have been reported in FTIR spectra obtained from cervical swab samples, these signals do not directly indicate specific conformational changes in protein structure. In particular, in the study by Bozdağ et al.(16), increases were observed at 1405 and 1450 cm^{-1} peaks in advanced-stage endometriosis groups. However, second derivative analyses of the Amide I-II regions did not reveal statistically significant differences in protein structure. These findings suggest that the ability of FTIR to detect conformational changes in proteins in cervical swab samples may be limited.

Therefore, future studies should be supported by simultaneous sampling from different anatomical sites and validation with proteomic methods.

A key strength of this study is the ability to analyze cervical swab samples via FTIR spectroscopy without resorting to invasive methods. This approach enables the rapid and precise detection of potential biochemical alterations arising from the presence of endometrioma. Additionally, the similarity of demographic and hormonal characteristics between the patient and control groups enhances the comparability of the findings and thereby strengthens the validity of the results. Another noteworthy advantage lies in the simplicity and speed of the protocol employed, which could facilitate the future integration of FTIR technology into clinical practice.

In recent years, FTIR spectroscopy has gained attention as a non-invasive diagnostic method capable of rapidly and sensitively detecting biochemical alterations at the molecular level. Several publications have reported successful use of FTIR spectroscopy in identifying molecular changes associated with endometriosis in various biological tissues. Researchers such as Kokot et al.[14] and Nsugbe[17] have proposed that combining FTIR or Raman spectroscopy with machine learning and other advanced analytical methods could accelerate the integration of these techniques into clinical practice. Our study demonstrates that this approach is feasible for cervical swab samples.

Study Limitations

Nevertheless, an important limitation of our study is the relatively small number of samples included in the final analysis (endometrioma group: 24, control group: 20). This may limit the generalizability and statistical power of the findings. Although the spectral quality control and optimization process was conducted meticulously, larger sample sizes, multicenter studies, and surgical confirmation will be required to validate these findings. Such studies will more clearly demonstrate the potential of this method for clinical application.

Another limitation of our investigation is that the diagnosis of endometrioma was based solely on ultrasonographic evaluation without surgical confirmation. This approach prevented staging and made it challenging to fully compare our findings with those of other studies in the literature. Future research with surgical confirmation and disease staging would allow more precise delineation of the spectral characteristics involved.

Conclusion

This study demonstrates that the use of FTIR spectroscopy on cervical swab samples can detect significant biochemical differences between women with endometrioma and healthy controls. In particular, the pronounced changes observed at 2350 cm^{-1} and 1050 cm^{-1} suggest alterations in carbohydrate metabolism and CO_2 levels associated with endometrioma. Although no significant differences were found in lipid and protein components between the groups-without excluding the clinical importance of these molecular categories-the findings imply that endometrioma may primarily affect carbohydrate metabolism and CO_2 balance. Taken together, these data indicate that FTIR analysis of cervical swab samples has the potential to contribute to non-invasive diagnostic processes for endometrioma in the future. Nonetheless, larger-scale studies incorporating surgical confirmation and disease staging will be instrumental in guiding the integration of this method into clinical practice.

Statement on the Use of Artificial Intelligence (AI) Tools

During the preparation of this work, the authors utilized OpenAI's ChatGPT and Grammarly to enhance language clarity, grammar, and readability of the manuscript. The AI-generated suggestions were carefully evaluated by comparing them with original author-written content, ensuring accuracy, consistency, and scientific correctness. After thorough review and necessary editing, the authors assume full responsibility for the manuscript's final content. This incorporation of AI tool usage primarily impacted the language quality, manuscript readability, and overall editorial refinement.

Ethics

Ethics Committee Approval: This study was approved by the Hitit University Faculty of Medicine Research Ethics Committee with approval number 115, dated 11.12.2019.

Informed Consent: Written informed consent was obtained from all participants before enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., Concept: A.K., Ü.G., C.T., E.Y., Design: A.K., Ü.G., C.T., E.Y., Data Collection or Processing: A.K., E.Y., D.A.K., Ö.Y., Analysis or Interpretation: A.K., Ü.G., D.A.K., Ö.Y., Literature Search: A.K., Writing: A.K., Ü.G., C.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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