DOI: https://doi.org/10.17816/aog630395

Correlation between inflammatory biomarkers in biological fluids in patients with ovarian endometriosis

Yana A. Mangileva[1], Elena V. Kudryavtseva[2], Larisa G. Polushina[2], Elvira I. Shakiryanova[3], Nikolay N. Potapov[4], Vladislav V. Kovalev[5]

[1] Medical Center « UMMC-Health», Ekaterinburg, Russia;
[2] Ural State Medical University, Ekaterinburg, Russia;
[3] City Clinical Hospital No. 14, Ekaterinburg, Russia;
[4] City Clinical Hospital No. 40, Ekaterinburg, Russia;
[5] Ural Institute of Health Management n.a. A.B. Blokhin, Ekaterinburg, Russia

ABSTRACT

BACKGROUND: To date, there are no available screening techniques allowing to distinguish groups of women with the risk of endometriosis. Therefore, many researchers are searching for meaningful biomarkers for non-invasive diagnosis. The peritoneal fluid is subject to multidirectional changes in patients with external genital endometriosis, although its sampling requires invasive procedure. Testing of the inflammatory markers in saliva is a simple and safe method of particular interest, given that its sampling is non-invasive.

AIM: To assess the correlations between the level of inflammatory biomarkers in the peritoneal fluid and saliva in patients with ovarian endometriosis.

MATERIAL AND METHODS: A prospective cohort comparative study of 46 women with ovarian endometriosis was carried out. Inclusion criteria: confirmed diagnosis of ovarian endometriosis; age between 18 and 40 years; written informed consent for surgical intervention and for participation in the study; no prior hormonal treatment. Non-inclusion criteria: patient's refusal to participate in the study; age below 18 and above 40 years; contraindications for surgical treatment; oral inflammatory diseases. Patients were excluded if the diagnosis could not be visually confirmed during surgery or if there were histological discrepancies. All patients underwent laparoscopic cystectomy. Peritoneal fluid samples were collected during surgery. Mixed unstimulated saliva was collected before surgery in the morning, on an empty stomach. The levels of interleukins and of vascular endothelial growth factor were assessed in biological fluids.

RESULTS: The mean age of the study subjects was 32,4±6,1 years. Correlation analysis showed a direct statistically significant moderate relationship between the levels of IL-6 (r=0.548; p=0.001) and IL-8 (r=0.360; p=0.026) in the peritoneal fluid and saliva, respectively.

CONCLUSION: These data suggest that the onset and progression of endometriosis are associated with the increase of inflammatory cytokine levels both in the peritoneal fluid and in saliva. This may serve a potential tool for diagnosis and assessment of the severity of endometriosis. Evaluation of IL-6 and IL-8 levels in saliva may be useful in clinical practice in patients with external genital endometriosis.

Keywords: endometriosis; endometrioma; interleukins; saliva; biomarker.

To cite this article:
Mangileva YA, Kudryavtseva EV, Polushina LG, Shakiryanova EI, Potapov NN, Kovalev VV. Correlation between inflammatory biomarkers in biological fluids in patients with ovarian endometriosis. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):460–469. DOI: https://doi.org/10.17816/aog630395

Received: 16.04.2024 **Accepted:** 29.09.2024 **Published online:** 12.12.2024

DOI: https://doi.org/10.17816/aog630395

Соотношение воспалительных маркеров в биологических жидкостях у пациенток с эндометриоидными гетеротопиями яичников

Я.А. Мангилева[1], Е.В. Кудрявцева[2], Л.Г. Полушина[2], Э.И. Шакирьянова[3], Н.Н. Потапов[4], В.В. Ковалёв[5]

[1] ООО «УГМК-Здоровье», Екатеринбург, Россия;
[2] Уральский государственный медицинский университет, Екатеринбург, Россия;
[3] Городская клиническая больница № 14, Екатеринбург, Россия;
[4] Городская клиническая больница № 40, Екатеринбург, Россия;
[5] Уральский институт управления здравоохранением им. А.Б. Блохина, Екатеринбург, Россия

АННОТАЦИЯ

Обоснование. На сегодняшний день не существует доступных скрининговых методик, позволяющих выделить группы риска женщин по эндометриозу, поэтому многие исследователи ведут поиск высокоинформативных маркеров для неинвазивной диагностики. Перитонеальная жидкость подвержена разнонаправленным изменениям при наружном генитальном эндометриозе, но её получение является инвазивной процедурой. Особый интерес представляет исследование слюны на содержание воспалительных маркеров, поскольку её получение является неинвазивной процедурой, относится к простым и безопасным методам.

Цель. Оценить наличие корреляционных зависимостей между концентрацией воспалительных маркеров в перитонеальной жидкости и слюне при эндометриоидном поражении яичников.

Материал и методы. Проведено проспективное когортное сравнительное исследование 46 женщин с эндометриоидными кистами яичников. Критерии включения: подтверждённый диагноз «эндометриоз яичников»; репродуктивный возраст (18–40 лет); согласие пациентки на оперативное вмешательство и на участие в исследовании; отсутствие гормонального лечения до операции. Критерии невключения: отказ пациентки от участия в исследовании; возраст младше 18 и старше 40 лет; противопоказания к оперативному лечению; воспалительные заболевания ротовой полости. Критерии исключения: отсутствие визуального подтверждения диагноза при оперативном вмешательстве и по результатам гистологического исследования. Всем пациенткам была проведена лапароскопическая кистэктомия. Образцы перитонеальной жидкости были собраны во время оперативного вмешательства. Смешанную нестимулированную слюну собирали накануне операции утром, натощак. В биологических жидкостях оценивали уровень интерлейкинов и васкулоэндотелиального фактора роста.

Результаты. Средний возраст пациенток, участвовавших в исследовании, составил 32,4±6,1 года. Корреляционный анализ показал прямую статистически значимую связь (средней силы) между концентрациями в перитонеальной жидкости и слюне IL-6 (r=0,548; p=0,001) и IL-8 (r=0,360; p=0,026).

Заключение. Полученные результаты позволяют предположить, что при возникновении и прогрессировании эндометриоза не только в перитонеальной жидкости, но и в слюне увеличивается концентрация воспалительных цитокинов, которые могут быть потенциальным инструментом для диагностики и оценки степени тяжести эндометриоза. Оценка IL-6 и IL-8 в слюне может быть полезной в клинической практике при наличии у пациентки наружного генитального эндометриоза.

Ключевые слова: эндометриоз; эндометриома; интерлейкины; слюна; биомаркер.

Как цитировать:
Мангилева Я.А., Кудрявцева Е.В., Полушина Л.Г., Шакирьянова Э.И., Потапов Н.Н., Ковалёв В.В. Соотношение воспалительных маркеров в биологических жидкостях у пациенток с эндометриоидными гетеротопиями яичников // Архив акушерства и гинекологии им. В.Ф. Снегирёва. 2024. Т. 11, № 4. С. 460–469. DOI: https://doi.org/10.17816/aog630395

Рукопись получена: 16.04.2024 **Рукопись одобрена:** 29.09.2024 **Опубликована online:** 12.12.2024

DOI: https://doi.org/10.17816/aog630395

卵巢子宫内膜异位性病灶患者生物液体中炎症标志物的相关性

Yana A. Mangileva[1], Elena V. Kudryavtseva[2], Larisa G. Polushina[2], Elvira I. Shakiryanova[3], Nikolay N. Potapov[4], Vladislav V. Kovalev[5]

[1] Medical Center « UMMC-Health», Ekaterinburg, Russia;
[2] Ural State Medical University, Ekaterinburg, Russia;
[3] City Clinical Hospital No. 14, Ekaterinburg, Russia;
[4] City Clinical Hospital No. 40, Ekaterinburg, Russia;
[5] Ural Institute of Health Management n.a. A.B. Blokhin, Ekaterinburg, Russia

摘要

背景。目前尚无有效的筛查方法能够识别女性子宫内膜异位症的高风险群体，因此许多研究者正在探索非侵入性诊断的高信息量标志物。虽然腹膜液在外生殖器子宫内膜异位症中发生多方向变化，但其采集需通过侵入性操作。相比之下，唾液炎症标志物的研究因其采集方式非侵入、简单且安全，具有特别的研究价值。

研究目的。评估卵巢子宫内膜异位病变患者腹膜液与唾液中炎症标志物浓度之间的相关性。

材料与方法。对46名卵巢子宫内膜囊肿患者进行了前瞻性队列比较研究。纳入标准包括：确诊卵巢子宫内膜异位症；生育年龄（18~40岁）；患者同意手术和参与研究；术前未接受激素治疗。排除标准包括：患者拒绝参与研究；年龄小于18岁或大于40岁；存在手术禁忌症；口腔炎症性疾病。排除病例为：手术和组织学检查未能确认诊断的患者。所有患者均接受腹腔镜囊肿切除术，并在手术中采集腹膜液样本。术前清晨空腹采集混合的非刺激性唾液样本。对生物液体中的白细胞介素（Interleukin，IL）和血管内皮生长因子（Vascular Endothelial Growth Factor，VEGF）水平进行了评估。

结果。参与研究患者的平均年龄为32.4±6.1岁。相关性分析显示，腹膜液与唾液中IL-6（r=0.548；p=0.001）和IL-8（r=0.360；p=0.026）浓度之间存在中等强度的正相关性，且具有统计学显著性。

结论。研究结果表明，在子宫内膜异位症的发生和进展过程中，不仅腹膜液中炎症细胞因子的浓度增加，唾液中的浓度也随之升高。这些炎症细胞因子可能成为诊断和评估子宫内膜异位症严重程度的潜在工具。唾液中IL-6和IL-8的检测在外生殖器子宫内膜异位症患者的临床实践中具有重要意义。

关键词：子宫内膜异位症；内膜囊肿；白细胞介素；唾液；生物标志物。

引用本文:
Mangileva YA, Kudryavtseva EV, Polushina LG, Shakiryanova EI, Potapov NN, Kovalev VV. 卵巢子宫内膜异位性病灶患者生物液体中炎症标志物的相关性. *V.F. Snegirev Archives of Obstetrics and Gynecology.* 2024;11(4):460–469. DOI: https://doi.org/10.17816/aog630395

收到: 16.04.2024 **接受:** 29.09.2024 **发布日期:** 12.12.2024

BACKGROUND

Endometriosis is one of the most common gynecological diseases in women of childbearing age. Endometriosis is estimated to affect 176 million women worldwide (approximately 10% of women of childbearing age) [1, 2]. This condition can cause severe dysmenorrhea, severe dyspareunia, chronic pelvic pain, infertility, bowel and bladder symptoms, and chronic fatigue [1, 3, 4]. In addition, the symptom severity often does not correspond to the disease severity. Symptoms of endometriosis have detrimental effects on women's functional status and physical, mental, social, and sexual well-being [4, 5].

Endometriosis significantly reduces fertility in women of childbearing age, alters abdominal parameters due to inflammatory reactions, and affects the pelvic anatomy. Up to half of people with endometriosis struggle to get pregnant [4, 6]. Many theories attempt to explain the development of endometriosis, but none is considered definitive. Endometrial-like cells can implant outside the uterus and respond to ovarian estrogen stimulation, causing inflammatory changes at the site of invasion, followed by scarring of the surrounding tissue and adhesion [7]. Ectopic endometrioid aggregates secrete chemokines into the surrounding tissue and recruit immune cells, which in turn secrete cytokines and growth factors such as *TNF*-α (tumor necrosis factor α), *IL-1β* (interleukin 1β), *IL-6* (interleukin 6), *IL-8* (interleukin 8), *IL-17* (interleukin 17), *FGF* (fibroblast growth factor), and *VEGF* (vascular endothelial growth factor), creating a specific local microenvironment that contributes to the reciprocal interaction with the peritoneal fluid (PF) [8–10]. Some publications have addressed the issue of diagnosing endometriosis, but it is still poorly understood. The lack of simple, accessible, and affordable screening techniques impedes the identification of at-risk women who need in-depth diagnosis. However, early recognition and diagnosis are key to timely treatment and prevention of the adverse effects of the advanced endometriosis [11, 12].

Of all the biological fluids, PF is the most susceptible to multidirectional changes in external genital endometriosis, since it is in direct contact with its lesions and both influences endometrioid heterotopias and changes under their influence. Previous studies have demonstrated the clinical diagnostic value of PF levels of various interleukins and *VEGF* [13]. However, PF sampling is an invasive and expensive procedure associated with certain risks that preclude its use as a screening technique and significantly limit its diagnostic value. Of course, it would be better to develop a reliable, ideally inexpensive and non-invasive test for diagnosing endometriosis with high sensitivity and specificity [11].

In this regard, specific attention should be paid to testing easily accessible biological fluids, especially saliva, for inflammatory markers [14, 15]. Saliva contains a high number of proteins, peptides, enzymes, electrolytes, hormones, antibodies, and cytokines from systemic and local sources and therefore can be used for diagnosis of various diseases and evaluation of their progression. Saliva collection is a simple and safe non-invasive procedure. We believe that the research of the saliva inflammatory profile is one of the most promising areas in the diagnosis and screening of endometriosis.

Study Aim. The aim of the study was to evaluate correlations between PF and salivary levels of inflammatory markers in patients with ovarian endometriosis.

MATERIALS AND METHODS

Study design

A prospective, observational, comparative cohort study enrolled 46 women of childbearing age with confirmed cystic ovarian endometriosis. Figure 1 shows the study design.

Eligibility criteria

Inclusion criteria were as follows: 1) diagnosis of ovarian endometriosis; 2) childbearing age (18–40 years); 3) patient consent for surgery and study participation; 4) no hormonal treatment prior to surgery.

Non-inclusion criteria were as follows: 1) patient refusal to participate in the study; 2) age under 18 years or over 40 years; 3) contraindications to surgical treatment; 4) inflammatory diseases of the oral cavity.

Exclusion criteria were the lack of diagnosis confirmation by intraoperative visual assessment and/or by histology.

Study setting

The study enrolled women who were residents of Yekaterinburg (Russia) and who underwent surgery in 2022–2023 in the Gynecology departments of the Sverdlovsk Regional State Autonomous Healthcare Institutions "City Clinical Hospital No. 40" and "City Clinical Hospital No. 14."

Study duration

The planned duration of the enrollment period was 12 months. The study did not include post-operative follow-up.

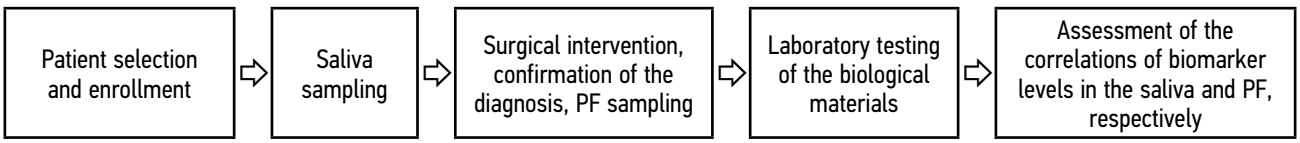

Fig. 1. Study design: PF — peritoneal fluid.

Intervention description

Clinical (medical history, gynecologic examination), laboratory tests, ultrasound, endoscopy, and histology were used to achieve the aim of the study. Saliva was obtained the day before surgery. The PF was obtained intraoperatively.

After insertion of a videoendoscope into the abdominal cavity, the pelvic organs (peritoneum, fallopian tubes, uterus, ovaries, uterine ligaments, rectouterine pouch) were examined. Endometrioid heterotopias were visualized and their location and color were identified, as well as the severity of external genital endometriosis using the revised American Fertility Society (r-AFS) classification (1985; renamed later American Society for Reproductive Medicine's classification, ASRM classification). Small trocars were then inserted into the abdomen. One was used to insert a surgical aspiration tube into the rectouterine pouch prior to any manipulation. A sterile disposable syringe was attached to the end of the tube to collect PF from the rectouterine and other peritoneal pouches. The syringe PF was then transferred to a 5 mL Eppendorf test tube.

Mixed unstimulated saliva was collected after rinsing the mouth with water in the morning on the day before surgery in the fasting and resting state. Patients were asked to keep their head down in a seated position, refrain from swallowing any saliva and moving their tongue or lips during the entire saliva collection process. Saliva was allowed to accumulate in the oral cavity for two minutes and then transferred to a SalivaCapsSet tube by spitting out the entire contents. All samples obtained were labeled no later than 4 hours after the collection, placed in a cold chamber and stored at -40°C in a biobank of the Central Research Laboratory of the Ural State Medical University. Biological material was thawed and centrifuged in a TsLMN-R10-01-Elekon laboratory centrifuge at 1,500 rpm for 10 minutes prior to testing. Immunochemistry of saliva and PF included determination of *IL-1β*, *IL-6*, *IL-8*, *IL-10*, *TNF*, *VEGF* by heterogeneous enzyme-linked immunosorbent assay using Vector BEST test systems (Russia). The analysis was performed using a system consisting of a Thermo Scientific Multiskan GO (Japan) plate enzyme immunoassay analyzer, a Thermo Scientific Wellwash (Japan) washer, and an Elmi shaker-thermostat (ST-3L, Latvia).

Main study outcome

The main study outcome was to assess the strength of the correlation between PF and salivary levels of cytokines.

Group analysis

The study group included 46 patients of childbearing age with histologically confirmed cystic ovarian endometriosis.

Methods for registration of outcomes

To report the main study outcome, correlation analysis for nonparametric quantitative data was performed using the Spearman's correlation coefficient, with the strength of association assessed using a Chaddock scale.

Ethical review

The study was approved by the local ethics committee of the Ural State Medical University (Protocol No. 11 dated 24 December 2021).

Statistical analysis

Statistical data were processed using the Jamovi licensed package (The Jamovi project, version 2.3 https://www.jamovi.org). For quantitative parameters, descriptive statistics such as median (Me) and interquartile range (Q1–Q3) were calculated as the distribution was not normal. The relationship between parameters for nonparametric quantitative data was assessed using the Spearman's correlation coefficient, with the strength of association assessed using the Chaddock scale. The association was considered insignificant at <0.1, weak at 0.1–0.3, moderate at 0.3–0.5, relatively strong at 0.5–0.7, strong at 0.7–0.9, and very strong at 0.9–0.99. The results were considered statistically significant at $p<0.05$.

RESULTS

Participant characteristics

Forty-six patients with cystic ovarian endometriosis were examined. The mean age of patients enrolled in the study was 32.4±6.1 years. All study participants were Caucasian and residents of the Sverdlovsk region.

Primary findings

Table 1 shows the PF and salivary levels of *IL* and *VEGF*.

Salivary levels of *TNF-α* were in most cases below the sensitivity threshold of the test system (<0.1 pg/mL). Therefore, a correlation between salivary and PF levels of TNF-α could not be assessed. Table 2 shows the analysis of the correlation between other parameters.

Correlation analysis showed a direct statistically significant association (moderate strength) between salivary and PF levels of *IL-6* ($r=0.548$; $p=0.001$) and *IL-8* ($r=0.360$; $p=0.026$). Figure 2 graphically shows a statistically significant correlation.

DISCUSSION

The cytokine profile of various biological fluids, especially PF, is altered in ovarian endometriosis. We demonstrated a significant correlation between PF and salivary levels of *IL-6* and *IL-8*. In the future, salivary cytokine levels may be used as a non-invasive diagnostic test for endometriosis.

Chronic inflammation plays a key role in the development and progression of endometriosis; both pro- and anti-inflammatory cytokines are involved in the disease pathogenesis [9]. Analysis of the cytokine profile in patients with cystic endometriosis demonstrated a weak positive direct correlation between PF and salivary levels of *IL-1β* (although the correlation coefficient in our study did not

Table 1. *IL* and *VEGF* levels (pg/ml) in peritoneal fluid and saliva

Parameter	Peritoneal fluid		Saliva	
	Me	Q1–Q3	Me	Q1–Q3
VEGF	239.5	184.2–313.6	963.6	242.6–1890.0
IL-1β	0.164	0.164–0.164	88.5	28.8–235.8
IL-6	29.4	6.3–128.4	0.726	0.726–0.726
IL-8	21.9	8.8–153.6	127.9	79.1–208.7
IL-10	16.9	8.4–27.6	0.42	0.20–0.63
TNF-α	3.7	3.7–3.7	0.01	0.01–0.01

achieve statistically significant levels). *IL-1β* is a potent pro-inflammatory cytokine produced primarily by monocytes and macrophages. There are some physiological and pathological effects attributed to *IL-1β* that may be associated with endometriosis. *IL-1β* induces prostaglandin synthesis and stimulates fibroblast proliferation, collagen deposition and fibrinogen formation, which could contribute to the fibrosis and adhesion formation associated with endometriosis [16]. In addition, *IL-1β* stimulates B-cell proliferation and antibody production, which could be related to the autoantibodies associated with the disease *IL-1β* also stimulates *IL-2* secretion by T cells and NK cells, which in turn can induce NK proliferation and T-cell growth [17].

IL-6 is the most investigated interleukin concerning endometriosis [18]. It is secreted in response to injury by various immune cells and participates in several immunological mechanisms. Many studies have demonstrated higher *IL-6* levels in serum, PF and follicular fluid in patients with endometriosis compared to healthy women. *IL-6* is a macrophage activator that enhances angiogenesis, promotes endometrial cell proliferation, and may regulate its immune environment. Therefore, elevated *IL-6* levels are thought to contribute to endometriosis-associated infertility. *IL-6* family proteins, especially leukemia inhibitory factor, also play an important role in the early stages of implantation, and one hypothesis is that their decreased expression may cause endometriosis-associated infertility [18–20]. A direct correlation between salivary and PF levels of *IL-6* was demonstrated.

IL-8 also plays an important role in the development and progression of endometriosis [11]. Our study demonstrated a statistically significant positive correlation between PF and salivary levels of IL-8. *IL-8* is a potent angiogenic, pro-inflammatory and cell proliferative cytokine found in the PF of patients with endometriosis. *IL-8*, which promotes endometrial cell adhesion, is secreted by leukocytes, macrophages, and endothelial cells stimulated by *IL-1β* or *TNF-α*. Studies evaluating *IL-8* levels in the PF found higher IL-8 levels in patients with endometriosis associated with infertility [21].

TNF-α levels are also being actively investigated in patients with endometriosis [13]. However, our study showed low salivary levels of *TNF-α*. In most cases, it was below the sensitivity threshold of the test system. Therefore, currently, it does not seem promising to measure salivary levels of TNF-α.

IL-10 is an anti-inflammatory interleukin produced by type-2 T helpers [13]. We found a positive direct correlation between PF and salivary levels of *IL-10*, but it was not statistically significant. In addition, in many cases, salivary levels of IL-10 were below the sensitivity threshold of the test system.

VEGF plays an important role in the neovascularization of new endometriotic implants [22]. A negative relationship was found between PF and salivary levels of *VEGF*, but it was not statistically significant.

Our findings for inflammatory markers are largely consistent with those of other investigators [8, 13]. Detectable salivary levels of inflammatory markers are relatively high, sometimes higher than blood levels, indicating the unique role of saliva in the assessment of inflammatory markers [23, 24]. However, we did not find any medical research showing an association between salivary levels of inflammatory markers and endometriosis. The significant correlation between PF and salivary levels of inflammatory cytokines that we found in women with cystic ovarian endometriosis suggests the use of these markers as a non-invasive diagnostic test for external genital endometriosis. Salivary levels of *IL-6* and *IL-8* are the most promising tests in this regard.

Table 2. Correlation between the levels of study parameters in peritoneal fluid and saliva

Parameter	*r*	*p*
VEGF	-0.130	0.436
IL-1β	0.100	0.546
IL-6	0.548	0.002*
IL-8	0.360	0.026*
IL-10	0.234	0.158

* The differences are statistically significant (p <0,05).

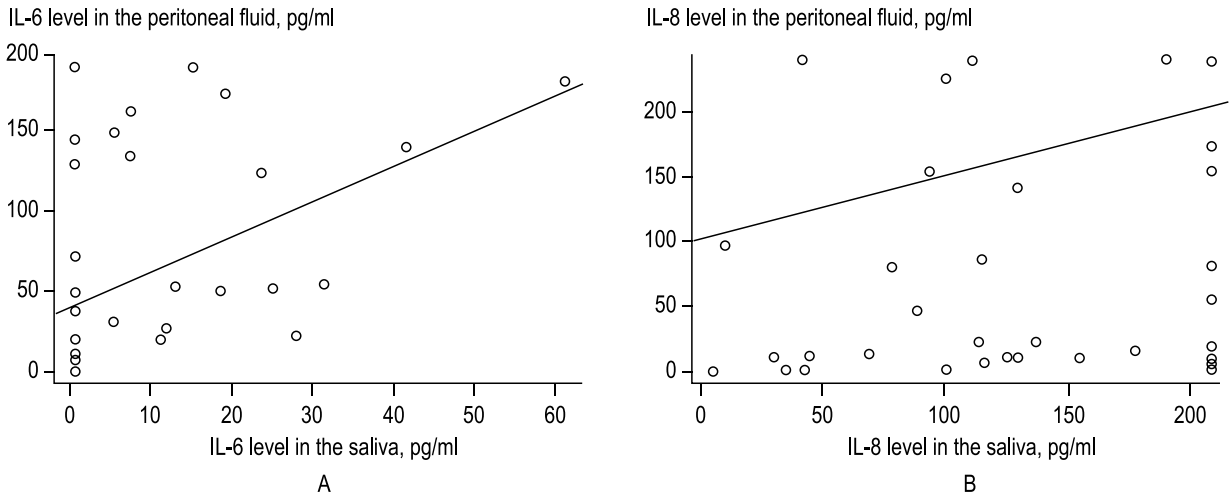

Fig. 2. Correlations of IL-6 (A) and IL-8 (B) levels in the peritoneal fluid and saliva

Study limitations

Based on our data, the use of a larger sample may yield statistically significant results for other parameters. A limitation of our study is the lack of a control group, since it is not ethical to refer healthy women for laparoscopy to obtain PF.

CONCLUSION

Our findings suggest that with the development and progression of endometriosis, levels of inflammatory cytokines increase in both PF and saliva and may be used to diagnose and assess the severity of endometriosis. Salivary levels of *IL-6* and *IL-8* can be used in clinical practice in patients with external genital endometriosis.

ADDITIONAL INFO

Authors' contributions. Ya.A. Mangileva reviewed literature data, collected and analyzed literature sources, wrote and edited the manuscript; E.V. Kudryavtseva reviewed literature data, collected and analyzed literature sources, wrote and edited the manuscript; L.G. Polushina collected and analyzed literature sources, prepared and wrote the manuscript; E.I. Shakiryanova performed surgical treatment of patients, reviewed the literature, collected and analyzed literature sources, prepared and wrote the manuscript; N.N. Potapov performed surgical treatment of patients, reviewed the literature, collected and analyzed literature sources, prepared and wrote the manuscript; V.V. Kovalev performed surgical treatment of patients, reviewed the literature, collected and analyzed literature sources, prepared and edited the manuscript. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made a significant contribution to the development of the concept, research and preparation of the article, read and approved the final version before publication).

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declares that there are no obvious and potential conflicts of interest associated with the publication of this article.

Patients' consent. Written consent was obtained from all the study participants before the study screening in according to the study protocol approved by the local ethic committee.

REFERENCES

1. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open*. 2022;2022(2):hoac009. doi: 10.1093/hropen/hoac009
2. Adamyan LV, Andreeva EN. Endometriosis and its global impact on a woman's body. *Russian Journal of Human Reproduction*. 2022;28(1):54–64. EDN: ELOTDZ doi: 10.17116/repro20222801154
3. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020;382(13):1244–1256. doi: 10.1056/NEJMra1810764
4. Sukhikh GT, Serov VN, Adamyan LV, et al. Algorithms for the management of patients with endometriosis: an agreed position of experts from the Russian Society of Obstetricians and Gynecologists. *Akusherstvo i Ginekologiya*. 2023;(5):159–176. EDN: DTJOZV doi: 10.18565/aig.2023.132
5. Glushich SYU, Lasachko SA, Rykov AA, et al. Review of recent data of etiopathogenesis and methods for diagnosing endometriosis (literature review). *Medical and social problems of the family*. 2020;25(4):54–68. EDN: IXQCRC
6. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet*. 2021;397(10276):839–852. doi: 10.1016/S0140-6736(21)00389-5
7. Orazov MR, Radzinsky VE, Khamoshina MB, et al. Endometriosis-associated infertility: from myths to harsh reality. *Difficult Patient*. 2019;17(1-2):6–12. EDN: WAJZQN doi: 10.24411/2074-1995-2019-10001
8. Symons LK, Miller JE, Kay VR, et al. The immunopathophysiology of endometriosis. *Trends Mol Med*. 2018;24(9):748–762. doi: 10.1016/j.molmed.2018.07.004
9. de Fáveri C, Fermino PMP, Piovezan AP, Volpato LK. The inflammatory role of pro-resolving mediators in endometriosis: an integrative review // Int J Mol Sci. 2021;22(9):4370. doi: 10.3390/ijms22094370
10. Ramírez-Pavez TN, Machado-Linde F, García-Peñarrubia P, et al. Optimization of peritoneal fluid and leukocyte collection in patients with endometriosis. *Fertil Steril*. 2023;120(4):917–919. doi: 10.1016/j.fertnstert.2023.06.030
11. Kudryavtseva EV, Geets AV, Mangileva YaA, et al. Modern non-invasive diagnosis of endometriosis. *Ural Medical Journal*. 2023;22(4):140–147. EDN: CONKMJ doi: 10.52420/2071-5943-2023-22-4-140-147
12. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.e1–354.e12. doi: 10.1016/j.ajog.2018.12.039
13. Wang XM, Ma ZY, Song N. Inflammatory cytokines IL-6, IL-10, IL-13, TNF-α and peritoneal fluid flora were associated with infertility in patients with endometriosis. *Eur Rev Med Pharmacol Sci*. 2018;22(9):2513–2518. doi: 10.26355/eurrev_201805_14899
14. Shields GS, Slavich GM, Perlman G, et al. The short-term reliability and long-term stability of salivary immune markers. *Brain Behav Immun*. 2019;81:650–654. doi: 10.1016/j.bbi.2019.06.007
15. Monnaka VU, Hernandes C, Heller D, Podgaec S. Overview of miRNAs for the non-invasive diagnosis of endometriosis: evidence, challenges and strategies. A systematic review. *Einstein (Sao Paulo)*. 2021;19:eRW5704. doi: 10.31744/einstein_journal/2021RW5704
16. Smolarz B, Szyłło K, Romanowicz H. Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature). *Int J Mol Sci*. 2021;22(19):10554. doi: 10.3390/ijms221910554
17. Kondera-Anasz Z, Sikora J, Mielczarek-Palacz A, Jońca M. Concentrations of interleukin (IL)-1alpha, IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2005;123(2):198–203. doi: 10.1016/j.ejogrb.2005.04.019
18. Incognito GG, Di Guardo F, Gulino FA, et al. Interleukin-6 as a useful predictor of endometriosis-associated infertility: a systematic review. *Int J Fertil Steril*. 2023;17(4):226–230. doi: 10.22074/ijfs.2023.557683.1329
19. Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. *Endocr Rev*. 2019;40(4):1048–1079. doi: 10.1210/er.2018-00242
20. Allaire C, Bedaiwy MA, Yong PJ. Diagnosis and management of endometriosis. *CMAJ*. 2023;195(10):E363–E371. doi: 10.1503/cmaj.220637
21. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. *BMJ*. 2022;379:e070750. doi: 10.1136/bmj-2022-070750
22. Nisenblat V, Bossuyt PM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. *Cochrane Database Syst Rev*. 2016;2016(5):CD012179. doi: 10.1002/14651858.CD012179
23. Nam Y, Kim YY, Chang JY, Kho HS. Salivary biomarkers of inflammation and oxidative stress in healthy adults. *Arch Oral Biol*. 2019;97:215–222. doi: 10.1016/j.archoralbio.2018.10.026
24. Szabo YZ, Slavish DC. Measuring salivary markers of inflammation in health research: A review of methodological considerations and best practices. *Psychoneuroendocrinology*. 2021;124:105069. doi: 10.1016/j.psyneuen.2020.105069

СПИСОК ЛИТЕРАТУРЫ

1. Becker C.M., Bokor A., Heikinheimo O., et al. ESHRE guideline: endometriosis // Hum Reprod Open. 2022. Vol. 2022, N 2. P. hoac009. doi: 10.1093/hropen/hoac009
2. Адамян Л.В., Андреева Е.Н. Эндометриоз и его глобальное влияние на организм женщины // Проблемы репродукции. 2022. Т. 28, № 1. С. 54–64. EDN: ELOTDZ doi: 10.17116/repro20222801154
3. Zondervan K.T, Becker C.M, Missmer S.A. Endometriosis // N Engl J Med. 2020. Vol. 382, N 13. P. 1244–1256. doi: 10.1056/NEJMra1810764
4. Сухих Г.Т, Серов В.Н., Адамян Л.В., и др. Алгоритмы ведения пациенток с эндометриозом: согласованная позиция экспертов Российского общества акушеров-гинекологов // Акушерство и гинекология. 2023. № 5. С. 159–76. EDN: DTJOZV doi: 10.18565/aig.2023.132
5. Глушич С.Ю, Ласачко С.А, Рыков А.А, Железная А.А. Обзор последних данных этиопатогенеза и методов диагностики эндометриоза (обзор литературы) // Медико-социальные проблемы семьи. 2020. Т. 25, № 4. С. 54–68. EDN: IXQCRC
6. Taylor H.S, Kotlyar A.M, Flores V.A. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations // Lancet. 2021. Vol. 397, N 10276. P. 839–852. doi: 10.1016/S0140-6736(21)00389-5
7. Оразов М.Р, Радзинский В.Е., Хамошина М.Б., и др. Бесплодие, ассоциированное с эндометриозом: от легенды к суровой реальности // Трудный пациент. 2019. Т. 17, № 1-2. С. 6–12. EDN: WAJZQN doi: 10.24411/2074-1995-2019-10001
8. Symons L.K, Miller J.E, Kay V.R., et al. The immunopathophysiology of endometriosis // Trends Mol Med. 2018. Vol. 24, N 9. P. 748–762. doi: 10.1016/j.molmed.2018.07.004
9. de Fáveri C., Fermino P.M.P., Piovezan A.P., Volpato L.K. The inflammatory role of pro-resolving mediators in endometriosis: an integrative review // Int J Mol Sci. 2021. Vol. 22, N 9. P. 4370. doi: 10.3390/ijms22094370
10. Ramírez-Pavez T.N., Machado-Linde F., García-Peñarrubia P., et al. Optimization of peritoneal fluid and leukocyte collection in patients with endometriosis // Fertil Steril. 2023. Vol. 120, N 4. P. 917–919. doi: 10.1016/j.fertnstert.2023.06.030
11. Кудрявцева Е.В., Геец А.В., Мангилева Я.А., и др. Современные неинвазивные методы диагностики эндометриоза // Уральский медицинский журнал. 2023. Т. 22, № 4. С. 140–147. EDN: CONKMJ doi: 10.52420/2071-5943-2023-22-4-140-147
12. Agarwal S.K., Chapron C., Giudice L.C., et al. Clinical diagnosis of endometriosis: a call to action // Am J Obstet Gynecol. 2019. Vol. 220, N 4. P. 354.e1–354.e12. doi: 10.1016/j.ajog.2018.12.039
13. Wang X.-M., Ma Z.-Y., Song N. Inflammatory cytokines IL-6, IL-10, IL-13, TNF-α and peritoneal fluid flora were associated with infertility in patients with endometriosis // Eur Rev Med Pharmacol Sci. 2018. Vol. 22, N 9. P. 2513–2518. doi: 10.26355/eurrev_201805_14899
14. Shields G.S., Slavich G.M., Perlman G., et al. The short-term reliability and long-term stability of salivary immune markers // Brain Behav Immun. 2019. Vol. 81. P. 650–654. doi: 10.1016/j.bbi.2019.06.007
15. Monnaka V.U., Hernandes C., Heller D., Podgaec S. Overview of miRNAs for the non-invasive diagnosis of endometriosis: evidence, challenges and strategies. A systematic review // Einstein (Sao Paulo). 2021. Vol. 19. P. eRW5704. doi: 10.31744/einstein_journal/2021RW5704
16. Smolarz B., Szyłło K., Romanowicz H. Endometriosis: epidemiology, classification, pathogenesis, treatment and genetics (review of literature) // Int J Mol Sci. 2021. Vol. 22, N 19. P. 10554. doi: 10.3390/ijms221910554
17. Kondera-Anasz Z., Sikora J., Mielczarek-Palacz A., Jońca M. Concentrations of interleukin (IL)-1alpha, IL-1 soluble receptor type II (IL-1 sRII) and IL-1 receptor antagonist (IL-1 Ra) in the peritoneal fluid and serum of infertile women with endometriosis // Eur J Obstet Gynecol Reprod Biol. 2005. Vol. 123, N 2. P. 198–203. doi: 10.1016/j.ejogrb.2005.04.019
18. Incognito G.G., Di Guardo F., Gulino F.A., et al. Interleukin-6 as a useful predictor of endometriosis-associated infertility: a systematic review // Int J Fertil Steril. 2023. Vol. 17, N 4. P. 226–230. doi: 10.22074/ijfs.2023.557683.1329
19. Bulun S.E., Yilmaz B.D., Sison C., et al. Endometriosis // Endocr Rev. 2019. Vol. 40, N 4. P. 1048–79. doi: 10.1210/er.2018-00242
20. Allaire C., Bedaiwy M.A., Yong P.J. Diagnosis and management of endometriosis // CMAJ. 2023. Vol. 195, N 10. P. E363–E371. doi: 10.1503/cmaj.220637
21. Horne A.W., Missmer S.A. Pathophysiology, diagnosis, and management of endometriosis // BMJ. 2022. Vol. 379. doi: 10.1136/bmj-2022-070750
22. Nisenblat V., Bossuyt P.M.M., Shaikh R., et al. Blood biomarkers for the non-invasive diagnosis of endometriosis // Cochrane Database Syst Rev. 2016. Vol. 2016, N 5. P. CD012179. doi: 10.1002/14651858.CD012179
23. Nam Y., Kim Y.-Y., Chang J.-Y., Kho H.-S. Salivary biomarkers of inflammation and oxidative stress in healthy adults // Arch Oral Biol. 2019. Vol. 97. P. 215–22. doi: 10.1016/j.archoralbio.2018.10.026
24. Szabo Y.Z., Slavish D.C. Measuring salivary markers of inflammation in health research: A review of methodological considerations and best practices // Psychoneuroendocrinology. 2021. Vol. 124. doi: 10.1016/j.psyneuen.2020.105069

AUTHORS' INFO

***Yana A. Mangileva,** Graduate Student;
address: 113 build. 2, Sheinkman Str., 620144 Yekaterinburg, Russia;
ORCID: 0000-0003-3413-1685;
eLibrary SPIN: 2388-0552;
e-mail: yanaamangileva@mail.ru

Elena V. Kudryavtseva, MD, Dr. Sci. (Medicine), Assistant Professor;
ORCID: 0000-0003-2797-1926;
eLibrary SPIN: 7232-3743;
e-mail: elenavladpopova@yandex.ru

Larisa G. Polushina, MD, Cand. Sci. (Medicine), Senior Research Associate;
ORCID: 0000-0002-4921-7222;
eLibrary SPIN: 4391-5873;
e-mail: polushina-larisa@bk.ru

Elvira I. Shakiryanova, Head of the Department of Planned Gynecology;
ORCID: 0009-0005-7306-4632;
e-mail: elechka175@mail.ru

Nikolay N. Potapov, MD, Cand. Sci. (Medicine);
ORCID: 0000-0002-0761-2785;
eLibrary SPIN: 5065-9485;
e-mail: poniknik@gmail.com

Vladislav V. Kovalev, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0001-8640-8418;
eLibrary SPIN: 2061-0704;
e-mail: vvkovalev55@gmail.com

*Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

***Мангилева Яна Андреевна,** аспирант;
адрес: Россия, 620144, Екатеринбург, ул. Шейнкмана, д. 113, корп. 2;
ORCID: 0000-0003-3413-1685;
eLibrary SPIN: 2388-0552;
e-mail: yanaamangileva@mail.ru

Кудрявцева Елена Владимировна, д-р мед. наук, доцент;
ORCID: 0000-0003-2797-1926;
eLibrary SPIN: 7232-3743;
e-mail: elenavladpopova@yandex.ru

Полушина Лариса Георгиевна, канд. мед. наук, старший научный сотрудник;
ORCID: 0000-0002-4921-7222;
eLibrary SPIN: 4391-5873;
e-mail: polushina-larisa@bk.ru

Шакирьянова Эльвира Ильсеновна, зав. отделением плановой гинекологии;
ORCID: 0009-0005-7306-4632;
e-mail: elechka175@mail.ru

Потапов Николай Николаевич, канд. мед. наук;
ORCID: 0000-0002-0761-2785;
eLibrary SPIN: 5065-9485;
e-mail: poniknik@gmail.com

Ковалёв Владислав Викторович, д-р мед. наук, профессор;
ORCID: 0000-0001-8640-8418;
eLibrary SPIN: 2061-0704;
e-mail: vvkovalev55@gmail.com