СПИСАНИЕ НА МАКЕДОНСКОТО ЛЕКАРСКО ДРУШТВО
Мак. мед. преглед, 2024; 78(3)

JOURNAL OF THE MACEDONIAN MEDICAL ASSOCIATION
Mac. Med. Preview, 2024; 78(3)

UDK: 61+061.231=866=20 CODEN: MKMPA3 ISSN: 0025-1097

Македонски Медицински Преглед

Macedonian Medical Review

Основано 1946
Founded 1946

www.mld.mk

3/24

MMP

Мак Мед Преглед

Списание на Македонското лекарско друштво

Journal of the Macedonian Medical Association

Наслов на Редакцијата и Издавачот / Address of the Editorial Office and Administration:
1000 Скопје, Даме Груев 3, Градски зид блок 2
tel. 02/3162 577
www.mld.org.mk / mld@unet.com.mk
Жиро сметка / Bank Account
300000000211884 - Komercijalna banka Skopje

Печати: Бранко Гапо графичко производство - Скопје

Македонски медицински преглед се печати три пати годишно. Претплатата за списанието изнесува 10 евра за лекари, 50 ера за установа, странство 80 евра.

Основано 1946 Founded 1946

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ETHICAL AND LEGAL ISSUES IN TELEMEDICINE APPLICATIONS: A COMPREHENSIVE REVIEW

ЕТИЧКИ И ПРАВНИ ПРАШАЊА ВО ТЕЛЕМЕДИЦИНСКИТЕ АПЛИКАЦИИ: СЕОПФАТЕН ПРЕГЛЕД

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Abstract

Introduction. Telemedicine has rapidly evolved into a core component of modern healthcare delivery, expanding access and continuity of care, particularly during the COVID-19 pandemic. However, its accelerated adoption has raised ethical and legal concerns regarding patient autonomy, data security, consent, and professional responsibility.
Aim. This review examines the ethical and legal dimensions of telemedicine, emphasizing autonomy, beneficence, non-maleficence, justice, confidentiality, and liability. It focuses on current frameworks in Turkey and the European Union, including the *Regulation on the Provision of Remote Health Services* (2022) and the *Law on the Protection of Personal Data (KVKK No. 6698)*.
Methods. A narrative review was conducted using PubMed, Scopus, and legal databases, along with WHO, WMA, and national policy documents. Ethical and legal themes were analyzed in relation to real-world telemedicine practice.
Results. Telemedicine adheres to the same ethical standards as conventional care but requires new safeguards for virtual contexts. Core challenges include ensuring valid informed consent, protecting confidentiality in digital systems, clarifying professional boundaries, and addressing disparities in access. Legally, telemedicine faces gaps in defining cross-border jurisdiction, liability sharing, and evidentiary standards for digital records**.**
Conclusion. Telemedicine can transform healthcare accessibility and efficiency if accompanied by strong ethical oversight and legal harmonization. Clear institutional protocols, secure data management, and patient-centered design are essential to uphold trust and professional integrity in digital medicine.

Keywords: telemedicine, ethics, law, data protection, informed consent, malpractice, privacy, Turkey

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Апстракт

Вовед. Телемедицината брзо се разви во клучна компонента на современото здравство, овозможувајќи поголем пристап и континуитет на грижата, особено за време на пандемијата со COVID-19. Сепак, нејзината забрзана примена отвори бројни етички и правни прашања поврзани со автономијата на пациентот, безбедноста на податоците, информираната согласност и професионалната одговорност.
Цел. Овој преглед ги анализира етичките и правните димензии на телемедицината, со акцент на принципите на автономија, добротворност, ненанесување штета, правичност, доверливост и одговорност. Фокусот е ставен на актуелните регулаторни рамки во Турција и Европската Унија, вклучувајќи го *Правилникот за обезбедување на здравствени услуги на далечина* (2022) и *Законот за заштита на личните податоци (KVKK бр. 6698).*
Методи. Спроведен е наративен преглед користејќи ги базите PubMed, Scopus и правни извори, како и документи на СЗО, СМА и национални политики. Етичките и правните теми се анализирани во контекст на практичната примена на телемедицината.
Резултати. Телемедицината се заснова на истите етички стандарди како и традиционалната здравствена грижа, но бара нови механизми за нивна примена во виртуелна средина. Клучните предизвици вклучуваат обезбедување валидна информирана согласност, заштита на доверливоста во дигиталните системи, јасно дефинирање на професионалните граници и надминување на нееднаквиот пристап до технологија. Правно, телемедицината се соочува со празнини во дефинирањето на прекуграничната надлежност, распределбата на одговорноста и доказната вредност на електронските записи.
Заклучок. Телемедицината може суштински да ја трансформира достапноста и ефикасноста на здравствената заштита, доколку биде придружена со силен етички надзор и усогласена правна рамка. Јасните институционални протоколи, безбедното управување со податоци и дизајнот ориентиран кон пациентот се неопходни за зачувување на довер-

бата и професионалниот интегритет во дигиталната медицина.

Клучни зборови: телемедицина, етика, право, заштита на податоци, информирана согласност, малпрактис, приватност, Турција

Introduction

Telemedicine, the remote delivery of healthcare using information and communication technologies, has transformed the traditional physician-patient interaction. It bridges geographical barriers, reduces waiting times, and allows for remote diagnosis, monitoring, and consultation. However, the rapid digitalization of healthcare introduces ethical and legal dilemmas concerning professional responsibility, patient autonomy, and data security. International organizations such as the World Medical Association (WMA) and the World Health Organization (WHO) emphasize that telemedicine must follow the same ethical principles as traditional medicine [1,2].

In Turkey, the **Regulation on the Provision of Remote Health Services** (published in the Official Gazette on 10 February 2022, No. 31746) formally established the legal framework for telemedicine. Nonetheless, questions remain regarding informed consent, malpractice liability, and compliance with the **Personal Data Protection Law (KVKK No. 6698)** [3].

Ethical Dimensions of Telemedicine

Physician-Patient Relationship

The physician-patient relationship is the ethical cornerstone of medical practice. In telemedicine, physical distance can weaken empathy and clinical judgment. The WMA states that teleconsultations must be clinically appropriate and should not replace in-person visits when a physical examination is required [1,4]. Physicians must ensure continuity of care, transparency about limitations, and readiness to refer patients for face-to-face evaluation when necessary.

Informed Consent

Informed consent in telemedicine must include details about the nature of the remote service, possible risks (technical failures, data breaches, miscommunication), and data-handling procedures. Consent should be explicit, voluntary, and documented prior to the session. Ethical practice requires that patients understand the constraints of virtual interaction and have the right to refuse telemedicine without compromising access to in-person care [5,6].

Privacy and Data Confidentiality

Health data are classified as *special categories of personal data* under both the **EU General Data Protection Regulation (GDPR)** and Turkey's **KVKK**. Physicians and healthcare institutions are responsible for ensuring confidentiality through encryption, secure transmission, restricted access, and data minimization principles [7]. Any data processor (e.g., software provider) must sign a *data-processing agreement* defining roles, responsibilities, and retention periods [8].

Digital Divide and Equity

Although telemedicine increases access to healthcare for remote or disabled populations, it may exacerbate inequities for individuals lacking digital literacy or reliable internet access. Ethical justice requires the design of inclusive systems that provide alternative channels, such as telephone consultations, for underserved populations [9].

Professional Boundaries and Documentation

Telemedicine introduces new communication modes (chat, email, mobile apps), challenging traditional professional boundaries. Physicians should establish clear communication policies and maintain comprehensive, time-stamped records of all interactions, as incomplete documentation can increase malpractice risk [10].

Artificial Intelligence and Decision Support

AI-based triage or diagnostic systems are increasingly integrated into telehealth platforms. However, algorithmic decision-making must remain *assistive*, not *determinative*. Physicians retain ultimate responsibility for clinical decisions. Bias, explainability, and accountability of AI systems are major ethical concerns [11].

Legal Framework

National Regulations

The Turkish **Regulation on the Provision of Remote Health Services (2022)** defines who may provide telemedicine, under which technological infrastructure, and how patient identification, prescription, referral, and emergency management must be handled [3]. The regulation requires institutions to record all teleconsultations and to comply with relevant data-protection laws.

Data Protection and Cybersecurity

According to **KVKK** and the **Regulation on the Processing and Protection of Personal Health Data**,

healthcare providers must:

- Process only necessary data for specific, lawful purposes,
- Obtain explicit consent, unless an exception applies,
- Implement technical and administrative security measures,
- Define retention and destruction policies,
- Conduct regular compliance audits [7,8].

Violations of data-protection rules can result in administrative fines and criminal liability.

Cross-Border Services

Telemedicine across borders raises issues of medical licensure, jurisdiction, and data transfer. Under international law, practitioners are typically bound by the regulations of the country where the patient is located. Hence, institutions must verify cross-border compliance and ensure that personal data transferred abroad meet adequate protection standards [12].

Malpractice and Professional Liability

Legal liability in telemedicine follows the same principles as conventional care. Physicians may be held responsible for negligence, misdiagnosis, or delayed treatment resulting from technical or procedural errors. Courts evaluate whether the standard of care was maintained, considering the available technology and established protocols [13,14]. Proper documentation and adherence to clinical guidelines are key defenses against malpractice claims.

Common Ethical–Legal Scenarios in Practice

Table 1. Common Ethical–Legal Scenarios in Practice

Scenario	Potential Risk	Recommended Mitigation
Patient identity not verified	Wrong-person consultation	Two-factor ID verification [3]
Consultation in non-private setting	Breach of confidentiality	Confirm environment privacy before session [6]
Low video/audio quality	Misdiagnosis	Define threshold for in-person referral [4]
Cloud storage without agreement	Unauthorized data access	Data-processing contract and encryption [8]
Incomplete documentation	Legal indefensibility	Timestamped electronic records [10]

Compliance and Risk Management Recommendations

- **Ethical Oversight:** Implement institutional ethics committees for telehealth policies.
- **Legal Compliance:** Align procedures with the 2022 Telemedicine Regulation, KVKK, and GDPR.
- **Consent Protocols:** Use standardized informed consent forms with clear explanations of risks and data handling.
- **Technical Safeguards:** Adopt end-to-end encryption, secure servers, and routine security audits.
- **Education:** Train healthcare professionals in digital ethics, privacy law, and telecommunication etiquette.
- **Audit and Quality Control:** Establish periodic reviews of consultation records, AI tools, and compliance documentation.
- **Accessibility:** Provide alternative methods for digitally disadvantaged populations.

Discussion

The ethical and legal implications of telemedicine represent a rapidly evolving area at the intersection of healthcare, technology, and law. As telemedicine becomes increasingly integrated into mainstream health systems, it is vital to ensure that innovation does not outpace ethical reasoning or legal safeguards. The ethical foundation of telemedicine remains grounded in the four classical principles of biomedical ethics: **beneficence**, **non-maleficence**, **autonomy**, and **justice**. Yet, their interpretation and application in virtual environments introduce new complexities that demand nuanced understanding and continuous evaluation.

Beneficence and Non-maleficence in telemedicine are challenged by the absence of direct physical examination and potential limitations of virtual assessments. While telemedicine enhances access and efficiency, it may also increase the risk of misdiagnosis due to poor video quality, incomplete data, or technological malfunction. Ethical beneficence therefore requires that telemedicine be used only when it truly benefits the patient and does not compromise diagnostic accuracy or safety. Physicians must remain vigilant in evaluating when a case is appropriate for remote management and when in-person evaluation is indispensable.

Autonomy in telemedicine must be reinforced through transparent communication and valid informed consent. Patients need to understand the scope, limitations, and potential risks of remote consultation, including privacy concerns, technical constraints, and data usage. The ethical obligation to respect patient autonomy extends to ensuring their right to withdraw consent, request face-to-face care, and control how their personal data are processed. However, the digital divide-differences in technological literacy, access to internet, or socioeconomic barriers-can limit true autonomy by constraining choice. Addressing these inequities is essential to uphold ethical fairness.

Justice, the principle of fairness and equal access, is particularly significant in telemedicine. While digital health technologies can democratize healthcare by reaching rural, disabled, or underserved populations,

they can also deepen disparities if not accompanied by infrastructural and educational support. Governments and institutions should develop inclusive telehealth policies that promote accessibility, subsidize necessary equipment, and provide multilingual or disability-adapted interfaces. Ethical justice in telemedicine requires proactive efforts to prevent exclusion of vulnerable groups.

From a **legal perspective**, telemedicine introduces both opportunities and uncertainties. National frameworks such as Turkey's *Regulation on the Provision of Remote Health Services* (2022) and the *Law on the Protection of Personal Data (KVKK No. 6698)* provide essential foundations for licensure, service authorization, and data protection. Yet, these laws must continue to evolve to reflect the realities of cross-border consultations, AI-assisted diagnostics, and the integration of third-party software providers. Key unresolved questions include the **definition of jurisdiction** when physician and patient are in different countries, the **legal validity and evidentiary weight of electronic health records**, and the **allocation of liability** among healthcare providers, institutions, and technology vendors when technical failures occur.

Furthermore, **malpractice liability** in telemedicine remains an underexplored area. Courts must determine whether the standard of care should mirror traditional in-person medicine or be adjusted for telehealth's inherent constraints. The absence of clear jurisprudence creates uncertainty for practitioners, potentially discouraging telemedicine adoption. A harmonized international legal framework, potentially guided by the WHO and EU recommendations, could mitigate such ambiguities and facilitate safe cross-border practice.

Data protection and cybersecurity are also central to maintaining public trust. Health data represent one of the most sensitive forms of personal information, and breaches can have profound ethical, legal, and reputational consequences. Compliance with KVKK, GDPR, and institutional cybersecurity standards must not be treated as mere formalities but as ongoing ethical commitments. Healthcare organizations should implement strong encryption, secure authentication, and transparent data governance structures, along with regular staff training and audits.

Another important dimension involves the **integration of artificial intelligence (AI)** into telemedicine platforms. AI can enhance diagnostic precision and resource allocation, yet it raises ethical concerns about algorithmic bias, explainability, and accountability. Ensuring that AI functions as a *decision-support* rather than a *decision-making* tool preserves the physician's moral and legal responsibility while safeguarding patient welfare.

Ultimately, the long-term sustainability of telemedicine depends on **education, interdisciplinary collaboration, and adaptive policy-making**. Physicians must receive continuous training in digital ethics, data protection, and communication in virtual settings. Legal experts, engineers, and ethicists should collaborate to design systems that are not only compliant but also ethically transparent and user-centered. Policymakers should anticipate technological evolution by creating flexible regulations that can adapt without compromising core ethical standards.

In conclusion, telemedicine offers a transformative pathway for global healthcare accessibility and efficiency. Yet, without a robust ethical and legal foundation, its benefits risk being undermined by mistrust, inequality, and misuse. The future of telemedicine must therefore rest on **integrity, transparency, accountability, and respect for human dignity,** principles that transcend technology and remain central to the art of medicine itself.

Conclusion

Telemedicine has progressed from an experimental adjunct to a fundamental pillar of contemporary healthcare. Its capacity to bridge geographical barriers, optimize resource utilization, and empower patients to actively participate in their care represents a profound transformation of the medical landscape. Yet this transformation also imposes new responsibilities on healthcare professionals, institutions, and regulators. As medicine increasingly intersects with technology, ethical reflection and legal preparedness must evolve in parallel to innovation.

The future success of telemedicine depends on maintaining the delicate balance between innovation and integrity. Ethical vigilance is essential to ensure that convenience and efficiency do not overshadow patient welfare or professional accountability. Physicians must remain committed to the classical principles of beneficence, non-maleficence, autonomy, and justice, translating them into digital practice through transparent communication, responsible data use, and continuous patient engagement. Informed consent should not be reduced to a formality but serve as an interactive process that reinforces patient understanding and autonomy in the virtual setting.

From a legal perspective, the establishment of comprehensive and harmonized regulatory frameworks, both nationally and internationally, is critical. Telemedicine operates across borders, making cooperation among jurisdictions inevitable. Laws must clearly define provider licensure, cross-border liability, and standards for electronic documentation and cybersecurity. Health authorities should develop certification mechanisms for telehealth platforms to guarantee technical reliability, data protection, and ethical compliance.

Institutional support also plays a decisive role. Hospitals and health ministries should invest in secure digital infrastructures, training programs on telemedical ethics and privacy, and interdisciplinary committees capable of auditing and improving telehealth services.

Continuous professional development, coupled with public awareness campaigns, can strengthen trust between patients and providers. Moreover, equitable access must remain a policy priority; telemedicine should narrow, not widen, existing disparities in healthcare access. Ultimately, telemedicine is not merely a technological innovation but a redefinition of the physician–patient relationship. Its success will be measured not only by speed and efficiency but by its ability to preserve compassion, confidentiality, and professional integrity in an increasingly digital world. The long-term vision should be to integrate telemedicine seamlessly into healthcare systems as an ethically governed, legally secure, and patient-centered modality of care. Through transparent governance, continuous education, and adherence to shared human values, telemedicine can fulfill its promise as a safe, equitable, and transformative force in global health.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 132-135

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Original article

EVALUATION OF HEALTH-RELATED QUALITY OF LIFE USING ST GEORGE'S RESPIRATORY QUESTIONNAIRE BEFORE AND AFTER PULMONARY REHABILITATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A PROSPECTIVE STUDY

ЕВАЛУАЦИЈА НА КВАЛИТЕТОТ НА ЖИВОТ ПОВРЗАН СО ЗДРАВЈЕТО СО КОРИСТЕЊЕ НА РЕСПИРАТОРНИОТ ПРАШАЛНИК НА „СВ. ЃОРЃИ„ ПРЕД И ПО ПУЛМОНАЛНА РЕХАБИЛИТАЦИЈА КАЈ ПАЦИЕНТИ СО ХРОНИЧНА ОПСТРУКТИВНА БЕЛОДРОБНА БОЛЕСТ: ПРОСПЕКТИВНА СТУДИЈА

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Abstract

Introduction. Chronic obstructive pulmonary disease (COPD) significantly impairs health-related quality of life (HRQoL). Pulmonary rehabilitation (PR) is a cornerstone intervention shown to improve clinical and functional outcomes.
Aim. To evaluate changes in HRQoL using the St George's Respiratory Questionnaire (SGRQ) before and after a standardized 4-week PR program in COPD patients.
Methods. A prospective observational study was conducted involving 32 patients with moderate to severe COPD (GOLD stage II–IV). Participants underwent a four-week PR program and completed the SGRQ at baseline and post-intervention. Statistical analysis assessed pre/post changes.
Results. The mean total SGRQ score improved significantly from 56.3±10.2 to 44.1±8.7 (Δ=-12.2±6.4; p< 0.001). Domain-specific improvements were also significant: Symptoms (Δ=-11.5±5.3), Activity (Δ=-13.7±6.8), and Impacts (Δ=-11.0±6.1).
Conclusion. PR significantly improves HRQoL in COPD patients. The SGRQ proved sensitive in capturing these changes, affirming its utility in clinical evaluation.

Keywords: COPD, pulmonary rehabilitation, SGRQ, quality of life, HRQoL, rehabilitation outcomes

Апстракт

Вовед. Хроничната опструктивна белодробна болест (ХОББ) значително го нарушува квалитетот на живот поврзан со здравјето (HRQoL). Пулмоналната рехабилитација (PR) е камен-темелник интервенција за која е докажано дека ги подобрува клиничките и функционалните исходи.
Цел. Да се проценат промените во HRQoL користејќи го прашалникот за респираторни проблеми на Св. Ѓорѓи [1] (SGRQ) пред и по стандардизирана 4-неделна програма за PR кај пациенти со ХОББ.
Методи. Беше спроведена проспективна опсервациска студија во која учествуваа 32 пациенти со умерена до тешка ХОББ (GOLD стадиум II–IV). Учесниците беа подложени на четиринеделна програма за PR и го завршија SGRQ на почетокот и по интервенцијата. Статистичката анализа ги процени промените пред/после.
Резултати. Просечниот вкупен резултат на SGRQ значително се подобри од 56,3±10,2 на 44,1±8,7 (Δ=-12,2±6,4; p<0,001). Подобрувањата специфични за доменот беа исто така значајни: Симптоми (Δ=-11,5±5,3), Активност (Δ=-13,7±6,8) и Влијанија (Δ=-11,0±6,1).
Заклучок. PR значително го подобрува HRQoL кај пациенти со ХОББ. SGRQ се покажа чувствителен во евидентирањето на овие промени, потврдувајќи ја неговата корисност во клиничката евалуација.

Клучни зборови: ХОББ, белодробна рехабилитација, SGRQ, квалитет на живот, HRQoL, резултати од рехабилитација

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, chronic respiratory symptoms, and structural lung changes, leading to substantial morbidity, mortality, and impaired health-related quality of life among affected individuals [1-4]

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Management strategies increasingly emphasize interventions that improve patient-centered outcomes, particularly health-related quality of life, recognizing that symptom burden, functional limitation, and psychosocial impacts represent core dimensions of disease severity in COPD. [5]

Pulmonary rehabilitation (PR) has emerged as a highly effective non-pharmacological therapy. It combines structured exercise training, patient education, and psychological support to alleviate symptoms, reduce functional disability, and enhance daily functioning in individuals with COPD. [6-10]

The St George's Respiratory Questionnaire (SGRQ) is a validated and widely used instrument for assessing health-related quality of life in patients with chronic respiratory diseases, providing standardized measurements across Symptoms, Activity, and Impacts domains [11-14].

Comprising three domains-Symptoms, Activity, and Impacts-the SGRQ quantifies patient-reported burden across clinical, physical, and psychosocial dimensions. Numerous studies have confirmed its sensitivity to change and robust responsiveness to interventions such as pulmonary rehabilitation, establishing it as a benchmark instrument in both research and clinical practice [8,15]

Material and methods

This prospective observational study was conducted at the Center of Pulmonary Rehabilitation, Leshok, North Macedonia, from April to July 2024. Inclusion criteria comprised patients aged ≥40 years with confirmed COPD (post-bronchodilator $FEV_1/FVC<0.70$), GOLD stages II–IV, and clinical stability for ≥4 weeks. Exclusion criteria included acute exacerbation within four weeks or comorbidities that precluded physical activity. Participants underwent a four-week PR program consisting of thrice-weekly sessions including aerobic and resistance training, respiratory physiotherapy, and educational modules. The Macedonian version of the SGRQ was administered pre- and post-program by trained clinicians. Statistical analysis included paired t-tests ($\alpha = 0.05$) using STATISTICA 12 software. Clinically meaningful improvement was defined as a ≥4-point reduction in the total SGRQ score.

Results

A total of 32 patients completed the study (20 men, 12 women; mean age: 66.4±7.8 years). The average smoking history was 38.6±9.4 pack-years. Most patients (90.6%) reported low to middle economic status and had a median of two comorbidities, including hypertension and diabetes.

Table 1. Demographic data

Characteristic	Value
Total participants	32
Sex distribution	20 men (62.5%), 12 women (37.5%)
Mean age (±SD)	66.4±7.8 years
Smoking history (mean±SD)	38.6±9.4 pack-years
Median comorbidities (IQR)	2(IQR: 1–3)
Common comorbidities	Hypertension, Type 2 Diabetes, CVD
Economic status	Low: 13(40.6%) Middle: 16(50%) High: 3(9.4%)
COPD severity	All with moderate to severe COPD (GOLD II-IV)
Clinical status at baseline	All clinically stable

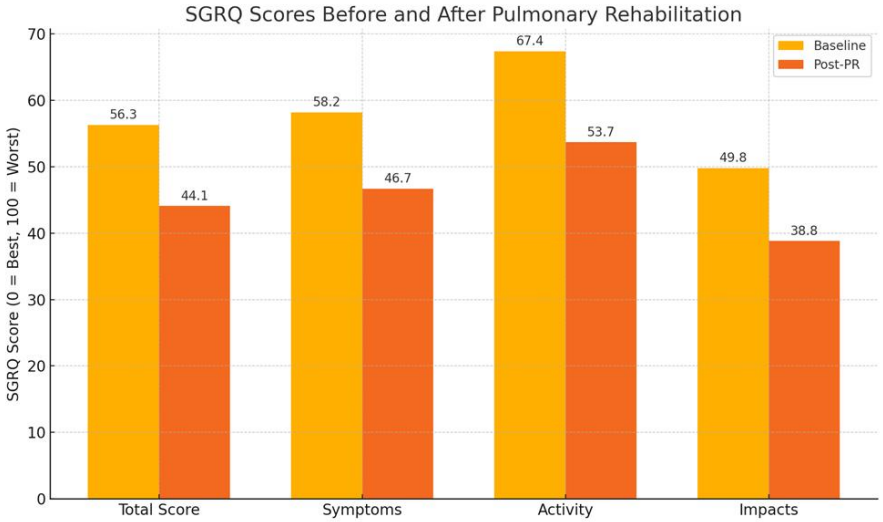

Fig. 1. Mean SGRQ Scores Before and After Pulmonary Rehabilitation

The total SGRQ score improved significantly from 56.3±10.2 to 44.1±8.7 (Δ=-12.2±6.4; p<0.001). Domain-specific improvements were observed: symptoms (Δ=-11.5±5.3), activity (Δ=-13.7±6.8), and impacts (Δ=-11.0±6.1; p=0.002).

Discussion

This study demonstrated that a structured, multidisciplinary pulmonary rehabilitation (PR) program led to significant and clinically meaningful improvements in health-related quality of life (HRQoL) among patients with moderate to severe COPD, consistent with evidence from previous randomized trials and meta-analyses showing that PR reliably enhances disease-specific health status as measured by validated instruments such as the SGRQ [6-8,16]

The reductions observed across all SGRQ domains indicated comprehensive benefits, reflecting improved symptom control, enhanced physical capacity, and better psychosocial well-being, consistent with prior evidence demonstrating the multidimensional efficacy of pulmonary rehabilitation in COPD [17,18].

These findings align with existing literature affirming the efficacy of pulmonary rehabilitation. McCarthy *et al*. [8] and Puhan *et al*. [19] have demonstrated that PR significantly enhances exercise tolerance, alleviates respiratory symptoms, and contributes to reductions in exacerbations and hospitalizations, underscoring its central role in comprehensive COPD management.

The observed 12.2-point reduction in the total SGRQ score substantially exceeds the established minimum clinically important difference (MCID) of approximately 4 points, underscoring the robust and clinically meaningful impact of the intervention [14].

Notably, younger patients and those with fewer comorbidities demonstrated greater improvement, consistent with previous evidence indicating that individuals with lower baseline disease burden and better physiological reserve tend to derive the greatest benefit from pulmonary rehabilitation. [7] [20]

The absence of a control group and the limited duration of follow-up represent key methodological limitations, constraining the ability to attribute observed improvements solely to the intervention and to determine the persistence of benefits over time.

Future randomized controlled trials with larger sample sizes and extended follow-up periods are needed to validate these findings and more comprehensively assess the long-term sustainability of the observed benefits.

Conclusion

A four-week pulmonary rehabilitation program significantly improved health-related quality of life in patients with moderate to severe COPD, as measured by the SGRQ. The consistent improvements across symptoms, activity, and impacts domains highlight the holistic value of Pulmonary rehabilitation. These findings support the integration of Pulmonary rehabilitation PR as standard care in COPD management, especially in resource-limited settings.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 136-142

MMP

Original Article

METABOLIC VARIATIONS AMONG WOMEN WITH POLYCISTIC OVARY SYNDROME ACCORDING TO BODY MASS INDEX

МЕТАБОЛНИ ВАРИЈАЦИИ КАЈ ЖЕНИ СО ПОЛИЦИСТИЧНО ОВАРИЈАЛЕН СИНДРОМ СПОРЕД ИНДЕКСОТ НА ТЕЛЕСНА МАСА

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Abstract

Introduction. There is a two-way relationship between obesity and polycystic ovary syndrome (PCOS). Although most individuals with PCOS are overweight or obese, a notable number maintain a normal body mass index (BMI). The conventional diagnostic approach to PCOS, based on phenotypic characteristics, categorizes patients according to ovulatory function and androgen levels. The aim of this study was to compare clinical, metabolic, and endocrine parameters in lean and obese women diagnosed with PCOS.
Methods. This cross-sectional study enrolled a total of 89 women, aged between 18 and 40 years, diagnosed with PCOS based on the Rotterdam criteria. Participants were stratified into groups according to their BMI. Anthropometric measurements and venous blood samples were obtained for the evaluation of glucose metabolism, lipid profile, and selected endocrine parameters. Calculated indices included BMI, waist-to-height ratio (WHR), and the homeostasis model assessment of insulin resistance (HOMA-IR).
Results. Among the 89 women with PCOS included in the study, 39.3% were classified as lean, while 60.7% were categorized as obese. Regardless of phenotypic variation, obese PCOS patients exhibited significantly elevated BMI and WHR, alongside increased levels of luteinizing hormone (LH), LH/FSH ratio, and free androgen index (FAI), higher insulin concentrations, insulin resistance, and dyslipidemia. Conversely, lean women with PCOS maintained normal insulin levels, lacked clinically relevant insulin resistance, and presented with normal lipid profiles.
Conclusion. The results indicated significant differences in metabolic profiles between lean and obese patients with PCOS, regardless of phenotypic classification. Metabolic abnormalities were particularly pronounced in women with increased body weight, emphasizing the need for focused care and implementation of preventive measures aimed at reducing the risk of long-term health complications. These findings highlight the importance of early metabolic screening in all PCOS patients, along with a personalized approach to management based on individual characteristics.

Keywords: polycystic ovary syndrome (PCOS); body mass index; obesity; insulin resistance; metabolic profile

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Абстракт

Вовед. Постои двонасочна врска помеѓу дебелината и полицистичниот оваријален синдром (ПЦОС). Иако повеќето лица со ПЦОС имаат прекумерна или зголемена телесна тежина, значителен број од нив имаат нормален индекс на телесна маса (ИТМ). Вообичаениот дијагностички пристап кон ПЦОС, воден според фенотипските карактеристики, ги категоризира пациентките врз основа на овулаторната функција и нивото на андрогени. Оваа студија има за цел да спроведе компаративна анализа на клиничките, метаболните и ендокрините параметри кај слаби и дебели жени со дијагностициран ПЦОС.
Методи. Оваа пресечна студија опфати 89 жени на возраст од 18 до 40 години, кај кои полицистичниот оваријален синдром (ПКС) беше дијагностициран согласно Ротердамските критериуми. Учесничките беа класифицирани во групи според ИТМ. Извршени беа антропометриски мерења и земени венски крвни примероци за анализа на метаболизмот на гликозата, липидниот профил и избрани хормонски параметри. Пресметани беа ИТМ, соодносот половина-висина и индексот за инсулинска резистенција според моделот на хомеостаза (ХОМА-ИР).
Резултати. Од вкупно 89 жени со ПКС опфатени во студијата, 39.3% беа класифицирани како слаби, додека 60.7% беа категоризирани како дебели. Без оглед на фенотипските варијации, пациентките со

ПЦОС и дебелина покажаа значително покачен ИТМ и сооднос половина-висина, како и зголемени нивоа на лутеинизирачки хормон (ЛХ), односот ЛХ/ФСХ и индексот на слободни андрогени (ФАИ), повисоки концентрации на инсулин, зголемена инсулинска резистенција и дислипидемија. Жените со ПЦОС и нормален ИТМ имаа нормални нивоа на инсулин, без клинички значајна инсулинска резистенција и нормални липидни профили.
Заклучок. Резултатите укажуваат на значајни разлики во метаболичките профили помеѓу слаби и дебели пациентки со синдром на полицистични јајници, независно од фенотипската класификација. Метаболичките абнормалности се особено изразени кај жените со зголемена телесна тежина, што ја нагласува потребата од насочена грижа и имплементација на превентивни мерки со цел намалување на ризикот од долгорочни здравствени компликации. Наодите ја истакнуваат важноста на раното метаболичко скринирање кај сите пациентки со ПЦОС, заедно со персонализиран пристап во третманот според индивидуалните карактеристики.

Клучни зборови: Полицистичен оваријален синдром (ПЦОС), индекс на телесна маса, дебелина, инсулинска резистенција, метаболен профил

Introduction

In recent decades, obesity has emerged as one of the major global health challenges [1-2]. Increasing evidence suggests a complex connection between obesity and female reproductive health [3]. A major concern for women with polycystic ovary syndrome (PCOS) is the high prevalence of obesity, with studies indicating that 38% to 88% of those affected are either overweight or obese [4-5]. Excess abdominal adipose tissue is strongly linked to insulin resistance, a common feature of PCOS. This insulin resistance leads to compensatory hyperinsulinemia, which stimulates ovarian androgen production, thereby intensifying hyperandrogenic symptoms. Additionally, hyperandrogenism negatively impacts various metabolic tissues, including adipose tissue, the liver, and pancreas, skeletal muscle, and further impairing systemic metabolism [6]. The interplay between obesity and PCOS also significantly elevates the risk of developing metabolic syndrome (MetS), which includes insulin resistance, dyslipidemia, hypertension, and impaired glucose tolerance [7]. According to the Rotterdam classification, significant differences exist among the four defined subtypes of women with polycystic ovary syndrome [8]. It remains unclear whether differences in metabolic abnormalities and adipose tissue distribution exist between PCOS patients with normal weight and those who are overweight, particularly when viewed through the lens of adipose tissue and obesity. Notably, there is a paucity of data regarding body composition, metabolic parameters, and insulin resistance in lean and obese women with PCOS. Therefore, this study aimed to examine body composition, metabolic characteristics, and insulin resistance in women with PCOS based on body mass index, thereby contributing to a more comprehensive understanding of the metabolic abnormalities associated with PCOS.

Materials and Methods

The study was carried out at the Department of Clinical Biochemistry, University Clinic for Gynecology and Obstetrics in the Republic of North Macedonia. All study procedures followed the ethical principles outlined in the Declaration of Helsinki. The study protocol, including all aspects involving human participants, was reviewed and approved by the Ethics Committee of the Faculty of Medicine at Ss. Cyril and Methodius University in Skopje. Informed consent was obtained from all participants prior to their inclusion in the study. Participants were informed of their right to withdraw at any time without consequence, and all data were anonymized to ensure confidentiality. All necessary measures were taken to minimize potential risks and to protect the rights and well-being of participants throughout the research process. This cross-sectional study included 89 premenopausal women, aged 18 to 40 years, who had been diagnosed with polycystic ovary syndrome. Diagnosis was based on the 2003 Rotterdam criteria, which require the presence of at least two of the following three characteristics: irregular menstrual cycles (including oligomenorrhea), defined as six or fewer menstrual periods per year, or amenorrhea, defined as the cessation of menstruation for longer than six months, clinical and/or biochemical evidence of hyperandrogenism, and polycystic ovarian morphology on ultrasound (defined as the presence of 10 or more follicles measuring 2–9 mm and/or increased ovarian volume greater than 10 mm^3) [9]. Participants completed a structured questionnaire that included questions on age, marital status, lifestyle habits, and vitamin supplement use. Anthropometric assessments were conducted, measuring body weight, height, waist circumference, and hip circumference.
Patients were excluded from the study if they had any of the following conditions: abnormal levels of prolactin or thyroid hormones, renal or hepatic dysfunction, type 1 or type 2 diabetes mellitus, congenital adrenal hyperplasia, use of medications such as hormonal supplements, insulin sensitizers, corticosteroids, or statins, or a history of cardiovascular disease or cancer.
Clinical and anthropometric variables were assessed by a trained nurse or resident for all participants. The following measurements were performed: height and

weight: measured using standardized equipment to calculate body mass index, waist circumference (WC) and waist-to-hip ratio: measured at the midpoint between the superior border of the iliac crest and the lower margin of the ribs; hip circumference: measured at the point of maximum circumference over the buttocks; BMI was calculated using the standard formula: weight (kg) divided by height (m^2). Based on the World Health Organization (WHO) classification [10], the cohort of PCOS patients was subdivided into two groups: lean PCOS (Group A): BMI <25 kg/m^2 (n= 35) and overweight/obese PCOS (Group B): BMI ≥25 kg/m^2 (n=54).

Glucose Homeostasis and Insulin Resistance Insulin resistance (IR) can be evaluated by various methods. In this study, we used static fasting glucose and insulin measurements as surrogate markers for insulin resistance [10-11]. IR was assessed using basal fasting insulin concentrations, fasting glucose concentrations, and the homeostasis model assessment (HOMA-IR). HOMA-IR was calculated using the equation: fasting plasma insulin × glucose / 22.5. A HOMA-IR value of 2.5 or above was considered indicative of insulin resistance, as previously established [12].

Laboratory procedures

Blood samples were collected from participants after 12-14 hours of overnight fasting, on the third day of their menstrual cycle. Samples were drawn between 8:00 and 10:00 a.m. from an antecubital vein after 5 minutes of rest in the supine position. Samples were allowed to clot for at least 30 minutes before centrifugation. Fasting plasma glucose levels were measured immediately after blood withdrawal using the enzymatic glucose oxidase method on an auto analyzer (Cobas Integra 400 Plus, Roche Diagnostics). All hormonal assays were evaluated using a chemiluminescent immunometric assay (Immulite 2000 HP, Diagnostics Products Corp) as explained previously [13].

Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 22.0 for Windows, SPSS Inc., Chicago, IL, USA). The categorical variables were presented as number (%), measurable variables with normal distribution were presented as mean ± standard deviation (SD), and those not following normal distribution were presented as median (interquartile range, IQR). Student's t-test, Chi-square test, and Mann-Whitney U tests were performed as applicable for comparing the variables between different groups. A *P*-value <0.05 was considered as statistically significant.

Results

No significant differences were observed in demographic characteristics between the two study groups. The mean age of women in Group A (lean women with PCOS, 24.17±3.3 years) was comparable to that of Group B (obese women with PCOS, 24.32±4.3 years).

The clinical and anthropometric characteristics of the study groups are summarized in Table 1. The mean BMI of Group A was 21.9±1.9 kg/m^2, while the mean BMI of Group B was 31.63±5.1 kg/m^2. The difference between the two groups was statistically significant (P<0.01). Waist circumference and waist-to-hip ratio were significantly higher in obese women with PCOS compared to their lean counterparts (WC: 105.03±12.0 cm *vs*. 82.65±8.2 cm; WHR: 0.91±0.08 *vs*. 0.84±0.05, respectively; P<0.01 for both comparisons).

Hormonal analysis revealed significantly higher levels of luteinizing hormone (LH) and ratio between LH and follicular stimulating hormone (FSH), LH/FSH ratio (P<0.01) in obese women with PCOS compared to lean women with PCOS. Additionally, sex hormone-binding globulin (SHBG) concentrations were significantly lower in the obese PCOS group (P<0.01), while the free androgen index (FAI) was significantly higher (P<0.01). The mean FAI in lean women with PCOS was 5.15±2.8, which was significantly lower than the mean FAI in obese women with PCOS (12.22±8.1). Conversely, SHBG levels were significantly higher in lean women with PCOS (50.37±25.6 nmol/L) compared to obese women with PCOS (22.81±10.6 nmol/L) (Table 2).

Table 1. Clinical and anthropometric characteristics PCOS patients stratified by BMI

	Group A (N=35); BMI < 25 kg/m^2		Group B (N=54); BMI ≥ 25 kg/m^2		*P* - value
	mean ±SD	min-max	mean ±SD	min-max	
Age (years)	24.17±3.3	19.0-31.0	24.32 ± 4.3	18.0-35.0	*P*=0.88
BMI (kg/m2)	21.9±1.9	18-24.74	31.63 ± 5.1	25.1-47.87	*P*<0.001
Waist (cm)	82.65±8.2	65.5-96.0	105.0±12.0	83.0-132.0	*P*<0.001
WHR	0.84±0.05	0.74-0.94	0.91±0.08	0.65-1.09	*P*<0.001

BMI - Body mass index; WHR-Waist-to-hip ratio; SD - Standard deviation; Min - minimum; Max - maximum; Mann-Whitney Wilcoxon test; *P* <0.05

Table 2. Endocrine features of PCOS patients stratified by BMI

Group A (N=35); BMI < 25 kg/m^2	Group B (N=54); BMI ≥ 25 kg/m^2

Variable	mean ±SD	min-max	median	Q25-Q75	mean ±SD	min-max	median	Q25- Q75	P -value
FSH (mIU/l)	5.58±1.2	3.1-7.8	5.95	4.7-6.2	5.66± 2.1	2.2- 9.5	5.1	3.8- 7.7	*P =0.87
LH (mIU/l)	11.82±4.7	4.5-20.6	11.66	8.25-14.95	7.84± 4.1	1.6-16.05	8.05	3.7- 10	*P <0.001
LH / FSH	2.16±0.8	0.69- 3.88	1.92	1.65- 2.82	1.5± 0.9	0.35-3.88	1.22	0.93-1.92	*P <0.05
PRL	11.43±4.8	4.6- 24	10.25	8.0- 14.95	11.42±5.5	3.0- 22.8	9.98	7.7- 14.0	**p=0.931
E2(pmol/l)	57.31±23.9	29.7-120	55	35.5- 73.8	55.9±22.1	29.72-128	47	40.7- 67.9	**p=0.912
TSH	2.56 ± 2.4	0.91-12.6	2.1	1.5- 2.6	2.1± 0.7	0.94- 3.5	2.1	1.58- 2.68	** *P*=0.912
DHEAS (µg/ml)	3.52 ± 2.7	0.5- 13	3.57	1.95-4.0	3.93± 2.0	0.9- 10.0	3.36	2.5- 5.0	***P*=0.173
Testosterone(nmol/l)	2.23 ± 0.8	0.69- 3.7	2.16	1.66- 2.92	2.3± 0.9	0.85-4.68	2.19	1.68-3.0	**P*=0.781
FAI	5.15 ± 2.8	2.24-14.52	4.37	3.11- 6.55	12.22 ±8.1	3.9- 44.1	10.7	6.1- 15.94	** *P*<0.001
SHBG (nmol/l)	50.37±24.6	15.2- 121	45.6	33.75-64.2	22.81±10.6	7.26- 52	19.2	15.9- 30	** *P*<0.001

FSH-Follicle-stimulating hormone, LH-Luteinizing hormone, PRL-Prolactin, E2-Estradiol, TSH-Thyroid-stimulating hormone, DHEAS-Dehydroepiandrosterone sulfate, FAI-Free androgen index, SHBG-Sex hormone binding globulin. *Student's t-test **Mann-Whitney Wilcoxon test; *P* <0.05

The analysis of metabolic parameters showed that fasting glucose levels did not significantly differ between the two groups (Table 3). However, fasting insulin levels were significantly higher in obese women with PCOS (P<0.01). The median fasting insulin level in lean women with PCOS was 6.37 µIU/mL (range: 4.3-10.2), compared to 17.3 µIU/mL (range: 11.4-23.4) in obese women with PCOS.

Table 3. Metabolic features of PCOS patients stratified by BMI

	Group A (N=35); BMI < 25 kg/m^2				Group B (N=54); BMI ≥ 25 kg/m^2				
Variable	**mean±SD**	**min-max**	**median**	**Q25-Q75**	**mean±SD**	**min-max**	**median**	**Q25-Q75**	***P*-value**
Fasting glucose (mmol/l)	5.15 ± 0.4	4.45- 6	5.1	4.85- 5.4	5.23 ± 0.4	4.5- 6.4	5.25	4.9- 5.5	***P*=0.5
Fasting insulin (mIU/l)	7.55 ± 4.4	2.0- 16.7	6.37	4.3- 10.2	17± 6.8	2.0- 28.7	17.3	11.4- 23.4	***P*<0.001
HOMA-IR	1.74 ± 1	0.4- 3.64	1.48	0.96- 2.44	3.97 ± 1.6	0.5- 6.8	4.0	2.58- 5.13	***P*<0.001

BMI - Body mass index; HOMA-IR - homeostatic model assessment of insulin resistance, *Student's t-test, **Mann-Whitney Wilcoxon test; P<0.05

The insulin-to-glucose ratio was also significantly elevated in the obese PCOS group (P<0.001). Moreover, the homeostatic model assessment of insulin resistance (HOMA-IR) was significantly higher in obese women with PCOS compared to lean women with PCOS (median: 4.0, range: 2.58-5.13 *vs*. median: 1.48, range: 0.96-2.44, respectively; P<0.01).

All analyzed lipid parameters differed significantly between the normal-weight and overweight PCOS groups, as shown in Table 4. Total cholesterol levels were significantly higher in the overweight PCOS group (4.97±1.0 mmol/L) compared to the normal-weight PCOS group (4.5±0.9 mmol/L; p=0.028). Triglyceride levels were significantly lower in the normal-weight group (0.85±0.4 mmol/L) compared to the overweight group (1.45±0.7 mmol/L; p<0.01). The mean high-density lipoprotein (HDL-C) cholesterol levels were 1.48±0.03 mmol/L in the normal-weight group and 1.04±0.03 mmol/L in the overweight group, showing a statistically significant difference (p<0.01). Similarly, low-density lipoprotein (LDL-C) cholesterol levels were significantly higher in the overweight PCOS group (3.24±0.9 mmol/L) compared to the normal-weight group (2.71±0.8 mmol/L; p=0.05).

Table 4. Lipid parameters of PCOS women stratified by BMI

Group A (N=35); BMI < 25 kg/m^2		Group B (N=54); BMI ≥ 25 kg/m^2	
Variable	**mean ±SD**	**mean ±SD**	**P-value**
Cholesterol (mmol/l)	4.5±0.9	4.97±1.0	* *P*=0.028
Triglycerides (mmol/l)	0.85±0.4	1.45±0.7	** *P*<0.001
HDL-C (mmol/l)	1.48±0.03	1.04±0.03	** *P*<0.001
LDL-C (mmol/l)	2.71±0.8	3.24±0.9	** *P*<0.005

BMI - Body mass index; HDL-C, High density cholesterol; LDL-C, Low density cholesterol *Student's t-test, **Mann-Whitney Wilcoxon test; P<0.05

Discussion

This study sought to assess the metabolic differences and indices of insulin resistance in obese PCOS and those with normal body weight.

Body mass index and waist circumference serve as surrogate markers of obesity, particularly visceral adiposity, in the general population. Other anthropometric parameters, such as percentage of body fat (PBF), WHtR, and waist-to-hip ratio, have demonstrated advantages in various aspects of obesity assessment [14]. While BMI primarily reflects overall body density, PBF quantifies body fat percentage, and WC provides a measure of abdominal width and central obesity, similar to WHtR and WHR. A large-scale study conducted among Chinese adults identified WHtR as a superior indicator of cardiovascular risk, with optimal cut-off values of 0.50 for men and 0.48 for women [15].

The cut-off points for overweight and obesity recommended by Meta-analysis Group of China Obesity Task Force was verified in the large sample survey conducted more recently. The cut-off points of BMI were 24.0 and 28.0 kg/m for overweight and obesity, and the cut-off point of WC was 85 cm in men, and 80 to 85 cm in women for central obesity are indicators for metabolic abnormalities and metabolic syndrome [2,14]. However, the most proper anthropometric parameters and their respective cut-off values for diagnosing obesity in women with polycystic ovary syndrome (PCOS) remain a subject of debate and require further investigation.

BMI is the most widely utilized measure of obesity in clinical practice, with specific cut-off values varying across different ethnic groups. In a population-based observational study involving 409 women with PCOS and 7,057 non-PCOS women, the mean BMI was significantly higher in the PCOS group compared to the control group [16]. Similarly, a prospective controlled study conducted in a Greek population with PCOS reported a significantly elevated BMI in the PCOS group, which was also associated with increased fasting plasma glucose, triglyceride levels, and a higher risk of metabolic syndrome [17]. Additionally, a prospective cross-sectional study in Indian women with PCOS determined that the BMI cut-off for predicting MetS was 22.5 kg/m² in PCOS patients, compared to 23 kg/m² in the general population, suggesting the need for early lifestyle interventions in affected individuals [18].

The comparison of clinical and metabolic characteristics between lean and obese women with polycystic ovary syndrome (PCOS) reveals significant differences that underscore the complexity of this condition. In our study, no significant differences were observed in demographic characteristics between the two groups, with mean ages of 24.17±3.3 years for lean women and 24.32±4.3 years for obese women, indicating that age does not appear to be a confounding factor in the analysis of metabolic and hormonal parameters. However, the distinct contrast in body mass index (BMI) is noteworthy, with lean women having a mean BMI of 21.9±1.9 kg/m² compared to obese women at 31.63±5.1 kg/m², a difference that was statistically significant ($p<0.01$).

The anthropometric measurements further illustrate the metabolic disparities between the two groups. Obese women with PCOS exhibited significantly higher waist circumference and waist-to-hip ratios, which are critical indicators of central obesity and associated metabolic risks. These findings align with existing literature that highlights the increased prevalence of insulin resistance and adverse lipid profiles in obese PCOS patients compared to their lean counterparts [14].

Furthermore, elevated levels of LH and a higher LH/FSH ratio in the obese group are consistent with the hyperandrogenic profile often observed in this population. The significantly lower levels of SHBG and FAI in obese women further corroborate the association between obesity and hyperandrogenism in PCOS. Zhang *et al*. suggests that in PCOS patients with IR, lower levels of SHBG and higher levels of FAI are associated with presence of obesity and that SHBG and FAI can be used as a biomarker for the initial identification and prognosis of IR in PCOS patients [19].

Metabolic parameters also showed differences between two studies groups, particularly fasting insulin levels and insulin resistance, as measured by the homeostatic model assessment of insulin resistance (HOMA-IR). Obese women had markedly higher fasting insulin levels (17.3μIU/mL) compared to lean women (6.37μIU/mL), with a corresponding increase in HOMA-IR values (median 4.0 *vs*. 1.74, $p<0.001$) [20]. This finding is consistent with previous studies that have established a strong link between obesity and insulin resistance in women with PCOS [20-21]. Interestingly, fasting glucose levels were not significantly different between the two groups, indicating that despite comparable glucose homeostasis, insulin resistance is more pronounced in the obese group of women with PCOS [20,22].

It has been found that more than 70% of PCOS women present with abnormal lipid profiles. Percentage of lipid disturbances is linked with increased body fat percentage and together they are essential metabolic risk factors in PCOS [23]. We have found a difference regarding lipid metabolism among women with PCOS, which is dependent on BMI. Women with elevated BMI more than 25 kg/m2 had higher levels of triglycerides and LDL-C, while the levels of HDL-C were significantly lower than lean counterparts, meaning that obesity per se is trigger of disturbed lipid metabolism in this relatively young population. The use of indirect metabolic risk indicators-such as the lipid accumulation product (LAP), triglyceride-to-high-density lipoprotein cholesterol ratio (TG/HDL-C), visceral adiposity index (VAI), and WHtR-serves as a valuable

approach for assessing metabolic syndrome in women with PCOS. Due to their strong predictive capacity, these markers are effective screening tools for identifying MetS in this high-risk population [24].

In many countries, the prevalence of obesity among women with PCOS and the general population is notably high, reaching 60-70% [4,25-26]. Despite this, at least one-third of PCOS patients diagnosed using the Rotterdam criteria in these regions are underweight or slightly overweight. Studies indicate that while the Rotterdam phenotypes effectively differentiate PCOS patients based on ovulatory patterns and androgen secretion, they do not adequately distinguish between obese individuals with metabolic dysfunction and lean individuals with normal metabolic profiles [27]. Our study also found that metabolic alterations in women with PCOS were associated with obesity, regardless of phenotypic characteristics. Obese PCOS patients showed elevated insulin levels, increased insulin resistance, and dyslipidemia, whereas lean PCOS patients maintained normal insulin levels, did not exhibit clinically significant insulin resistance, and had normal lipid profiles.

The metabolic patterns between lean and obese PCOS patients are particularly distinct in the classic NIH-defined phenotypes A and B. While obesity is common in these phenotypes and strongly associated with severe metabolic dysfunction, a significant proportion of individuals are of normal weight and exhibit a metabolically healthy profile [8,27]. These findings suggest that the mechanisms underlying chronic anovulation in PCOS may not be directly or solely driven by metabolic disturbances such as insulin resistance, although its presence appears to exacerbate the condition.

The multifaceted impact of PCOS highlights the need for a comprehensive understanding of its metabolic and reproductive disturbances to inform effective management strategies. Further research is necessary to refine the classification of PCOS, incorporating body weight as an independent factor, separate from ovulatory status. Such a revised classification system would enhance diagnostic accuracy, improve treatment strategies, and facilitate more effective long-term management of PCOS. Additionally, it could contribute to a deeper understanding of the syndrome pathophysiology.

Conclusion

This study underscores the significant metabolic and hormonal differences between lean and obese women with PCOS, emphasizing the critical role of obesity in exacerbating insulin resistance, hyperandrogenism, and central adiposity. The findings show that while age and fasting glucose levels may not differ significantly between the two groups, obesity is strongly associated with elevated insulin resistance markers, adverse lipid profiles, and a pronounced hyperandrogenic state. These results highlight the need for tailored management strategies that address both the metabolic and reproductive aspects of PCOS.

Given the complex and multifactorial nature of PCOS, an integrated approach incorporating lifestyle modifications, pharmacological interventions, and psychological support is essential to improve clinical outcomes. Future research should focus on longitudinal studies to further elucidate the long-term metabolic implications of PCOS in different body weight categories and to develop targeted therapeutic interventions that improve both metabolic and reproductive health. Understanding these dynamics will contribute to more personalized and effective treatment strategies, ultimately enhancing the quality of life for women with PCOS.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 143-150

ММР

Original article

THE ROLE OF PLACENTAL ANGIOGENIC MARKERS IN DIFFERENTIATING FETUSES WITH INTRAUTERINE GROWTH RESTRICTION FROM THOSE SMALL-FOR-GESTATIONAL-AGE

УЛОГАТА НА ПЛАЦЕНТАРНИТЕ АНГИОГЕНИ МАРКЕРИ ВО ДИФЕРЕНЦИЈАЦИЈАТА ПОМЕЃУ ФЕТУСИ СО ИНТРАУТЕРИНИ ЗАСТОЈ ВО РАСТОТ И МАЛИ ЗА ГЕСТАЦИСКАТА ВОЗРАСТ

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Abstract

Introduction. Fetal growth restriction (FGR) is a condition of impaired fetal growth and one of the leading causes of perinatal morbidity and mortality. Small fetuses are defined as those with an ultrasound-estimated fetal weight below the 10th percentile. While some are constitutionally small, others present with true growth restriction, failing to reach their genetic growth potential. Accurate diagnosis and monitoring of FGR remain challenging, requiring repeated ultrasound and Doppler assessments, which place a burden on healthcare systems and contribute to patient anxiety. Angiogenic markers, particularly the sFlt-1/PlGF ratio, have emerged as promising tools for distinguishing FGR from small-for-gestational-age (SGA) fetuses, thereby improving risk stratification for adverse neonatal outcomes.
Methods. This pilot prospective, observational cohort study included 20 pregnant patients with an ultrasound-estimated fetal weight below the 10th percentile beyond the 24th gestational week. Patients were divided into two groups: 10 with FGR and 10 with SGA. Levels of angiogenic markers (sFlt-1/PlGF) were analyzed and compared between the groups.
Results. The sFlt-1/PlGF ratio was significantly higher in patients with FGR compared to those with SGA fetuses.
Conclusion. The findings suggest that angiogenic markers, particularly the sFlt-1/PlGF ratio, may play a key role in differentiating between FGR and SGA fetuses, potentially improving early diagnosis and management of high-risk pregnancies.

Keywords: intrauterine growth restriction, small for gestational age, angiogenic markers, PlGF, sFlt-1

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Апстракт

Вовед. Интраутериниот застој во растот (IUGR) претставува состојба на нарушен фетален раст и е една од водечките причини за перинатален морбидитет и морталитет. Мали фетуси се дефинираат како оние со ултразвучно проценета тежина под 10-та перцентила. Додека дел од нив се конституционално мали, други имаат вистински застој во растот и не го достигнуваат својот генетски потенцијал за раст. Точната дијагноза и следење на IUGR остануваат предизвици, бидејќи бараат повторени ултразвучни и Доплер процени, што претставува оптоварување за здравствениот систем и придонесува за анксиозност кај пациентките. Ангиогените биомаркери, особено сооднос sFlt-1/PlGF, се издвојуваат како ветувачки алатки за диференцијација помеѓу FGR и фетуси мали за гестациската возраст (SGA), со што се овозможува попрецизна стратификација на ризикот за неповолен неонатален исход.
Методи. Оваа студија е пилот проект за изработка на проспективна, опсевациона, кохортна студија кај бремени пациентки со плод со ултразвучно проценета фетална тежина под 10^{та} перцентила. Во студијата се вклучени 20 пациентки со гестатиска старост над 24^{та} гестациска недела. Пациентките беа поделени во две групи: 10 со IUGR и 10 со SGA. Нивото на ангиогените маркери (sFlt-1/PlGF) беше анализирано и споредено меѓу групите.
Резултати. Соодносот sFlt-1/PlGF беше значително повисок кај пациентките со IUGR во споредба со оние со SGA фетуси.
Заклучок. Наодите сугерираат дека ангиогените маркери, особено соодносот sFlt-1/PlGF, може да имаат клучна улога во разликувањето на IUGR од SGA фетусите, со што потенцијално се подобрува

раната дијагноза и менаџментот на бремености со висок ризик.

Клучни зборови: Интраутерини застој во растот, мали за гестациска возраст, ангиогени маркери, PlGF, sFlt-1

Introduction

Fetal growth restriction (FGR) is a condition characterized by inadequate fetal growth and represents one of the leading causes of perinatal morbidity and mortality [1-5]. It is among the main contributors to intrauterine fetal death in highly and moderately developed countries and is associated with up to one-third of neonatal deaths in low-income settings [6-8].

Small fetuses are defined as those with an ultrasound-estimated fetal weight below the 10th percentile on standardized growth curves. The term *small for gestational age* (SGA) refers to fetuses below the 10th percentile without Doppler abnormalities, typically representing constitutionally small but healthy fetuses. In contrast, *intrauterine growth restriction* (IUGR) occurs when a fetus fails to reach its genetic growth potential and is often accompanied by Doppler changes in placental and maternal circulation [9,10].

Despite advances in understanding the pathophysiology of IUGR, its accurate diagnosis and optimal management remain major challenges in modern obstetrics. Current diagnostic strategies rely primarily on ultrasound-based fetal weight estimation and Doppler assessment of maternal and fetal circulation. However, universal third-trimester ultrasound screening has shown limited predictive value for perinatal morbidity and mortality [11]. Consequently, ineffective antenatal recognition of IUGR remains associated with an increased risk of stillbirth, adverse perinatal outcomes, and long-term health complications [3-5].

Placental insufficiency is considered the primary cause of IUGR. It results from inadequate trophoblastic invasion and abnormal remodeling of the spiral arteries, leading to impaired placental perfusion [12,13]. Chronic placental ischemia alters the balance of angiogenic factors, characterized by decreased placental growth factor (PlGF) and increased soluble fms-like tyrosine kinase-1 (sFlt-1) production. This imbalance leads to an elevated sFlt-1/PlGF ratio, which correlates with the degree of placental dysfunction [14].

Currently, management of IUGR and SGA varies considerably across countries, with no consensus on the optimal frequency of ultrasound growth assessments or Doppler evaluations [15-18]. Furthermore, the use of different growth charts introduces additional variability, as the choice of diagnostic criteria directly affects the classification of fetuses and their associated outcomes [19-22]. This highlights the need for additional diagnostic methods that can complement existing approaches and improve risk stratification.

Recent evidence suggests that maternal serum angiogenic markers, particularly the sFlt-1/PlGF ratio, may significantly aid in the early identification and monitoring of pregnancies affected by IUGR. These biomarkers offer the potential to differentiate IUGR from constitutionally small fetuses, thereby enhancing clinical decision-making and improving perinatal outcomes.

Aim

The aim of this study was to determine the maternal serum levels of the angiogenic markers-placental growth factor (PlGF), soluble fms-like tyrosine kinase-1 (sFlt-1)-and their ratio (sFlt-1/PlGF) in pregnancies complicated by intrauterine growth restriction (IUGR) compared with those involving small-for-gestational-age (SGA) fetuses.

Hypothesis

We hypothesized that the sFlt-1/PlGF ratio would be significantly higher in pregnancies with IUGR compared to those with SGA fetuses, reflecting more severe placental dysfunction and aiding in the differentiation between these two conditions.

Materials and Methods

This study was designed as a pilot prospective, observational cohort study conducted at the University Clinic for Gynecology and Obstetrics (UCGO) in Skopje. Twenty pregnant women with an ultrasound-estimated fetal weight below the 10th percentile were included and evaluated.

Study Groups

Participants were divided into two groups:

- **IUGR group (n=10):** fetuses meeting Delphi consensus criteria for early- or late-onset growth restriction [23];
- **SGA group (n=10):** fetuses with an ultrasound-estimated fetal weight between the 3rd and 10th percentile without maternal or fetal Doppler abnormalities.

Definitions

- *Early-onset IUGR*: <32 weeks' gestation, with estimated fetal weight (EFW) or abdominal circumference (AC) <3rd percentile, or EFW/AC between the 3rd-10th percentile plus either umbilical artery PI> 95th percentile or uterine artery PI>95th percentile.
- *Late-onset IUGR*: ≥32 weeks' gestation, with EFW or AC <3rd percentile, or two of the following:

EFW/AC 3rd-10th percentile, drop >50 percentiles in growth trajectory, cerebroplacental ratio (CPR) <5th percentile, or uterine artery PI>95th percentile.

Eligibility Criteria

- *Inclusion*: maternal age >18 years, singleton pregnancy with EFW <10th percentile, gestational age ≥24+0 weeks, availability for follow-up, and signed informed consent.
- *Exclusion*: preeclampsia diagnosed before enrollment, confirmed structural fetal anomalies, multiple pregnancies, chromosomal/genetic abnormalities, or active labor.

Clinical Data Collection

Patient history included demographic information (age, BMI), obstetric history (parity, prior complications such as preeclampsia, eclampsia, HELLP, or IUGR), and current pregnancy data (LMP, gestational age, number of fetuses).

Gestational Age Assessment

Gestational age was determined by CRL at 8+0–13+6 weeks [24]. If unavailable and >10 days' discrepancy existed between menstrual age and fetal size, head circumference (HC) between 14+0–21+6 weeks was used [24].

Ultrasound and Doppler Assessment

All patients underwent ultrasound for fetal biometry (BPD, HC, AC, FL) according to ISUOG guidelines [25].

- EFW was calculated using the Hadlock formula [26] and plotted against the Hadlock percentile chart [27].
- Doppler indices included UA PI, MCA PI, and CPR (MCA PI/UA PI), measured according to ISUOG recommendations [28].
- Oligohydramnios was defined as MVP <2 cm or AFI <5 cm. Ultrasound assessments were performed with Voluson E6, E8, and E10 systems (GE Healthcare).

Biochemical Analysis

Maternal serum levels of PlGF and sFlt-1 were measured in the Biochemistry Laboratory at UCGO using a fully automated electrochemiluminescence immunoassay (ECLIA) analyzer (Cobas e 411). The sFlt-1/PlGF ratio was calculated.

Monitoring for Preeclampsia

All IUGR patients and those with marker levels predictive of preeclampsia [29] were monitored for blood pressure, liver enzymes (AST, ALT), LDH, serum creatinine, platelet count, and proteinuria. Preeclampsia was defined as new-onset hypertension (≥140/90 mmHg on two occasions ≥4 h apart) with proteinuria ≥300 mg/24 h or other organ dysfunction (renal, hepatic, hematologic, neurologic, or pulmonary).

Delivery and Neonatal Outcomes

Indications for timing and mode of delivery were based on established guidelines for FGR management, including abnormal Doppler findings, non-reassuring CTG, positive stress test, biophysical profile <4, or oligohydramnios. Neonatal outcomes assessed included birth weight, Apgar scores at 1 and 5 minutes, and neonatal mortality.

Future Directions

This pilot study is intended to be expanded with a larger sample size, enabling correlation of angiogenic marker levels with neonatal outcomes.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 25.0; IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess the normality of data distribution.

Qualitative variables are presented as absolute and relative frequencies. Quantitative variables are expressed as mean±standard deviation (SD) for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data, along with minimum and maximum values.

Comparisons between the IUGR and SGA groups were performed using the Fisher's exact test for categorical variables. For continuous variables, the Student's *t*-test was applied when data followed a normal distribution, and the Mann–Whitney U test was used otherwise. A two-tailed p-value <0.05 was considered statistically significant.

As this was a **pilot study** with a total of 20 participants, no formal sample size calculation was performed. The limited sample was chosen to assess feasibility and generate preliminary data to inform the design and power calculation of a larger follow-up study.

Results

A total of 20 pregnant women were included: 10 with intrauterine growth restriction (IUGR) and 10 with small-for-gestational-age (SGA) fetuses.

Maternal Characteristics

The mean maternal age was slightly higher in the IUGR group compared with the SGA group (33.4±9.9 *vs.* 29.2±5.8 years), though the difference was not statistically significant (p=0.265). No significant differences were observed in maternal height (164.3±5.8 cm *vs*. 160.0±6.2 cm, p=0.126), weight (78.4±14.6 kg *vs*. 73.6±19.7 kg, p=0.540), or body mass index (23.78

±4.2 *vs*. 23.0±5.8 kg/m², *p*=0.735). The mean gestational age at the time of the study was slightly lower in the IUGR group compared to the SGA group (31.2±4.4 *vs*. 34.5±2.5 weeks), with the difference approaching significance (*p*=0.056). Obstetric history distributions did not differ substantially between groups (Table 1).

Table 1. Maternal Baseline Characteristics

Baseline maternal characteristics of the study population	IUGR	SGA	p-level
Maternal age (mean ± SD)	33.4±9.9	29.2±5.8	t=1.15 p=0.265
Hight/cm (mean ± SD)	164.30±5.8	160.0±6.2	t=1.6 p=0.126
Weight/kg (mean ± SD)	78.40±14.6	73.60±19.7	t=0.62 p=0.54
BMI (kg/m^2) (mean ± SD)	23.78±4.2	23.0±5.8	t=0.34 p=0.735
Gestational age at US (mean ± SD)	31.2±4.4	34.5±2.5	t=2.05 p=0.056
parity			Fisher's exact test
n(%)			p=0.37
0	5 (50)	3 (30)	
1	4 (40)	6 (60)	
2	0	1 (10)	
3	1 (10)	0	

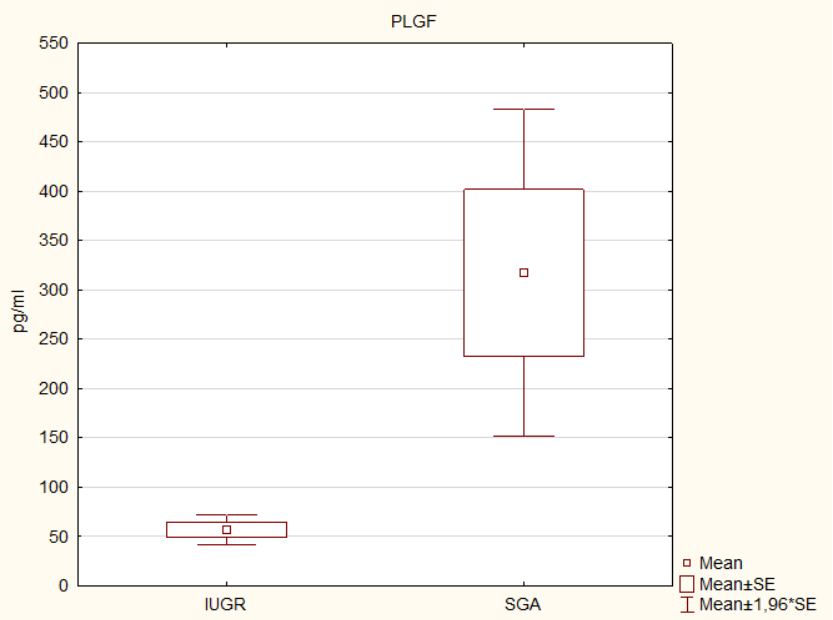

Fig. 1. Distribution of PLGF in IUGR and SGA pregnancy

Angiogenic Markers (Table 2)

- **PlGF:** Significantly lower in the IUGR group (mean 56.7±24.8 pg/mL; median 54.5 pg/mL) compared with the SGA group (mean 317.2±267.1 pg/mL; median 223 pg/mL) (*p*=0.00018) (Figure 1).
- **sFlt-1:** Significantly higher in the IUGR group (mean 12,666.5±9,454.4 pg/mL; median 9,121.5 pg/mL) compared with the SGA group (mean 5,003.7±1,854.0 pg/mL; median 4,522 pg/mL) (*p* =0.0375) (Figure 2).
- **sFlt-1/PlGF ratio:** Markedly elevated in the IUGR group (mean 274.0±217.2; median 247.5) compared with the SGA group (mean 20.5±10.9; median 22.8) (*p*=0.00018) (Figure 3).

Table 2. Placental Angiogenic Markers

Variable	Statistical parameters	IUGR	SGA	p-level
PLGF (pg/ml)	mean ± SD	56.70 ± 24.8	317.20 ± 267.1	Z=3.74
	median (IQR)	54.5 (34 – 77)	223 (213 – 306)	***p=0.00018
sFlt-1 (pg/ml)	mean ± SD	12666.50 ± 9454.4	5003.70 ± 1854.0	Z=2.08
	median (IQR)	9121.5 (5976 – 17209)	4522 (4314 – 6325)	*p=0.0375
sFlt-1/PLGF	mean ± SD	273.99 ± 217.2	20.45 ± 10.9	Z=3.74
	median (IQR)	247.5 (89 – 397)	22.8 (12.5 – 29.4)	***p=0.00018

*Mann-Whitney U test: *p < 0.05, ***p < 0.0001

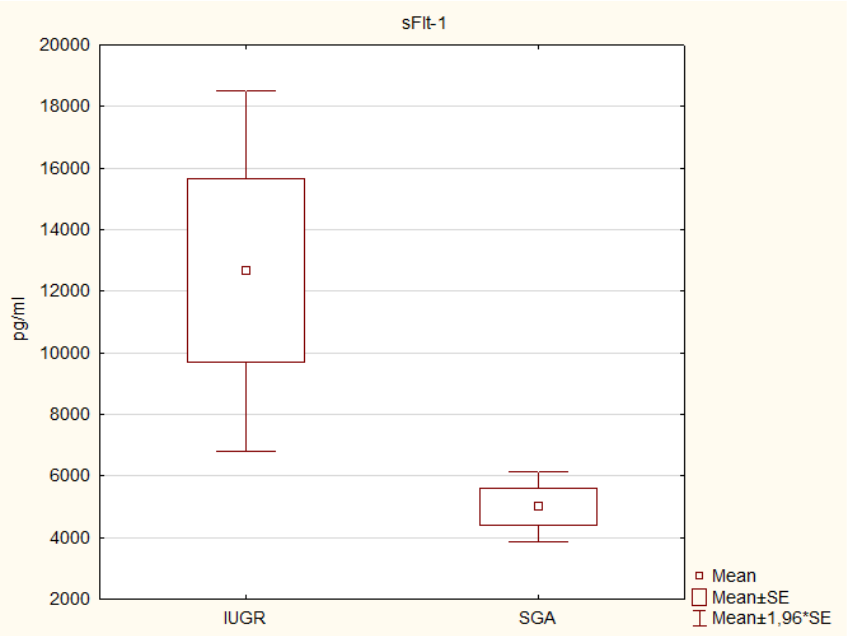

Fig. 2. Distribution of sFLT-1 in IUGR and SGA pregnancy

Table 3. Doppler Parameters

Variable	IUGR Group	SGA Group	p-level
PI a. umbilicalis	1.45±0.52	1.07±0.15	t=2.23, *p=0.039
PI a. cerebri media	1.44±0.32	1.79±0.14	t=3.08, **p=0.0064
CPR	1.04±0.31	1.68±0.13	t=6.08, ***p=0.00001

*Student's t-test: *p<0.05, **p<0.01, ***p<0.0001

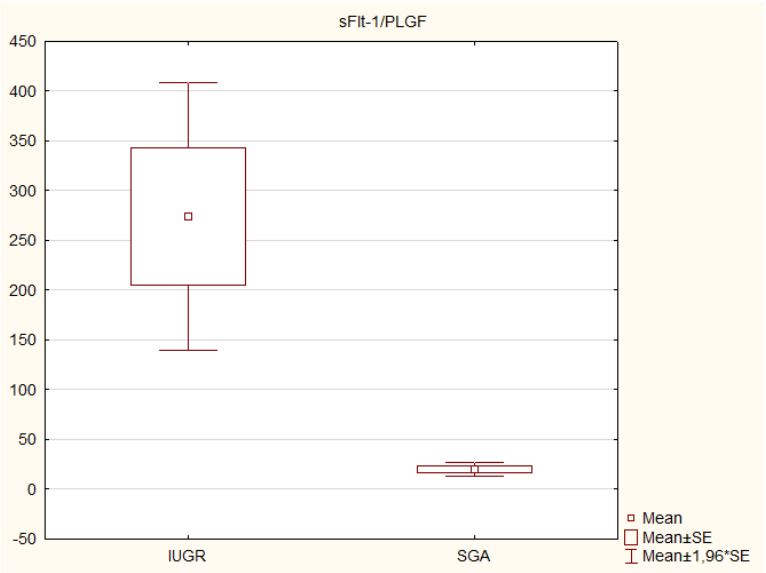

Fig. 3. Distribution of sFLT-1/PLGF ration in IUGR and SGA pregnancy

Doppler Indices (Table 3)

- **Umbilical artery PI:** Significantly higher in the IUGR group (1.45±0.52) compared to the SGA group (1.07±0.15) (p=0.039).
- **Middle cerebral artery PI:** Significantly lower in the IUGR group (1.44±0.32) compared to the SGA group (1.79±0.14) (p=0.0064).
- **Cerebroplacental ratio:** Significantly reduced in the IUGR group (1.04±0.31) compared to the SGA group (1.68±0.13) (p=0.00001).

Summary of Findings

Pregnancies complicated by IUGR were characterized by significantly lower PlGF, higher sFlt-1, and markedly elevated sFlt-1/PlGF ratios compared to SGA. These biochemical changes were paralleled by abnormal Doppler indices, supporting more severe placental dysfunction in the IUGR group.

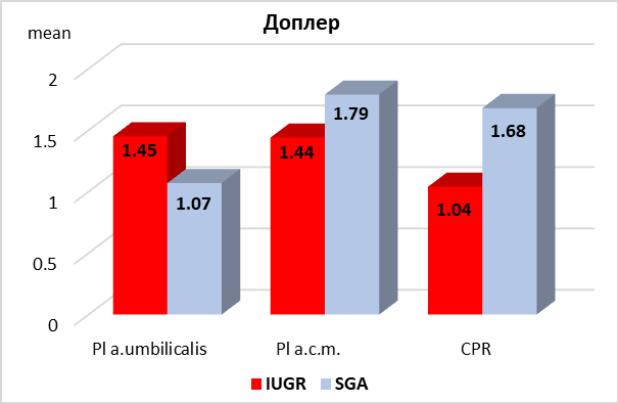

Fig. 4. Comparison on Doppler measurement between IUGR and SGA fetuses

Discussion

This pilot study demonstrated a statistically significant difference in maternal serum angiogenic markers between pregnancies complicated by intrauterine growth restriction (IUGR) and those with small-for-gestational-age (SGA) fetuses. Specifically, the sFlt-1/PlGF ratio was markedly elevated in the IUGR group, reflecting more pronounced placental dysfunction. These findings suggest that an increased sFlt-1/PlGF ratio may aid in distinguishing fetuses with IUGR due to chronic placental insufficiency from constitutionally small but otherwise healthy SGA fetuses.

The IUGR group exhibited significantly lower PlGF levels and higher sFlt-1 concentrations compared to the SGA group. This aligns with previous studies showing that low maternal PlGF levels are strongly associated with placental insufficiency and fetal growth restriction [30]. For example, a large prospective cohort study found that PlGF concentrations below the 5th percentile identified IUGR with high sensitivity, outperforming conventional fetal biometry and Doppler indices in detecting placental dysfunction.

The sFlt-1/PlGF ratio, a composite marker reflecting the balance between pro- and antiangiogenic signals, has been consistently reported to be elevated in IUGR [31-33]. Our findings corroborate this association, particularly in early-onset IUGR, which is typically characterized by more severe placental impairment. Prior research has shown that sFlt-1/PlGF levels correlate with IUGR staging, Doppler abnormalities, and adverse neonatal outcomes, highlighting their potential utility in clinical decision-making [33-35].

Several studies have emphasized the value of angiogenic markers in differentiating constitutionally small fetuses from those with pathologic growth restriction. While many fetuses below the 10th percentile achieve favorable perinatal outcomes, identifying the subset at risk due to placental insufficiency remains a major clinical challenge [36,37].

A case-control study evaluated the angiogenic sFlt-1/PLGF ratio in patients with fetuses classified via ultrasound as normally growing, constitutionally small, or with IUGR. The study found that patients with IUGR had significantly higher sFlt-1/PLGF ratios compared to those with normal or constitutionally small fetuses. The authors concluded that sFlt-1/PLGF levels in IUGR correlate with IUGR staging, Doppler parameters, and adverse outcomes, and may aid in disease classification and clinical management [33].

In an observational study, sFlt-1/PLGF ratios were significantly higher in pregnancies with IUGR and adverse neonatal outcomes compared to those with normal fetal growth. Angiogenic markers were analyzed between 24–28+6 and 29–36+6 weeks of gestation in 530 patients. The study highlighted the potential utility of angiogenic markers as objective tools for identifying fetuses at risk of poor neonatal outcomes [34].

Our results align with previous studies reporting similar findings. In a retrospective study, Rajiv *et al.* analyzed angiogenic marker levels (PLGF, sFlt-1, and their ratio) in patients with IUGR and SGA fetuses and concluded that sFlt-1/PLGF ratios were significantly higher in the IUGR group than in the SGA group (37). Our results support the incorporation of angiogenic markers into risk stratification strategies, allowing for individualized monitoring and timely intervention.

The primary limitation of this study is the small sample size, which may limit the generalizability of the findings. Nevertheless, these preliminary results provide compelling evidence that maternal serum angiogenic markers, particularly the sFlt-1/PlGF ratio, are valuable adjuncts in the antenatal distinction between IUGR and SGA.

Conclusion

Maternal serum angiogenic markers, including PlGF, sFlt-1, and the sFlt-1/PlGF ratio, are significantly altered in pregnancies complicated by IUGR compared to SGA. These markers have the potential to improve the antenatal diagnosis of IUGR, facilitate more accurate risk stratification, and guide appropriate monitoring and clinical management. Incorporating angiogenic marker assessment into routine prenatal care may enhance the identification of fetuses at risk for adverse outcomes. Further research with larger cohorts is required to validate these findings and support their implementation in clinical practice.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 151-158

MMP

Original article

WORK-RELATED BURNOUT DIMENSIONS AS PREDICTORS OF THE RISK OF PERSISTENT HUMAN PAPILLOMAVIRUS INFECTION

ДИМЕНЗИИТЕ НА СИНДРОМОТ НА ПРЕГОРУВАЊЕ ПОВРЗАНИ СО РАБОТАТА КАКО ПРЕДИКТОРИ НА РИЗИКОТ ОД ПЕРЗИСТЕНТНА ИНФЕКЦИЈА СО ХУМАН ПАПИЛОМА ВИРУС

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Abstract

Introduction. Persistent infection with high-risk human papillomavirus (HPV) is the main prerequisite for the development of cervical precancer and cancer. While most HPV infections are transient, psychosocial and work-related factors, such as occupational stress and burnout, may impair immune responses and increase susceptibility to viral persistence.
Methods. A total of 146 women were enrolled, including 95 with persistent HPV infection and 51 without persistence after 24 months. HPV genotyping was performed using multiplex real-time PCR. Work-related psychological factors were assessed with standardized questionnaires, including the Maslach Burnout Inventory (MBI). Statistical analyses included Mann-Whitney U test, Fisher's exact test, and binary logistic regression.
Results. HPV 16 was the most prevalent genotype in persistent infections (46.3%), followed by HPV 31, HPV 52, HPV 18, HPV 45, HPV 33, HPV 53, and HPV 73. Women with persistent HPV infection were significantly older compared to those without persistence (35.3±8.7 *vs*. 32.7±8.9 years, p=0.04). Sociodemographic variables such as education, job sector, and work experience were not significant predictors of persistence. In logistic regression, the burnout dimension personal Accomplishment was a strong protective factor, reducing the risk of persistent HPV infection by 31% (Exp(B)=0.690; 95% CI: 0.602-0.791; p<0.001). Emotional exhaustion showed no significant association. The predictive model demonstrated an overall accuracy of 82.2% (sensitivity 91.6%, specificity 64.7%).
Conclusion. Personal accomplishment, reflecting higher professional efficacy and psychological resilience, emerged as the strongest protective factor against persistent HPV infection. These findings highlight the importance of integrating psychosocial assessments into occupational and public health strategies. Interventions aimed at reducing workplace stress and enhancing self-efficacy may strengthen immune responses and lower the burden of persistent HPV infections.

Keywords: human papillomavirus (HPV), persistent infection, burnout, emotional exhaustion, personal accomplishment, work-related stress

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Апстракт

Вовед. Перзистентната инфекција со високо ризичните хуман папилома вируси (ХПВ) претставува главен предуслов за развој на цервикалните преканцерозни и цервикален карцином. Иако повеќето ХПВ инфекции се транзиторни, психосоцијалните и факторите поврзани со работата, како што се професионалниот стрес и синдромот на прегорување, можат да го нарушат имунолошкиот одговор и да ја зголемат подложноста на вирусна перзистентност.
Методи. Во студијата беа вклучени 146 жени, од кои 95 со перзистентна ХПВ инфекција и 51 без инфекција по 24 месеци. ХПВ генотипизацијата беше извршена со помош на мултиплекс real-time PCR метода. Психолошките фактори поврзани со работата беа оценети со стандартизирани прашалници, вклучувајќи го и прашалникот Maslach Burnout Inventory (MBI). За статистичка анализа беа применети Mann-Whitney U тест, Fisher's exact тест и бинарна логистичка регресија.
Резултати. ХПВ 16 беше најзастапениот генотип кај перзистентните ХПВ инфекции (46,3%), по што следеа типовите ХПВ 31, ХПВ 52, ХПВ 18, ХПВ 45, ХПВ 33, ХПВ 53 и ХПВ 73. Жените со перзистентна ХПВ инфекција беа значително постари во

споредба со контролната група (35,3±8,7 наспроти 32,7±8,9 години, p=0,04). Социодемографските варијабли како образованието, секторот на вработување и работното искуство не се покажаа како значајни предиктори на перзистенција. Во логистичката регресија, димензијата на прегорување Личен успех, се покажа како силен заштитен фактор, кој го намалува ризикот од перзистентна ХПВ инфекција за 31% (Exp(B)=0,690; 95% CI: 0,602-0,791; p <0,001). Димензијата Емоционална исцрпеност не покажа значајна асоцијација. Предиктивниот модел демонстрираше вкупна точност од 82,2% (сензитивност 91,6%, специфичност 64,7%).

Заклучок. Димензијата Личен успех, која ја одразува поголемата професионална ефикасност и психолошка резилиентност, се издвојува како најсилен заштитен фактор против перзистентната ХПВ инфекција. Овие наоди ја потенцираат важноста од интеграција на психосоцијални проценки во стратегиите за јавно и професионално здравје. Интервенциите насочени кон намалување на работниот стрес и зајакнување на самоефикасноста може да го подобрат имунолошкиот одговор и да го намалат товарот на перзистентните ХПВ инфекции.

Клучни зборови: хуман папилома вирус (ХПВ), перзистентна инфекција, синдром на прегорување, емоционална исцрпеност, лична успех; стрес

Introduction

Burnout has become a prominent topic in occupational health research over the last decades, reflecting the growing recognition of work-related psychological stressors and their impact on overall health. Burnout is traditionally conceptualized as a three-dimensional construct, consisting of emotional exhaustion, cynicism or depersonalization, and reduced personal accomplishment [1]. These dimensions capture the chronic response to sustained job-related stress and are widely recognized in both clinical and organizational settings.

The burnout construct is defined as a psychological syndrome caused by a prolonged response to interpersonal stressors, mainly at the workplace, which encompasses three dimensions: emotional exhaustion, depersonalization, and a decrease in personal achievements. Recently, the World Health Organization (WHO) has included burnout in the International Classification of Diseases (ICD-11) in the section 'Factors influencing health status or contact with health services' under the definition of 'Burnout' (QD85) [2].

According to some studies, emotional exhaustion is a core dimension of burnout, while reduced achievement and depersonalization occur with varying intensity depending on the professional context [3]. In healthcare professionals, burnout has been extensively studied, with evidence showing that it contributes not only to diminished work performance and increased medical errors, but also to negative health outcomes [4,5].

The consequences of burnout extend beyond psychological well-being. A systematic review of prospective studies revealed that burnout is associated with a wide spectrum of adverse outcomes, including cardiovascular diseases, musculoskeletal disorders, sleep problems, depression, and impaired immune function [6]. These consequences may increase susceptibility to chronic diseases and infections. Furthermore, burnout shows strong correlations with depression and anxiety [7], which may mediate biological mechanisms such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and impaired cellular immunity. These pathophysiological mechanisms are of particular importance in relation to the persistence of viral infections, as they may compromise the host's ability to mount an effective immune response, thereby facilitating viral survival, replication, and the progression toward chronic or recurrent infection [4,5].

Human papillomavirus (HPV) is one of the most frequent sexually transmitted infections [8]. Nearly all sexually active individuals will encounter an HPV infection at some point in their life. Most infections resolve spontaneously within 1–2 years. However, an HPV infection can become persistent and lead to precancer or cancer at female anogenital sites, including the cervix, vulva, vagina and anal canal. Virtually all high-grade cervical intraepithelial neoplasia (CIN) and cervical cancers are caused by high-risk HPV (hrHPV) infections [9-11]. HPV infection has been closely associated with cervical invasive squamous cell carcinoma (SCC) and most cervical adenocarcinoma lesions [10,12]. To date, 227 HPV types have been identified in humans, of which approximately 40 alpha-types are recognized as causative agents of over 750,000 malignancies annually. Among these, HPV 16 and HPV 18 are the most prevalent, together accounting for more than 80% of the global cervical cancer burden, while additional high-risk types such as HPV 31, HPV 33, HPV 45, and HPV 58 are also strongly associated with cervical and anogenital cancers. Notably, HPV 16 is not only the predominant oncogenic type in cervical cancer but is also linked to head and neck cancers. These oncogenic HPV types are classified as high-risk (HR), in contrast to low-risk (LR) types such as HPV 6 and HPV 11, which are associated primarily with benign, self-limiting lesions [13-15].

Taken together, the evidence suggests that work-related psychological stressors, manifested through burnout, may have influence not only on mental health but also on vulnerability to persistent infections. Investigating the role of burnout and its psychological dimensions as predictors of persistent HPV infection could therefore provide new insights into the intersection of

occupational health, mental well-being, and infectious disease outcomes.

Materials and methods

This case control study included 146 women: 95 with persistent HPV infection (infection present ≥24 months after initial diagnosis) and 51 in whom the infection had cleared. All participants provided written informed consent, and the study was approved by the Ethics Committee for Human Research, Faculty of Medicine, Skopje.

The analysis of the samples, cervical swabs taken from patients, was performed in the Laboratory for molecular diagnostics and HPV typing at the University Clinic for Gynecology and Obstetrics, Skopje. DNA was extracted using a commercial kit for urogenital samples, followed by detection and genotyping with a multiplex real-time PCR assay (cyclic-CMTA). This method enables simultaneous amplification, detection, and differentiation of 19 high-risk HPV types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70), including an internal control.

Sociodemographic and occupational data were collected with a structured questionnaire addressing education, job sector, and work experience. Burnout was assessed using the Maslach Burnout Inventory-General Survey (MBI-GS), covering emotional exhaustion, depersonalization, and personal accomplishment. Items were rated on a 7-point Likert scale (0=never to 6= every day), with higher exhaustion and depersonalization scores indicating greater burnout, and higher accomplishment scores reflecting greater professional efficacy.

Statistical analysis was performed using SPSS, v23. Descriptive statistics were calculated, and group differences were tested with the Mann-Whitney U test and Fisher's exact test (Monte Carlo correction). Logistic regression was applied to assess predictors of persistent HPV infection. The predictive values for persistent HPV infection were quantified by applying binary logistic regression analysis [Wald, Exp (B), 95.0% CI for Exp (B), p], using the Enter method. Reliability of the MBI subscales was assessed using Cronbach's alpha. Statistical significance was considered for values of $p<0.05$, while highly significant values were $p<0.01$. For the purposes of our study, only some of the obtained results are presented.

Results

Out of a total of 146 participants, 95 had persistent HPV infection, of which 58 presented with a single HPV type, while 37 had mixed HPV infections. Table 1 presents the structural percentages of HPV types among patients with persistent HPV infection.

Table 1. HPV type / Persistent HPV infection

HPV type	Count	Cumulative Count	Percentage	Cumulative Percentage	HPV type	Count	Cumulative Count	Percentage	Cumulative Percentage
16	27	27	28.42	28.42	52; 40	1	70	1.053	73.68
18	3	30	3.16	31.58	16; 56	1	71	1.053	74.74
31	8	38	8.42	40.00	16; 54	1	72	1.053	75.79
33	3	41	3.16	43.16	45; 59	1	73	1.053	76.84
35	1	42	1.05	44.21	16; 6	2	75	2.11	78.95
39	1	43	1.05	45.26	31; 53; 56; 73	1	76	1.053	80.00
45	4	47	4.21	49.47	16; 45	2	78	2.11	82.11
52	4	51	4.21	53.68	16; 52; 73	1	79	1.053	83.16
53	1	52	1.053	54.74	18; 33; 59; 73	1	80	1.05	84.21
56	1	53	1.053	55.79	31; 59; 61	1	81	1.053	85.26
58	3	56	3.16	58.95	31; 42	2	83	2.11	87.37
66	1	57	1.05	60.00	31; 82; 42	1	84	1.053	88.42
73	1	58	1.05	61.05	52; 58	1	85	1.053	89.47
16; 51; 56	1	59	1.05	62.11	31; 59	1	86	1.053	90.53
16; 51	1	60	1.053	63.16	16; 73; 6	1	87	1.053	91.58
39; 59	1	61	1.053	64.21	18; 33; 45; 6	1	88	1.053	92.63
51; 52; 53	1	62	1.053	65.26	16; 42	1	89	1.053	93.68

16; 31	2	64	2.11	67.37	16,;53	1	90	1.053	94.74
68; 42	1	65	1.053	68.42	16; 73	1	91	1.053	95.79
18; 52; 40	1	66	1.053	69.47	16; 33	1	92	1.053	96.84
18; 31; 54	1	67	1.053	70.53	53; 11	1	93	1.053	97.89
18; 51	1	68	1.053	71.58	33; 67; 42	1	94	1.053	98.95
53; 59; 61	1	69	1.053	72.63	16; 66	1	95	1.053	100.00

The most frequently isolated type was HPV 16, detected in 44 patients (46.3%), of which 27(28.42%) had HPV 16 as a single infection, while 17(17.9%) had HPV 16 as part of mixed HPV infections. The next most prevalent types were: HPV 31, HPV 52, HPV 18, HPV 45, HPV 33, HPV 53, and HPV 73.

Table 2 presents the descriptive statistics of patients' age. The age of patients with persistent HPV infection was 35.32±8.73 years (95% CI: 33.54-37.09) and of patients without persistent HPV infection 32.73 ± 8.88 years (95% CI: 30.23-35.22).

Table 2. Descriptive statistics of patients' age

Age	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Median	Minimum	Maximum	Std. Dev.
Persistent HPV infection	95	35.32	33.54	37.09	34.00	21.00	57.00	8.73
Non-persistent HPV infection	51	32.73	30.23	35.22	30.00	21.00	57.00	8.88

The age of patients with persistent HPV infection was significantly higher compared to those with non-persistent HPV infection (Z = 2.04, p = 0.04)

In the performed crosstabulation between patients' HPV status and their employment sectors, Fisher's exact test yielded a value of 5.101 with p>0.05 (p=0.535; Monte Carlo Sig. [2-sided]=0.522-0.548), indicating no significant difference or association.

Figure 1 presents the results regarding the education of employed patients. Crosstabulation between patients' HPV status and their level of education yielded Fisher's exact test=3.437 with p >0.05 (p=0.652; Monte Carlo Sig. [2-sided]=0.639-0.664), indicating no significant difference or association.

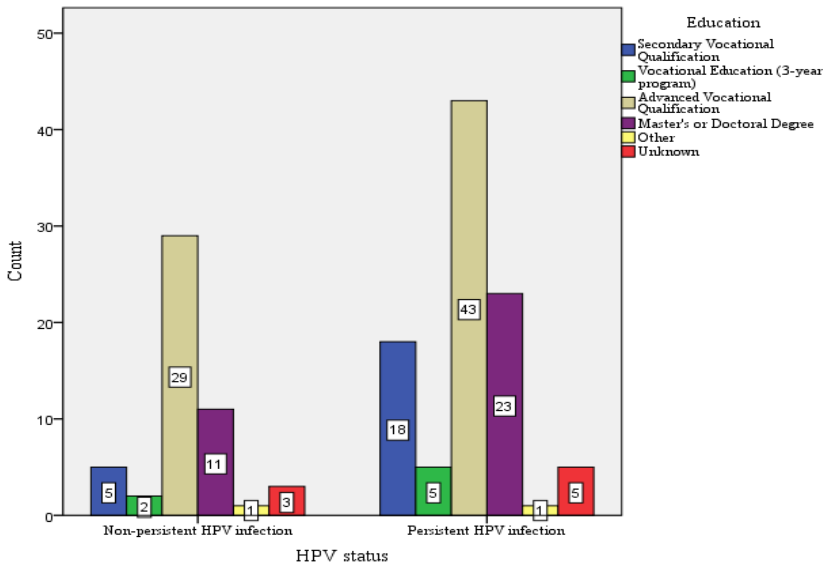

Fig. 1. HPV status & Education

Patients with persistent HPV infection had a nonsignificant longer work experience compared to those with non-persistent HPV infection (Z=1.72, p= 0.09).

An increase in age by one year was associated with a 6.6% higher risk of persistent HPV infection (Exp (B) =1.066; 95% CI for Exp (B): 0.977-1.164), although this was not statistically significant (p=0.153). Patients with a secondary vocational qualification had a 2.37-fold higher risk of persistent HPV infection compared to those with an advanced vocational qualification (Exp (B)=2.371; 95% CI for Exp (B): 0.726-7.741), a difference that did not reach statistical significance (p =0.153). Employment in the Production, Energy, and Construction sectors was associated with a 1.84-fold higher risk compared to those employed in Finance, Business, and Consulting (Exp (B)=1.844; 95% CI for Exp (B): 0.533-6.379), but also not statistically significant (p=0.334).

Table3. Binary Logistic Regression Analysis for Prediction of Persistent HPV Infections

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B) Lower	Upper
Step 1[a]	Age	.064	.045	2.047	1	.153	1.066	.977	1.164
	Production, Energy and Construction Sectors (1)	.612	.633	.934	1	.334	1.844	.533	6.379
	Trade, Services and Transportation (1)	.003	.525	.000	1	.996	1.003	.358	2.808
	Public and Social Services (1)	(.151)	.490	.095	1	.758	.860	.329	2.246
	Culture, Arts and Recreation (1)	(1.363)	1.260	1.170	1	.279	.256	.022	3.024
	Secondary Vocational Qualification (1)	.863	.604	2.044	1	.153	2.371	.726	7.741
	Vocational Education (1)	.763	.902	.716	1	.398	2.145	.366	12.577
	Masters or Doctoral Degree (1)	.145	.460	.099	1	.753	1.156	.469	2.850
	Unknown (1)	.048	.834	.003	1	.954	1.049	.205	5.373
	Work experience	(.035)	.055	.415	1	.520	.965	.866	1.075
	Constant	(1.532)	1.152	1.769	1	.184	.216		

To determine the predictive values of emotional exhaustion, personal accomplishment for persistent HPV infections, the Enter method was applied. The overall accuracy of this model in predicting persistent HPV infections was 82.2%, with a sensitivity of 91.6% and a specificity of 64.7%.

Table 4. Binary Logistic Regression Analysis for Prediction of Persistent HPV Infections

		B	S.E.	Wald	df	Sig.	Exp (B)	95% C.I. for EXP (B) Lower	Upper
Step 1[a]	Total1	.027	.032	.707	1	.400	1.027	.965	1.093
	Total2	(.371)	.070	28.368	1	**.000**	.690	.602	.791
	Constant	12.172	2.205	30.479	1	.000	193357.860		

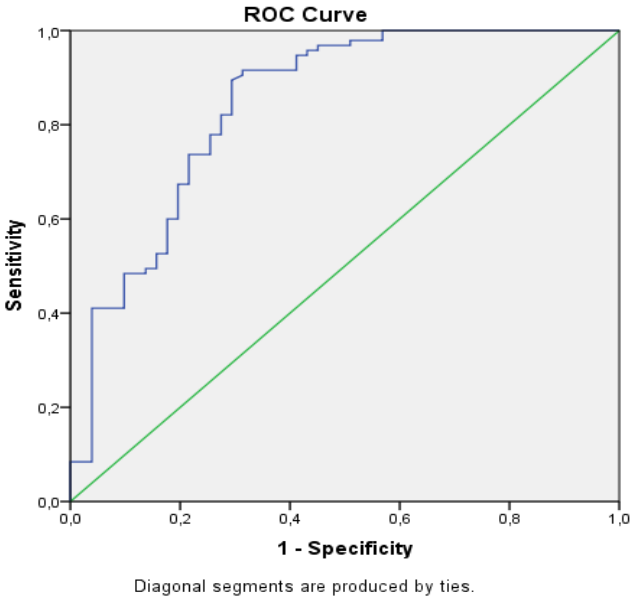

Fig. 2. ROC area

In assessing the significance of predictors for persistent HPV infection, the strongest effect was observed for personal accomplishment (Total 2) (Wald=128.368, p<0.001), while emotional exhaustion (Total 1) showed the weakest and non-significant effect (Wald=0.707, p=0.400) (Table 19.1). An increase of one unit in emotional exhaustion (Total 1) raised the risk of persistent HPV infection by 2.7% (Exp (B)=1.027; 95% CI: 0.965-1.093; p=0.400, not significant). Conversely, an increase of one unit in personal accomplishment (Total 2) reduced the risk by 31% (Exp (B)=0.690; 95% CI: 0.602-0.791; p<0.001, significant).
The ROC area is 0.842, which means that in 84.20% /95%CI:0.770-0.915/ p<0.001 (p=0.000) / of all possible pairs in which one has persistent HPV infection and the other does not have persistent HPV infection, this model will determine a higher probability of persistent HPV infection (Figure 2).

Discussion

Our findings confirm HPV 16 as the dominant genotype in persistent infections, both as a single infection and in combination with other high-risk types. This dominance of HPV 16 aligns closely with multiple recent studies which report HPV 16 as the leading high-risk type associated with persistent infection and oncogenic outcomes. Zhao *et al.* found that HPV 16 was the most prevalent persistent genotype, followed by HPV 52, 31, 35, and 53 [16,17]. Similarly, Jing *et al*. reported HPV 16 among the most common types in both single and multiple infections in their population [18].
The pattern of mixed *versus* single infections in our findings, where nearly half of the persistent infections involved mixed HPV types, is consistent with broader epidemiologic evidence. Studies such as those by Kim *et al.* and Damgaard *et al.* show that mixed infections, including HPV 16 plus other HR types, are common and sometimes associated with higher severity of lesions [19,20].
Notably, genotypes HPV 31, HPV 52, HPV 18, HPV 45, HPV 33, HPV 53, and HPV 73 appear in our results among the next most prevalent types. This matches with the findings in recent studies by Zhao *et al.* where HPV 52 and HPV 31 follow HPV 16 in prevalent rank, reinforcing the global pattern that these HR types are among key contributors to persistent HPV burden [16]. Our results support the hypothesis that HPV 16 has the strongest oncogenic potential in persistent infection settings.
Our study demonstrated that the mean age of patients with persistent HPV infection was significantly higher than that of patients without persistent infection. These findings are consistent with previous reports, such as those by Castle *et al*. and Plummer *et al*., which showed that increasing age is associated with reduced viral clearance and a higher likelihood of persistent HPV infection [21,22]. This effect has been attributed to age-related changes in immune competence and the cumulative exposure to risk factors across the lifespan. Although our results showed only a nonsignificant trend toward longer work experience in the persistent group, this finding may reflect the role of prolonged exposure to occupational stressors in impairing immune responses. This interpretation is in line with findings by Kuebler *et al.* [23] and Fang *et al.* [24], who reported that psychological stress can influence immune function and increase susceptibility to persistent viral infections, as well as broader psychoneuroimmunology research highlighting the role of stress in immune dysregulation and disease susceptibility [3-5].
No significant differences were found between groups concerning educational attainment. However, women with only secondary vocational qualifications showed a higher, though nonsignificant, risk of persistent infection compared to those with advanced vocational training or higher academic degrees. These observations are in line with studies by Kops *et al*. [25] and Swai *et al.* [26], which demonstrated that lower educational level and socioeconomic status are associated with increased risk of HPV infection and persistence due to reduced screening participation and delayed healthcare access.
Our analysis did not reveal significant differences between women with persistent and non-persistent HPV infections regarding employment sector. On the contrary, Shoji *et al.* found significant differences between the occupational groups in the self-efficacy burnout associations, and the strongest associations were found for teachers [27]. The observed differences may be due to the relatively small number of patients included in our study compared to the meta-analysis by Shoji *et al.*
Among the burnout dimensions, personal accomplishment emerged as the strongest protective factor, reducing the risk of persistent HPV infection by 31%, whereas emotional exhaustion did not show a significant effect. This pattern aligns with the conceptual framework of Maslach and Leiter [1] and with evidence from Edú-Valsania *et al.* [2], who emphasized that positive psychological resources such as efficacy and accomplishment mitigate the negative impact of stress on health outcomes. In addition, findings by Koutsimani *et al.* [6] support the view that burnout dimensions are differentially associated with psychological well-being and biological responses. These results suggest that professional efficacy and accomplishment may strengthen adaptive coping and immune function, consistent with previous work on coping mechanisms and psychological outcomes [28-31]
This interpretation is further supported by studies examining the biological mechanisms of stress. For example, Glaser and Kiecolt-Glaser [32] and Cohen *et al.* [33] demonstrated that chronic stress was linked to immune dysregulation and higher susceptibility to vi-

ral infections. Similarly, Dhabhar (34) and Steptoe and Kivimäki [35] showed that psychosocial stress was associated with changes in immune competence and health outcomes, providing a plausible explanation for the association observed in our study. This is consistent with psychoneuroimmunology literature, which demonstrated that stress alters cytokine profiles and weakens antiviral defense [32-38].

Our findings have important implications for both clinical practice and occupational health. They suggest that psychosocial resources, particularly professional efficacy and personal accomplishment, may play a protective role against persistent HPV infection. This interpretation is consistent with evidence from Koutsimani *et al.* [6], who showed that burnout was closely related to psychological distress and health outcomes, and with Kuebler *et al.* [23], who highlighted the role of stress in influencing immune function. Furthermore, the review by Edú-Valsania *et al.* [2] emphasized that positive psychological factors such as accomplishment can mitigate the effects of work-related stress, thereby supporting resilience. Future research should focus on larger and more diverse populations, adopt longitudinal designs, and integrate biological markers of stress alongside psychosocial assessments in order to better understand the interplay between burnout, immunity, and viral persistence.

Conclusion

This study highlights the influence of work-related psychological factors on the persistence of high-risk HPV infection. While sociodemographic and occupational variables such as age, education, and job sector did not emerge as significant predictors, trends suggest that contextual stressors may interact with psychological resources to shape outcomes. Among burnout dimensions, personal accomplishment was identified as the strongest protective factor, reducing the risk of persistence by 31%, whereas emotional exhaustion showed no significant effect. These findings emphasize that resilience and professional efficacy may play a critical role in supporting immune function and controlling viral infections. Incorporating psychosocial assessments into preventive and occupational health strategies could improve early risk identification and guide interventions aimed at enhancing resilience, thereby contributing to better HPV control and reduced burden of HPV-related malignancies.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 159-163

MMP

Original article

QUALITY OF ANTICOAGULATION IN PATIENTS WITH ATRIAL FIBRILLATION ON ACENOCOUMAROL

КВАЛИТЕТ НА АНТИКОАГУЛАЦИЈА КАЈ ПАЦИЕНТИ СО ПРЕТКОМОРНА ФИБРИЛАЦИЈА НА АЦЕНОКУМАРОЛ

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Abstract

Introduction. Acenocoumarol remains the predominant oral anticoagulant prescribed for patients with atrial fibrillation (AF) in the Republic of North Macedonia. Despite contemporary clinical guidelines that emphasize the superiority of novel oral anticoagulation drugs (NOAC) in terms of efficacy and safety, the utilization of acenocoumarol persists largely driven by economic constraints.

Aim. To evaluate the impact of age on quality of oral anticoagulant therapy (OAT) in patients with AF placed on acenocoumarol and the impact of seasonal variation on the quality of OAT.

Methods. This retrospective, cross-sectional study comparised 91 patients with permanent AF receiving acenocoumarol during the period from January 2020 to December 2022. Recommended optimal therapeutic range of the international normalized ratio (INR) was 2.0-3.0. Rosendaal method was used for calculating time in therapeutical range (TTR). Participants in the study were selected by using inclusion and exclusion criteria.

Results. The mean age of participants was 76 years (±7.9). The majority of them (65%) were women (n=59). Optimal anticoagulation with TTR >70% was not achieved in any age group. The average TTR among all participants was 46.18% (±27.21). The highest value of TTR was 56.82% in the group aged 60–69, while the lowest TTR was 43.01% in the group aged 80–89. The study confirmed seasonal variation of the INR values, although the highest levels were recorded during the coldest months.

Conclusion. Identification of factors contributing to suboptimal anticoagulation is essential to achieve optimal anticoagulation in patients with AF. Personalized care (frequent follow-up and potential to adhere to the prescribed therapy) lead patients to better choice and decision that affect their health and wellbeing.

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Keywords: Rosendaal method, INR, acenocoumarol, TTR

Апстракт

Вовед. Во Република Северна Македонија аценокумаролот останува доминантен орален антикоагулант препишан за пациенти со преткоморна фибрилација (ПФ). И покрај постоечките клинички водичи кои ја нагласуваат супериорноста на новите антикоагулантни лекови (НОАК) во однос на ефикасноста и безбедноста, употребата на аценокумарол и понатаму е во тек во голема мера заради економски ограничувања.

Цел. Да се евалуира влијанието на возраста врз квалитетот на оралната антикоагулантна терапија (ОАТ) кај пациенти со ПФ поставени на аценокумарол и влијанието на сезонските варијации врз квалитетот на ОАТ.

Методи. Ова е ретроспективна, пресечна студија на 91 пациент со перманентна ПФ поставени на аценокумарол во периодот од јануари 2020 до декември 2022. Препорачаниот оптимален тераписки ранг на интернационалниот нормализиран однос (INR) беше 2,0-3,0. Беше користен методот по Розендал за калкулирање на времето во терапевтски ранг (TTR). Селекцијата на учесници во студијата беше направена со користење инклузиони и ексклузиони критериуми.

Резултати: Средната возраст на учесниците беше 76 години (±7,9). Мнозинството од нив (65%) беа жени (n=59). Оптимална антикоагулација со TTR>70% не беше постигната во ниту една возрасна група. Просечното TTR на целата група беше 46,18% (±27,21). Највисока вредност на TTR 56,82% беше постигнат во возрасната група од 60-69 години, додека најниска вредност на TTR од 43,01% имаше кај возрасната група од 80-89 години. Во студијата беше потврдена сезонска варијација на INR, иако највисоки вредности на INR беа забележани во најстудените месеци.

Заклучок. Идентификацијата на факторите кои придонесуваат до субоптимална антокоагулација е од суштинско значење за да се постигне оптимална антикоагулација кај пациентите со ПФ. Персонализираната грижа (често следење и придржување кон препишаната терапија) доведува до подобар избор и одлука кои влијаат врз нивното здравје и благосостојба.

Клучни зборови: Розендал метод, INR, аценокумарол, TTR

Introduction

For patients diagnosed with atrial fibrillation (AF) in the Republic of North Macedonia acenocoumarol remains the most commonly prescribed anticoagulant reflecting a notable divergence from current clinical guidelines which advocate the use of novel oral anticoagulants (NOACs). Despite the strong recommenddations favoring NOACs due to their favorable safety profiles, ease of use and predictable pharmacokinetics, acenocoumarol's persistent presence in clinical practice can predominantly be attributed to economic considerations [**Error! Reference source not found.**]. Initiation of acenocoumarol therapy poses significant challenges, primarily due to numerous factors that can markedly affect the appropriate dosing of this anticoagulant. Management of acenocoumarol treatment is particularly complex because several variables, including potential interacttions with other medications, presence of acute illnesses and dietary influences-particularly consumption of green leafy vegetables-can lead to substantial variations of the international normalized ratio (INR) values [2]. Unwanted challenges to the regular use of vitamin K antagonists include also frequent INR checks at transfusions, and frequent adjustments to the daily dosage.

Aim

The primary aim of this study was to evaluate the quality of oral anticoagulant therapy (OAT) in patients with non-valvular AF receiving acenocoumarol. This was achieved by assessment of the time in therapeutic range (TTR), identifying factors contributing to suboptimal anticoagulation such as age. The secondary aim was to evaluate the variation of the INR value based on factors like season variation.

Material and methods

This retrospective, cross-sectional study comprised 91 patients with permanent AF receiving acenocoumarol during the period from January 2020 to December 2022.
Inclusion criteria were:

- Patients with permanent AF;
- Patients receiving acenocoumarol with AF longer the two years;
- Patients with estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m²;
- Patients with CFS (Clinical Frailty Scale), fragility 4 points or less [3].

Exclusion criteria were:

- Patients with paroxysmal type of AF;
- Patients switched to NOAC, then returned on vitamin K antagonist;
- Patients with implanted mechanical valve;
- Patients with active malignant disease and/or active chemotherapy;
- Patients receiving dual antiplatelet therapy;
- Patients with high HAS-BLED score (>3);
- Patients with previous stroke history.

We performed statistical analysis of INR values extracted from patients' electronic medical records at the Institute for Transfusion Medicine of the Republic of N. Macedonia. The TTR was calculated using the Rosendaal method [4]:

- INR-Standardized prothrombin time, international standard for prothrombin time (PT) represents the calculated value as a ratio of the patient's PT to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization[1] using the formula: [4]
- INR = Patient PT ÷ Control PT
- The recommended INR range for patients with atrial fibrillation and non-mechanical heart valves is between 2 and 3 [1]. No special preparation is required for blood sampling for this test. Since our patients had recommendation for taking their medication at 5 p.m., delaying therapy for the test was not necessary.
- TTR - Time in therapeutic range (TTR) represents the proportion of INR values within the target range relative to the total number of INR measurements. The simplest method to calculate TTR is the Rosendaal method. According to the latest ESC guidelines for atrial fibrillation (2024), adequate anticoagulation is defined as a TTR > 70% [1];
- The Rosendaal method assumes a linear progression of INR changes between patient visits. This method estimates the number of days spent within the therapeutic range since the last visit. We utilized the online INR Pro calculator for this calculation [4].

Results

The average age of patients was 76 (±7.9) years. Majority of patients (65%) were female (59) and 35% were male (32) (Figure 1).

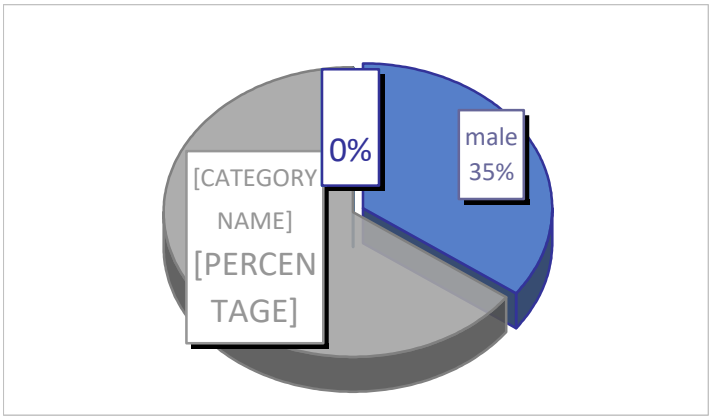

Fig. 1. Gender distribution

The largest age group was 70-79 years, consisting of 41 patients (45%). The smallest group was 60-69 years, with 11 patients (12.1%). There were 27 patients (29.7%) in the 80-89 years age range, and 12 patients (13%) were in the 90-99 years age group (Figure 2). Over the three-years study period, a total of 1,890 INR results were processed corresponding to an average of 20.9 (±4.4) measurements per patient. On average, patients had seven INR measurements per year, with an average interval of 54 days between two consecutive INR tests. All INR check-ups were predetermined with date and time from the transfusions. The majority of INR tests were conducted during the winter months (December, January, and February), with a total of 540 results, and the highest number performed in December. In contrast, the fewest tests were performed during the spring months (March, April, May), totaling 398 results, with April having the fewest at 115 checks (Figure 3).

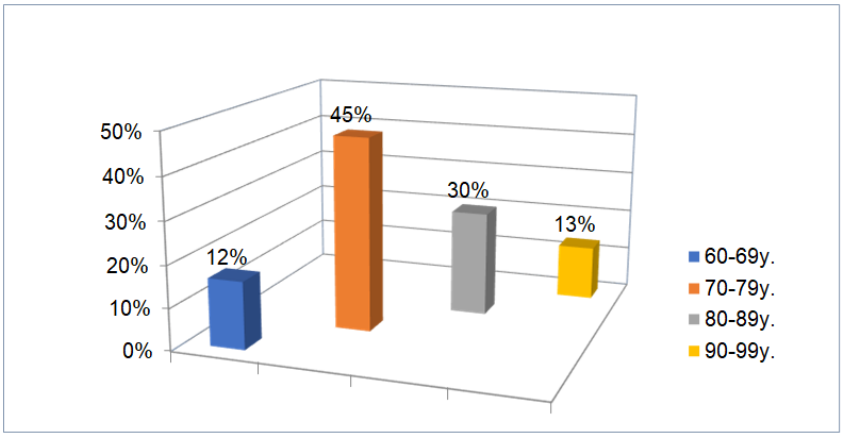

Fig. 2. Age distribution

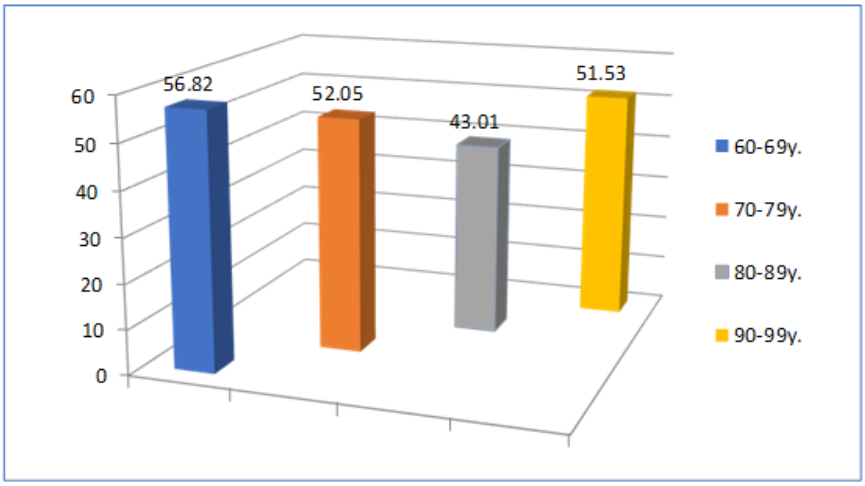

Fig. 3. Distribution of TTR according to age

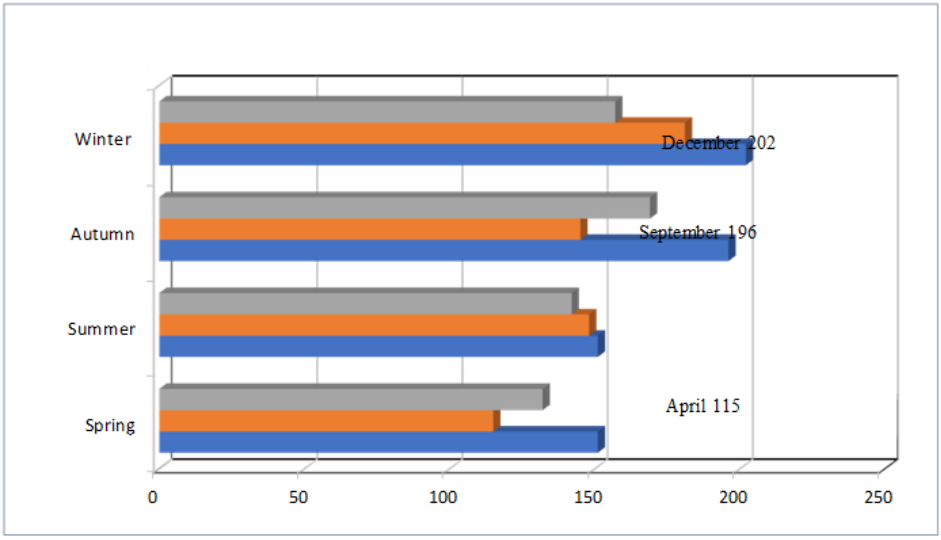

Fig. 4. Distribution of the INR results by season

The overall mean TTR of all participants was 46.18 (±27.21) indicating suboptimal anticoagulation control. The best anticoagulation control was observed in the youngest age group (56.82%). The lowest TTR (43.01%) was observed in the 80-89 years age group. None of the age groups achieved a TTR above 70%. Difference in the TTR values between the age group with highest and lowest value of TTR, 56.82% in the group of 60-69 years and 43.01% in the group of 80-89 years, accordingly, was statistically significant (p=0.003) (Figure 4). Seasonal variations in TTR values were observed throughout the year, indicating that INR levels fluctuated with the seasons.

The highest INR values were recorded during the autumn (2.3±1.03) and winter (2.25±0.88) months. Conversely, the lowest INR values were observed during the spring (2.05±0.68) and summer (2.03±0.69) months. Analysis of the seasonal variation in INR value revealed significantly higher levels during the coldest months (autumn and winter; mean INR 2.27±0.96, n=1,050) compared to warmer months (spring and summer; mean INR 2.04±0.68, n=839). This difference was statistically significant (t=6.10, df≈1863, p<0.001), indicating a clear seasonal pattern in anticoagulation control.

Discussion

In this study, the overall anticoagulation control among patients with permanent AF on acenocoumarol was suboptimal, with mean TTR of 46.18%, well below the recommended 70%. This low TTR underscores the challenges in maintaining consistent and optimal anticoagulation in real-world clinical settings, which was important implication for preventing thromboembolic events and bleeding complications in the high-risk population. A noteworthy aspect of the findings is the significant influence of age on anticoagulation quality [5-7]. Younger patients exhibited better INR control and higher TTR values, whereas older patients, particularly those 80-89 years, showed the lowest TTR. This observation aligns with prior research suggesting that advanced age is more associated with variable INR control [5-7]. Several factors likely contribute to this disparity: older adults frequently have multiple comorbidities that necessitate complex medication regimens (polypharmacy), which can interfere with pharmacokinetics and pharmacodynamics of vitamin K antagonist like acenocoumarol. Additionally, age-related physiological changes-such as altered liver metabolism, decreased renal function and variable dietary vitamin K intake-may further destabilize anticoagulant response, making management more challenging in this subgroup. Besides patient-related factors, the study highlights the impact of the environmental and behavioral influences on anticoagulation efficacy by demonstrating clear seasonal variation.

Seasonal variation and TTR values during the colder months (autumn and winter) compared to the warmer months (spring and summer), suggest that temperature, lifestyle changes or other seasonal factors may enhance stability of anticoagulation control. The statistically significant difference (t=6.10, df≈1863, p<0.001) confirms the robustness of the seasonal effect. This pattern might be explained by multiple potential mechanisms: colder weather may increase vitamin K intake through altered dietary habits, such as the consumption of vitamin potassium–rich winter vegetables; changes in physical activity levels and illness patterns across seasons may affect metabolism and drug response; and differences in exposure to sunlight, influencing vitamin D levels might indirectly modulate coagulation pathway [8].

Moreover, the study found that the frequency and number of INR measurements were higher in colder months, which likely contributed to better anticoagu-

lation control. More frequent monitoring allows timely dose adjustments, preventing prolonged periods of sub- or supratherapeutic INR value [9]. This finding suggests that intensified monitoring strategies during periods of increased risk improve overall anticoagulation quality.

These results emphasize the multifactorial nature of anticoagulation management, where patients' demographics, comorbid conditions, environmental factors and healthcare processes all interplay to determine therapeutic outcomes. From a clinical perspective, these data advocate for incorporating considerations as closer follow-up, medication review to reduce polypharmacy and patient education on lifestyle factors that may influence INR stability.

Furthermore, awareness of seasonal variation could inform clinical decision-making and resource allocation, including more intensive INR monitoring and patients counseling during warmer months, when control tends to be poorer, to mitigate risks of adverse events. Integration of new technology such as INR monitoring or digital health platforms could also help bridge seasonal gaps and enhance patient adherence.

This study adds important knowledge about how demographic and seasonal factors influence anticoagulation in patients with permanent AF treated with acenocoumarol. These findings call for multifaceted interventions targeting at risk groups, especially older adults and adaptive management strategies that reflect seasonal patterns to optimize safe and effective anticoagulant therapy.

Conclusion

This study demonstrates that overall anticoagulation control in patients with AF on acenocoumarol is suboptimal, with TTR values well below the recommended target. Age significantly influences therapy quality, with older patients exhibiting poorer control. Additionally, seasonal variation affects INR levels, with higher TTR observed during colder months. These findings underscore the need for closer monitoring and individualized management of oral anticoagulation, particularly in elderly patients and during warmer periods, required to improve therapeutic outcomes and to reduce the risk of thromboembolic or hemorrhagic complications.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 164-168

ММР

Original article

THE IMPACT OF *GARDNERELLA VAGINALIS* INFECTION ON PRETERM BIRTHS IN OUR CLINICAL CASES

ВЛИЈАНИЕТО НА ИНФЕКЦИЈАТА СО GARDNERELLA VAGINALIS ВРЗ ПРЕДВРЕМЕНОТО ПОРОДУВАЊЕ НА НАШИОТ МАТЕРИЈАЛ

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Abstract

Introduction. The causes of preterm birth are multifactorial and include genetic, social, anatomical, hormonal and infectious factors. Among the most common pathogens of vaginal infections associated with preterm birth is *Gardnerella vaginalis*, a facultative anaerobic bacterium that is often present in cases of bacterial vaginosis.
Aim. The aim of this study was to analyze the impact of *Gardnerella vaginalis* infection on the incidence of preterm birth, based on clinically collected data from our patients.
Methods. The study was prospective, analytical, and included 819 pregnant women with preterm birth in the period from 01.01.2023 to 31.12.2023 at the University Hospital Center in Prishtina, Kosovo. Cervicovaginal samples were collected and analyzed for *Gardnerella vaginalis* infection with standard microbiological and PCR methods. Preterm birth was defined according to the WHO guidelines as birth before the 37th week of gestation. Collected data were statistically analyzed and presented in tables.
Results. The prevalence of *Gardnerella vaginalis* infection in patients delivered preterm was 9.43% (61 cases). Infection was associated with significantly increased leukocytes and CRP in mothers and newborns, lower birth weight, lower Apgar score, and a higher probability of cesarean section. The correlation between *Gardnerella vaginalis* infection and preterm birth was statistically significant ($p<0.0001$).
Conclusions. *Gardnerella vaginalis* infections significantly contributes to preterm birth through inflammatory mechanisms and damage to the integrity of fetal membranes. Early screening and treatment of cervicovaginal infections with *Gardnerella vaginalis* are essential for the prevention of premature births.

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Keywords: *Gardnerella vaginalis*, premature birth, bacterial vaginosis, pregnancy, inflammation

Абстракт

Вовед. Причините за предвремено породување се мултифакторијални и вклучуваат генетски, социјални, анатомски, хормонални и инфективни фактори. Помеѓу главните патогени агенси од вагиналните инфекции асоцирани со предвремено породување е Gardnerella vaginalis, факултативно анаеробна бактерија која е често присутна кај случаевите со бактериска вагиноза.
Цел. Целта на оваа студија е да се анализира влијанието на инфекцијата со Gardnerella vaginalis на инциденцијата на предвремени породувања, базирано на клинички добиените резултати од нашите пациентки.
Методи. Студијата беше проспективна, аналитичка, и вклучуваше 819 бремени жени со предвремено породување во периодот од 01.01.2023 до 31.12.2023 во Универзитетскиот Болнички Центар во Приштина, Косово. Цервико-вагиналните примероци беа собрани и анализирани за инфекција со Gardnerella vaginalis со стандарден микробиолошки и PCR метод. Предвремено породување беше дефинирано според водичите на СЗО како породување пред 37-та гестациска недела. Добиените податоци беа статистички обработени и презентирани во табели.
Резултати. Преваленцијата на инфекција со Gardnerella vaginalis кај предвремено породените пациентки изнесуваше 9,43% (61 случај). Инфекцијата беше асоцирана со сигнификантно зголемени леукоцити и ЦРП кај мајките и новородените, пониска родилна тежина, понизок Апгар Скор, како и поголема можност за Царски Рез. Корелацијата помеѓу инфекцијата со Gardnerella vaginalis и предвременото породување беше статистички сигнификантна ($p<0,0001$).
Заклучок. Инфекцијата со Gardnerella vaginalis сигнификантно придонесува за предвременото поро-

дување преку инфламаторни механизми и оштетување на интегритетот на феталните мембрани. Раниот скрининг и третман на цервиковагиналните инфекции со Gardnerella vaginalis се есенцијални за превенција од предвремено породување.

Клучни зборови: Gardneralla vaginalis, предвремено породување, бактериска вагиноза, бременост, инфламација

Introduction

Preterm birth is one of the greatest challenges in obstetrics and neonatology, being one of the leading causes of neonatal mortality and morbidity worldwide. The World Health Organization (WHO) defines preterm birth as birth occurring before the 37th week of gestation, including the interval from 28+0 to 36+6 weeks of pregnancy [1]. The causes of preterm birth are multifactorial and include genetic, social, anatomical, hormonal and infectious factors. However, studies in recent years have increasingly emphasized the role of cervicovaginal infections, especially those that cause changes in the vaginal microbiota [2,3]. Among the most common pathogens of vaginal infections associated with preterm birth is *Gardnerella vaginalis*, a facultative anaerobic bacterium that is often present in cases of bacterial vaginosis. Bacterial vaginosis is characterized by a disruption of the balance of the normal vaginal flora, with a reduction in *Lactobacillus spp.* and an increase in anaerobic bacteria such as *Gardnerella vaginalis*, *Mobiluncus*, *Prevotella* and *Mycoplasma hominis* [4]. This condition can lead to an inflammatory response at the level of the cervix and amniotic membranes, stimulating the production of proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF-α), which play a role in promoting uterine contractions and premature rupture of the membranes [5].

During pregnancy, the vaginal microbiota maintains a delicate balance that contributes to protection against infections. Hormonal and immune changes during pregnancy can affect this balance, creating favorable conditions for the colonization of *Gardnerella vaginalis*. The presence of this microorganism in the vagina has been associated in many studies with an increased risk of preterm birth, low birth weight and neonatal infections [6]. The mechanisms through which *G. vaginalis* affects these complications include increased degradation of cervical mucus, activation of inflammatory pathways and production of proteolytic enzymes that affect the integrity of amniotic membranes.

Assessing the impact of *Gardnerella vaginalis* infections on preterm birth is of particular clinical importance, as it helps prevent obstetric complications and improve the health of the mother and the baby. Early identification of women at high risk of vaginal infections allows for preventive interventions such as antibacterial treatment, regular obstetric monitoring, and education on intimate hygiene. In this sense, studying the relationship between Gardnerella vaginalis colonization and preterm birth constitutes an area of research with important values for clinical practice and health policies [7,8].

Aim

The aim of this paper was to analyze the impact of *Gardnerella vaginalis* infection on the incidence of preterm birth, based on the data collected from our clinical cases. The basic hypothesis of this study was that the presence of *Gardnerella vaginalis* in the vaginal flora significantly increased the probability of birth before the 37th gestational week, due to the stimulation of inflammatory mechanisms and damage to the integrity of the fetal membranes.

Materials and methods

This was a prospective study with an analytical character, conducted in the period from 01.01.2023 to 31.12.2023 in the Clinic for Gynecology and Obstetrics at the University Hospital Center in Prishtina, Kosovo.

The study was approved by the Ethics Committee of the Kosovo Medical Association. All participants provided written informed consent for the anonymous use of their data for research purposes, in accordance with the Declaration of Helsinki [9].

A total of 819 women with preterm births were included in the study. Bacterial infection was found in 647 women and *Gardnerella vaginalis* infection was detected in 61 cases.

In the group of patients without bacterial infection, there were 172 women.

Inclusion criteria: age 18-40 years, singleton pregnancy, no other obstetric pathologies such as preeclampsia, placenta previa, or gestational diabetes.

Demographic and obstetric data were obtained from medical records, including data on the week of birth, patient's WBC, patient's CRP, newborn's WBC, newborn's CRP, mode of delivery, newborn's weight, and Apgar score at the first and fifth minute.

Samples were taken from the vagina and cervix with sterile swabs and immediately placed in transport medium for microbiological analysis.

Diagnosis of *Gardnerella vaginalis* infection was based on the Amsel criteria, positive bacterial culture and identification with the automated VITEK 2 system (bioMérieux, France), and in some cases with PCR for confirmation of *Gardnerella vaginalis* DNA.

Preterm birth was defined as spontaneous birth occurring before the end of the 37th week of pregnancy,

with or without premature rupture of the amniotic membranes, according to the WHO guidelines.

Statistical analysis

Data were analyzed using SPSS v. 26 (IBM Corp., USA). Chi-square (χ^2) test was used for comparison of categorical variables, while Student's t-test was used for numerical variables. Relative risk (RR) and confidence intervals (CI 95%) were calculated to assess the association between *Gardnerella vaginalis* infection and preterm birth. A p-value <0.05 was considered as statistically significant.

Results

This part of the study presents the results obtained by the processing and statistical analysis of medical data of 819 patients from the University Clinical Hospital of Kosovo, Clinic for Gynecology and Obstetrics, who experienced premature birth.

Bacterial infection was found in 647 of the 819 patients included in the study, representing a prevalence of bacterial infections of 79% (Table 1).

Table 1. Distribution of patients in terms of frequency of bacterial infection

Bacterial infection	n(%)
yes	647(79)
no	172(21)
total	819

t (Student t-test), ***sig p<0.0001

Gardnerella vaginalis was present in 61 (9.43%) patients with bacterial infection.

Based on the gestational age at birth of the fetus, 2 groups were created: preterm birth, between 32-36+6 weeks of pregnancy, and preterm birth, between 28+0-31+6 weeks of pregnancy.

Gardnerella vaginalis infection was more frequently detected among patients who delivered between 28+0-31+6 weeks of gestation compared to patients with preterm births between 32-36+6 weeks of pregnancy (77% *vs*. 24%, p=0.00006) (Table 2).

Table 2. Isolated bacteria in patients with infection depending on gestational week of birth

Bacteria	n	Gestational week 28 +0– 31+6 n (%)	Gestational week 32 – 36+6 n (%)	p-level
Gardnerella vaginalis	61	54(77)	7(24)	X^2=16.12 ***p=0.00006

X^2(Chi-square test), **sig p<0.01, ***sig p<0.0001

Table 3. Leukocyte count in patients with *Gardnerella vaginalis* infection

Bacteria		n	WBC mother (x 10^9/L) mean ± SD	WBC mother (x 10^9/L) median (IQR) / min – max	p-level
Gardnerella vaginalis	yes	61	18.55±2.8	13.4-28.7	t=28.4
	no	172	9.07±1.9	6.1-19.8	p<0.0001

Z (Mann-Whitney U test), t (Student t-test), ***sig p<0.0001

There was a difference in the leukocyte count between patients with *Gardnerella vaginalis* infection and patients without infection (18.55±2.8 *versus* 9.07±1.9 x 109/L) (Table 3).

Significantly higher CRP level was observed in patients with *Gardnerella vaginalis* infection compared to patients without infection (mean 45.46±18.4 *vs*. 4.45±3.7 mg/dL, p<0.0001) (Table 4).

Table 4. CRP level in patients with *Gardnerella vaginalis* infection

Bacteria		n	CRP / mother (x 10^9/L) mean ± SD	CRP / mother (x 10^9/L) median (IQR)	p-level
Gardnerella vaginalis	yes	61	45.46±18.4	42(33.9-56)	Z=11.52
	no	172	4.45±3.7	4.1(3.1-4.8)	p<0.0001

Z (Mann-Whitney U test), t (Student t-test), sig p<0.0001

Table 5. Leukocyte values in newborns with bacterial infection with Gardnerella vaginalis

Bacteria		n	WBC / newborn (x 10^9/L) mean ± SD	WBC / newborn (x 10^9/L) min – max	p-level
Gardnerella vaginalis	yes	61	19.05±2.9	12.4-29.5	t=30.19
	no	172	8.87±1.9	6.1-19.1	p<0.0001

t (Student t-test), sig p<0.0001

The mean value of leukocytes was19.05 ± 2.9 x 109/L in newborns from mothers with *Gardnerella vaginalis* infection (Table 5).
Newborns from mothers with with *Gardnerella vaginalis* infections had significantly higher CRP levels compared to newborns from mothers without *Gardnerella vaginalis* infection (42.55±13.4 *vs*. 4.07±3.4 mg/dL) (p<0.0001) (Table 6).

Table 6. CRP level in newborns with bacterial infection with *Gardnerella vaginalis*

Bacteria		CRP / newborn (mg/dL) n	mean ± SD	median (IQR) / min – max	p-level
Gardnerella vaginalis	yes	61	42.55±13.4	46.1 (32-49.3)	Z=11.55
	no	172	4.07±3.4	3.45 (3-4.3)	p<0.0001

Z (Mann-Whitney U test), sig p<0.0001

Table 7. Mode of delivery in patients with bacterial infection with *Gardnerella vaginalis*

Bacteria		Birth method n	spontaneous (%)	cesarean section n (%)	p-level
Gardnerella vaginalis	no	172	167(97.09)	5(2.91)	X^2=13.6
	yes	61	51(83.61)	10(16.39)	***p=0.00023

X^2 (Pearson Chi-square test), ***sig p<0.0001

Infection in pregnant mothers with *Gardnerella vaginalis* was significantly associated with the mode of delivery, i.e. with termination of pregnancy by cesarean section (p<0.0001) (Table 7).
Birth weight less than 2500 grams was significantly more common in newborns delivered by mothers with *Gardnerella vaginalis* infection (95.08% *vs*. 10.47%) (Table 8). The tested difference in the distribution of newborns with birth weights lower and greater than 2500 grams in patients with and without infection with the bacteria presented in Table 8 was statistically significant (p<0.0001).

Table 8. Body weight of newborn less/more than 2500 g with bacterial infection with *Gardnerella vaginalis*

Bacteria		Body weight / newborn (g) n	< 2500 n (%)	≥ 2500 n (%)	p-level
Gardnerella vaginalis	no	172	18 (10.47)	154 (89.53)	X^2=146.69
	yes	61	58(95.08)	3(4.92)	p<0.0001

X^2 (Pearson Chi-square test), ***sig p<0.0001

In newborns delivered by mothers infected with *Gardnerella vaginalis*, the Apgar score at the first minute ranged from 4 to 7, most often with a score of 6 (42.62% of newborns). At the 5th minute, the Apgar score ranged from 5 to 8, most often with a score of 7 (44.26% of newborns) (Table 9).

Table 9. Apgar scores at 1st and 5th minute - Gardnerella vaginalis infection

Apgar score	n	Gardnerella vaginalis 1st minute n (%)	5th minute n (%)
4	5	5(8.2)	0
5	13	8(13.11)	5(8.2)
6	33	26(42.62)	7(11.48)
7	46	22(36.07)	27(44.26)
8	22	0	22(36.07)
9	122	61	61

Discussion

The results of this study support the hypothesis that *Gardnerella vaginalis* infection plays an important role in promoting preterm birth. This finding is consistent with international studies that have shown similar associations between disruption of the vaginal microbiota and increased risk of preterm birth [5].
The biological mechanisms by which *Gardnerella vaginalis* influences preterm birth are multiple. The bacterium secretes proteolytic enzymes that damage cervical mucus and amniotic membranes, reducing their protective capacity. This damage can induce the release of prostaglandins and inflammatory cytokines, such as interleukin-1β and TNF-α, which contribute to the induction of uterine contractions and premature rupture of membranes [2].
Another aspect of clinical importance is the fact that many cases of bacterial vaginosis are asymptomatic, which makes early identification and treatment more difficult. Previous studies have suggested that routine diagnosis of bacterial vaginosis during pregnancy, especially in women with a history of preterm birth, can significantly reduce the incidence of new cases [6]. In line with this, our results suggest that microbiological screening and prompt treatment of *Gardnerella vaginalis* infections should be included in obstetric preventive protocols. However, our study has several limita-

tions. Firstly, the number of cases was limited and the retrospective design did not allow for definitive determination of causality between infection and preterm birth. Secondly, although PCR analysis was included in some cases, complete identification of the vaginal microbiota through sequencing techniques was not performed. Despite these limitations, the results constitute a solid basis for further prospective research with larger samples.

In conclusion, the study emphasizes the importance of maintaining the balance of vaginal flora during pregnancy and the need for a multidisciplinary approach to the prevention of preterm birth. Education of pregnant women on intimate hygiene, regular microbiological screening and timely treatment of bacterial vaginosis are measures that can significantly reduce the burden of preterm birth at the population level.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 169-170

MMP

Case Report

RECONSTRUCTION OF COMPLEX SCALP DEFECT WITH LOCAL FLAP AND SKIN GRAFT

РЕКОНСТРУКЦИЈА НА КОМПЛЕТЕН ДЕФЕКТ НА СКАЛПОТ СО ЛОКАЛЕН ФЛАП И КОЖЕН ГРАФТ

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Abstract

The scalp consists of specialized tissue composed of dense hair follicles and inelastic, thick galea aponeurotica, unlike other tissues of the body. Reconstruction of the scalp can be challenging because of the convexity of the underlying skeleton, the inelasticity of the galea, and the paucity of the adjacent tissue, which make even small defects difficult to close.

The creation of a local flap associated with skin grafting is a surgical procedure performed in a single stage, providing coverage of devitalized areas with viable and well-vascularized tissue.

Keywords: scalp, reconstruction, local flap, skin grafting

Абстракт

Склапот анатомски се разликува со својата градба, кожата е слабо подвижна, нееластична и богата со фоликули на влакна и галеа апонеуротика за разлика од кожата на другите делови од телото. Затоа е посебен предизвик да се направи реконструкција на дефект на поглавината.

Реконструкција со локален резен и комбинација со трансплантација на кожа за секундарниот дефект во еден хируршки акт дава многу добри резултати за покривање на девитализирани и длабоки дефекти.

Клучни зборови: скалп, реконструкција, локален резен, трансплантација на кожа.

Introduction

The scalp consists of specialized tissue composed of dense hair follicles and inelastic, thick galea aponeurotica, unlike other tissues of the body [1]. Reconstruction of the scalp can be challenging because of the convexity of the underlying skeleton, the inelasticity of the galea, and the paucity of the adjacent tissue, which make even small defects difficult to close [2-4].

Different reconstruction methods have been described, such as external table drilling, skin grafts, local scalp flaps, pedicled flaps, microsurgical flaps and reimplantation.

The creation of a local flap associated with skin grafting is a surgical procedure performed in a single stage, providing coverage of devitalized areas with viable and well-vascularized tissue [5].

Case report

A 56-year-old male patient had a car accident. He came to the hospital with a complex scalp defect (Figure 1), fracture of C6 vertebrae and cerebral commotion.

Because the wound was infected and *Acinetobacter baumannii* was isolated during the first surgery, debridement was performed (Figure 2). After having 3 sterile results from the wound, reconstructive surgery was performed.

A scalp transposition flap based on the occipital artery was used for bone coverage and split-thickness skin graft (STSG) from the upper leg was performed in the donor area of the flap (Figure 3), which remained with intact periosteum. A Brown dressing was maintained on the grafted area for 5 days.

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Fig. 1. After the accident

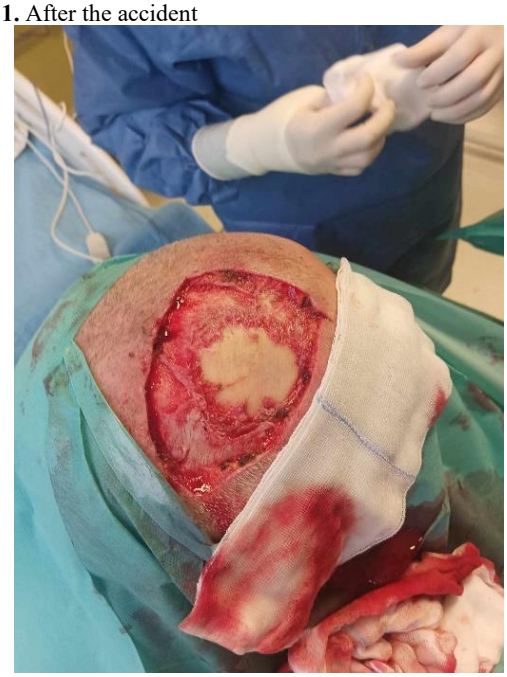

Fig. 2. After first surgery debridement

Fig. 3. Intraoperative period with flap and skin grafting

Fig. 4. Three months after surgical treatment

Outpatient follow-up was conducted every two weeks, demonstrating absolute viability of the flap and the skin graft 3 months after surgical treatment (Figure 4).

Conclusion

Reconstructing extensive scalp defects requires planning and consideration of multiple factors, including the size and location of the defect, number of anatomical structures involved, availability of donor tissue, quality of the surrounding skin, vascularization of the recipient area, infection, need for adjuvant therapies, and patient comorbidities. These defects present a therapeutic challenge for the reconstructive surgeon because of the need to provide a significant amount of coverage to an area with limited adjacent tissue, and in several cases, because of the etiology of the injury, with a poorly vascularized recipient bed due to involvement of the periosteum, bone, and/or dura mater.

The scalp flap technique, combined with skin grafting from the donor area of the flap, has proven to be a safe technique. This is not possible when direct grafting is used, which requires the integrity of the periosteum for success. On the contrary, techniques such as healing by secondary intention results in a longer recovery period.

Conflict of interests: None declared.

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Мак Мед Преглед 2024; 78(3): 171-176

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Case report

LEG PAIN OR LIMB THREAT ANKLE-BRACHIAL INDEX AS A GATEWAY TO PERIPHERAL ARTERIAL DISEASE DETECTION

БОЛКА ВО НОГАТА ИЛИ ЗАКАНА ЗА ЗАГУБА НА ЕКСТРЕМИТЕТ, ГЛУЖДНО-НАДЛАКТЕН ИНДЕКС КАКО ПРИОД КОН ДЕТЕКЦИЈА НА ПЕРИФЕРНА АТЕРИСКА БОЛЕСТ

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Abstract

Introduction. Peripheral arterial disease (PAD) remains an underrecognized yet clinically significant condition in patients with type 2 diabetes mellitus (T2DM), particularly when presenting with subtle symptoms such as exertional leg pain.

Aim. The aim of this case report was to highlight the importance of early recognition and evaluation of PAD in patients with T2DM presenting with exertional leg pain in the general practice setting. By illustrating the diagnostic utility of the ankle-brachial index (ABI) and the role of primary healthcare in initiating timely management and specialist referral, this report emphasizes the value of proactive screening and multidisciplinary coordination in preventing progression to limb-threatening ischemia.

Case presentation. A 68-year-old female, smoker, with a five-year history of T2DM, hypertension, and hyperlipidemia, presented during a routine primary care visit with complaints of right calf pain, described as cramping, relieved by rest and magnesium supplementation recommended by a pharmacist. Physical examination revealed diminished distal arterial pulses and delayed capillary refill in the right foot with neither trophic skin changes nor neurological deficits. ABI measurements demonstrated moderate PAD on the right (0.62) and borderline normal values on the left (0.90). Duplex ultrasonography confirmed complete occlusion of the proximal segment of the right superficial femoral artery. Management included initiation of antiplatelet therapy, low-dose rivaroxaban and adding ezetimibe to ongoing high-intensity statin therapy. Referral for multislice computed tomography angiography (MSCTA), glycemic control optimization, smoking cessation and supervised exercise therapy were also recommended.

Conclusion. This case underscores the importance of PAD screening in general medical practice, particularly among diabetic patients and highlights the role of primary healthcare in early detection, risk stratification, and coordination of multidisciplinary management to prevent progression to limb-threatening ischemia.

Keywords: PAD, ABI, intermittent claudication, limb-threatening ischemia, primary healthcare

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Апстракт

Вовед. Периферната артериска болест (ПАБ) останува недоволно препознаена, но клинички значајна состојба кај пациенти со дијабетес мелитус тип 2 (ДМТ2), особено кога се манифестира со суптилни симптоми како болка во нозете при физички напор.

Цел. Целта на овој приказ на случај е да се истакне значењето на раната идентификација и проценка на ПАБ кај пациенти со ДМТ2 кои се жалат на болка во нозете при физички напор во амбуланта по општа медицинска пракса. Преку илустрација на дијагностичката вредност на глуждно-надлактниот индекс (ankle-brachial index, ABI) и улогата на примарната здравствена заштита во навремено започнување на терапија и упатување кај специјалист, овој извештај го нагласува значењето на проактивниот скрининг и мултидисциплинарната координација во превенција на прогресијата кон загрозувачка исхемија на екстремитетот.

Презентација на случај. Станува збор за 68-годишна пациентка, пушач, со петгодишна историја на ДМТ2, хипертензија и хиперлипидемија која се јави на рутински преглед во примарна здравствена

установа со жалби на болка во десниот лист, опишана како грчење која се намалува при одмор и по земање магнезиум, а препорачан од фармацевт. При физичкиот преглед беа забележани ослабени дистални артериски пулсации и забавено капиларно полнење на десното стапало, без трофични промени на кожата или невролошки дефицити. Измереният ABI покажа умерена ПАБ на десната страна (0.62) и гранично нормални вредности на левата страна (0.90). Дуплекс ултразвукот потврди целосна оклузија на проксималниот сегмент од десната површна феморална артерија. Во третманот беше вклучено започнување антитромбоцитна терапија, ниска доза ривароксабан и додавање езетимиб кон веќе постоечкатата терапија со високодозен статин. Дополнително беа препорачани мултислајс КТ ангиографија (MSCTA), оптимизација на гликемиската контрола, прекин со пушење цигари и надгледувана терапија со вежби.

Заклучок. Овој случај го нагласува значењето на скринингот за ПАБ во општата медицинска пракса, особено кај пациенти со дијабетес и ја истакнува улогата на примарната здравствена заштита во раната детекција, проценката на ризикот и координацијата на мултидисциплинарниот пристап со цел превенција на прогресија кон исхемија што го загрозува екстремитетот.

Клучни зборови: периферна артериска болест, глуждно-надлактен индекс, исхемија што го загрозува екстремитетот, примарна здравствена заштита

Introduction

Lower extremity pain is a frequent complaint in general medicine practice, often attributed to musculoskeletal or neuropathic causes. However, in patients with cardiovascular risk factors such as diabetes, hypertension, and hyperlipidemia, clinicians must maintain a high index of suspicion for peripheral arterial disease (PAD) (Figure 1). Clinical presentation of PAD can be categorized into four subsets: asymptomatic PAD, chronic symptomatic PAD, chronic limb-threatening ischemia (CLTI), and acute limb ischemia (ALI) (Figure 2). Patients with PAD may develop different symptoms over time and may move into and out of different subsets during their disease development, such as deterioration of chronic symptomatic PAD to CLTI or ALI or improvement of symptoms after treatment [1].

Although all patients with PAD are at increased risk of major adverse cardiovascular events (MACE) and major adverse limb events (MALE), diabetes is a well-established risk factor escalating the risk for further development of PAD, including CLTI and risk of amputation. Diabetic patients are particularly vulnerable due to accelerated atherosclerosis and impaired collateral circulation. Estimates are that 75% of diabetics with PAD are asymptomatic. When symptoms are present, they are most commonly claudication or rest pain. Diabetes mellitus is present in around 30% of patients with claudication and 50% of patients with critical limb ischemia (CLI).

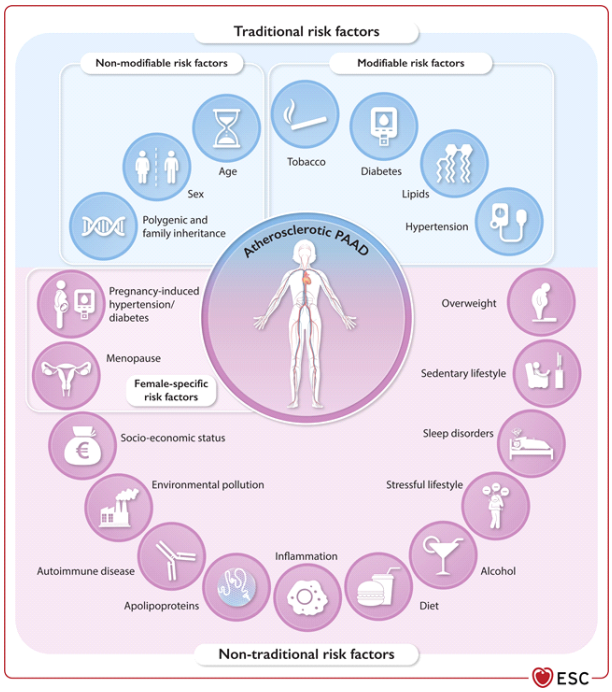

Fig. 1. Main risk factors associated with atherosclerosis in peripheral arterial and aortic diseases
ESC Scientific Document Group, 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases

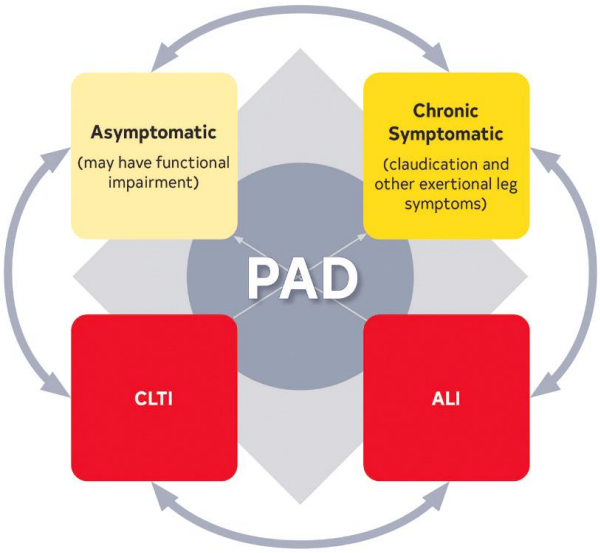

Fig. 2. Clinical subsets of PAD
Legend: PAD - peripheral artery disease, ALI - acute limb ischemia; CLTI - chronic limb-threatening ischemia.
2024 AHA/ACC Guideline for the management of lower extremity peripheral artery disease: Executive summary. Journal of the American College of Cardiology.

Moreover, individuals with DM and PAD are at a higher risk for infra-popliteal or tibial vessel disease and calcification with sparse collaterals than non-diabetics [1]. PAD in diabetics also manifests earlier and progresses more rapidly to CLI. Rest pain and claudication can go unrecognized in diabetics due to co-existing sensory neuropathy. Amputation rates are high in diabetics due to associated recurrent ulcers, comorbidities and target organ damage [2].

Given the high prevalence of asymptomatic PAD in diabetic patients and their predisposition to distal vessel involvement, proactive vascular assessment is essential to prevent progression to limb-threatening stages [3]. This case illustrates the diagnostic value of ankle-brachial index (ABI), and the role of general practitioners in early detection, risk stratification, and coordination of care for patients with limb-threatening vascular disease.

Case presentation

A 68-year-old female, current smoker, with a history of T2DM, hypertension, and hyperlipidemia presented for routine check-up. T2DM was diagnosed five years ago, when she was placed on oral antidiabetic therapy with Metformin 1000 mg twice daily. When she came to our institution, her HbA1c was 8.3%, LDL-c was 3.7 mmol/L, BMI 31.2kg/m², and blood pressure 115/70 mmHg.

On examination, diminished right *dorsalis pedis* and posterior tibial pulses were noted, along with delayed capillary refill on the right foot. Neither trophic skin changes nor neurological deficit was present. The patient reported cramping pain in the right calf after prolonged walking, relieved by rest and magnesium supplementation advised by a pharmacist. Neither rest pain nor skin discoloration/ulcers were observed.

ABI was measured using the oscillometric method with a digital automatic blood pressure device (Omron HBP-1100), with the patient in a supine position following a 15-minute rest period [4,5]. Systolic pressures

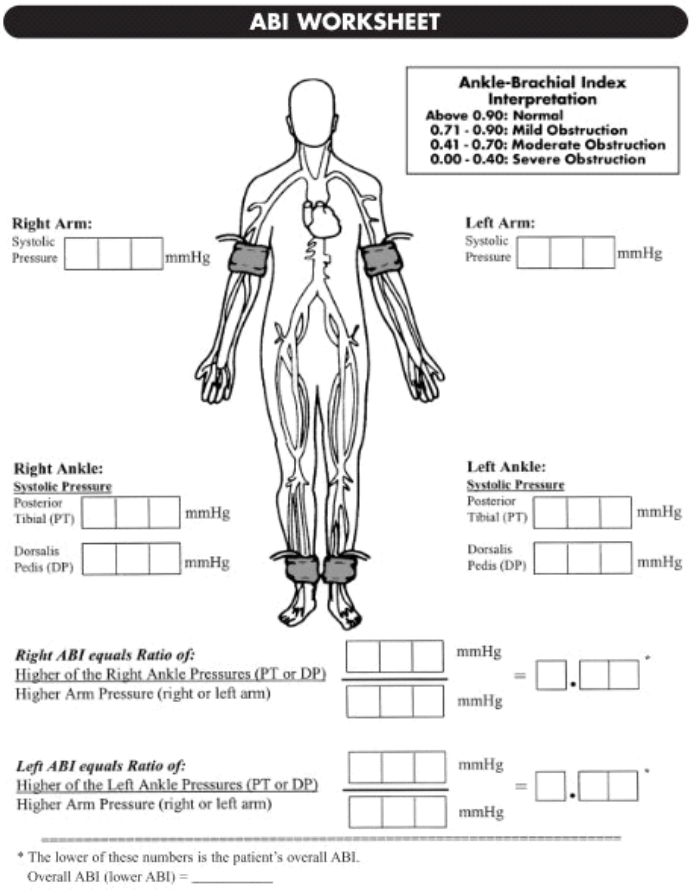

Fig. 3. Ankle-brachial index worksheet
Source: Yumpu, ABI Worksheet.
https://www.yumpu.com/en/document/view/12299485/abi-worksheet

were recorded at the brachial artery and both *dorsalis pedis* and posterior tibial arteries. ABI was calculated as the ratio of the highest ankle systolic pressure to the highest brachial systolic pressure. The right ABI was 0.62, indicating moderate PAD, while the left ABI was 0.90, considered borderline normal (Figure 3).

A treatment was started with acetylsalicylic acid (ASA) 100 mg daily and she was referred for duplex

ultrasound, which confirmed moderate PAD of the right lower extremity. Findings included complete occlusion of the upper third of the right superficial femoral artery and a monophasic signal in the remaining proximal segment to the common femoral artery, consistent with intermittent claudication in the context of diabetes.

Cardiology and vascular surgery consultations were obtained to facilitate further vascular assessment via scheduled MSCTA. Her therapy regimen was augmented with low-dose rivaroxaban (2.5 mg twice daily) taking into account the bleeding risk, and intensification of ongoing high-intensity statin therapy by adding ezetimibe (10 mg once daily); glycemic control optimization, smoking cessation, and supervised exercise therapy were also recommended.

Dual pathway inhibition (DPI) consisting of once-daily low-dose ASA and twice-daily rivaroxaban 2.5 mg has been shown to significantly reduce the incidence of MALE, including acute limb ischemia and amputation, as well as major cardiovascular events such as myocardial infarction, stroke, and cardiovascular death. These findings have been supported by robust evidence from the COMPASS and VOYAGER PAD trials which underscore the efficacy of DPI in patients with symptomatic peripheral artery disease [6,7].

For patients with PAD already receiving high-intensity statin therapy (e.g., atorvastatin 40-80 mg or rosuvastatin 20-40 mg), the addition of ezetimibe 10 mg daily is a guideline-supported strategy to further reduce LDL-c and lower the risk of both MACE and MALE. Both the 2024 European Society of Cardiology (ESC) and the 2024 American College of Cardiology/American Heart Association (ACC/AHA) guidelines emphasize lipid-lowering therapy as a Class I recommendation, with statins as first-line agents and ezetimibe as an adjunct when LDL-c targets are not achieved [1,8]. Sustained adherence to lipid-lowering therapy is essential for achieving target LDL-c levels and maximizing long-term cardiovascular and limb-related outcomes. This reinforces the need for patient education, regular follow-up, and multidisciplinary support [9].

Glycemic control optimization was pursued through the addition of a second glucose-lowering agent with established cardiovascular benefit. A glucagon-like peptide-1 (GLP-1) receptor agonist, specifically semaglutide, was selected based on its demonstrated efficacy in reducing MACE and promoting weight loss in patients with T2DM. This therapeutic choice aligns with current guideline recommendations for individuals with coexisting PAD and suboptimal glycemic control [10].

Smoking is a major modifiable risk factor in PAD, strongly associated with limb loss and systemic vascular complications. Smoking cessation remains a primary strategy of PAD management, shown to improve claudication symptoms, reduce the need for revascularization, and lower long-term pharmacologic burden. Both the 2024 AHA/ACC and ESC guidelines emphasize lifestyle modification, particularly smoking cessation as a foundational strategy to prevent disease progression and reduce cardiovascular risk. They endorse a Class I recommendation for structured cessation counseling and pharmacotherapy, including nicotine replacement therapy, bupropion, and varenicline, with a multimodal approach led by primary care and vascular teams [1,8].

Supervised exercise therapy (SET) is a cornerstone non-invasive intervention for patients with PAD, particularly those with intermittent claudication. Endorsed as first-line therapy by both the AHA and ACC, SET improves walking performance, functional capacity, and quality of life. It significantly increases claudication onset time and peak walking distance, often outperforming pharmacologic agents such as cilostazol. Regular treadmill-based training enhances muscle metabolism, aerobic efficiency, and pain tolerance, while also reducing systemic inflammation and cardiovascular risk through favorable effects on endothelial function, lipid profile, and blood pressure [11].

Discussion

PAD remains a frequently overlooked and underdiagnosed condition in general practice due to its subtle presentation, overlap with other nonspecific leg pain misattributed to musculoskeletal or neuropathic causes. In diabetic patients, the challenge is compounded by atypical presentations and coexisting sensory neuropathy which can obscure hallmark symptoms like claudication or rest pain. Yet, the stakes are high: diabetes accelerates atherosclerosis and impairs wound healing, dramatically increasing the risk of progression to CLI, ulceration, and eventual amputation.

ABI is a simple, cost-effective diagnostic tool that can and should be routinely performed in primary healthcare, especially in patients with cardiovascular risk factors. Although simple to perform, ABI is a powerful initial diagnostic tool that can uncover PAD before it leads to irreversible complications like ulceration or limb loss.

While doppler-based ABI remains the gold standard for diagnosing PAD due to its superior accuracy and reproducibility, oscillometric ABI offers a practical alternative in primary healthcare settings. Oscillometric devices are easier to use, require less training, and allow faster screening, making them ideal for routine evaluations. However, they may underestimate or overestimate ABI values, especially in patients with arterial calcification or low perfusion, leading to potential misclassification [12].

General practitioners are uniquely positioned and play a pivotal role in early interception of PAD. Their responsibilities extend beyond initial recognition; they serve as frontline agents in risk factor modification,

optimizing glycemic control, lipid management, and smoking cessation, initiating evidence-based therapy, and coordinating multidisciplinary care. Timely referral to vascular specialists is essential to prevent limb-threatening complications. Both the 2016 and 2024 AHA/ACC guidelines reinforce this approach, emphasizing the importance of collaboration among primary healthcare providers, vascular specialists, and rehabilitation teams. Such a coordinated model is critical for optimizing clinical outcomes, particularly in preventing limb loss and reducing cardiovascular morbidity and mortality [1,13].

This case underscores the transformative potential of proactive primary healthcare approach. Timely ABI screening, clinical vigilance, and early therapeutic intervention can shift the trajectory of PAD from silent progression to strategic prevention, ultimately reducing long-term morbidity and preserving limb function.

Conclusion

In general practice, leg pain, particularly in patients with diabetes and other cardiovascular risk factors should prompt careful evaluation for vascular causes. The ABI remains a critical diagnostic tool for identifying PAD, enabling timely referral and targeted management. This case emphasizes the importance of early recognition, conservative treatment, and aggressive risk factor modification supported by a multidisciplinary care model that enhances patient's outcomes and preserves limb function.

Routine ABI screening and early intervention are essential to prevent progression to limb-threatening stages such as critical limb ischemia, ulceration and amputation. General practitioners, uniquely positioned at the frontline of healthcare, must maintain a high index of suspicion for PAD in diabetic patients presenting with exertional leg pain. By incorporating ABI into routine evaluations, initiating guideline-based therapy, and coordinating multidisciplinary care, they can significantly alter the disease trajectory.

Despite their central role in PAD detection, many primary healthcare clinicians face educational gaps and low diagnostic confidence, which hinder early recognition. As highlighted in recent research, targeted and practical education, especially in the context of multimorbidity is essential to empower frontline clinicians and improve PAD outcomes [14].

In alignment with the AHA 2022, PAD National Action Plan, strengthening the role of primary healthcare is imperative to address the systemic underdiagnosis and undertreatment of PAD. By equipping general practitioners with targeted education, practical diagnostic tools such as the ABI, and clear referral pathways, healthcare systems can facilitate earlier detection and intervention. This approach not only mitigates progression to CLI and amputation but also addresses disparities in PAD outcomes, particularly among high-risk and underserved populations. A coordinated, multidisciplinary model anchored in primary healthcare remains essential for optimizing vascular health, preserving limb function, and reducing cardiovascular morbidity and mortality [15].

Conflict of interests: None declared.

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MMP

Case report

INCIDENTAL STUMP DURING CESAREAN SECTION IN IVFEGG DONATION PREGNANCY: A CASE EMPHASIZING THE IMPERATIVE OF ROUTINE HISTOPATHOLOGICAL EVALUATION OF MYOMAS

ИНЦИДЕНЕНТАЛЕН STUMP ЗА ВРЕМЕ НА ЦАРСКИ РЕЗ ВО БРЕМЕНОСТ СО ДОНАЦИЈА НА ЈАЈЦЕ-КЛЕТКА ПО ИВФ: СЛУЧАЈ ШТО ЈА ПОТЕНЦИРА ПОТРЕБАТА ОД РУТИНСКА ХИСТОПАТОЛОШКА ЕВАЛУАЦИЈА НА МИОМИТЕ

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Abstract

Uterine myomas are commonly benign tumors of the female reproductive system. Although many are diagnosed preoperatively, some are incidentally discovered during obstetric surgery, such as the cesarean section. This case illustrates the necessity of routinely sending any excised uterine myoma for histopathological evaluation to determine its true biological potential and guide further management.

We report the case of a 45-year-old primiparous woman (G1P0A1) with a history of *in vitro* fertilization (IVF) and egg donation, admitted at 37+4 weeks of gestation for elective cesarean section. The procedure was uncomplicated, yet multiple small intramural and subserous myomas were incidentally observed and excised. Histopathological analysis revealed a Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP), characterized by areas of focal necrosis, mild cytologic atypia, and low mitotic activity-features straddling benign leiomyoma and malignant leiomyosarcoma designations.

STUMP comprises a rare histologic category representing 0.3-0.9% of presumed fibroids, with unpredictable behavior. Recurrence rates vary from 7% to 36%, with occasional progression to leiomyosarcoma (median time to recurrence ~79 months) [1-5]. Because of this uncertain prognosis, we recommended followup imaging and multidisciplinary consultation. A postoperative MRI followed by hysterectomy revealed additional subserous leiomyomas and chronic granulomatous inflammation. Given the potential risk of progression, the patient underwent definitive hysterectomy with ovarian preservation.

This case highlights the crucial role of histopathological evaluation in incidental uterine myomas. Even small lesions may harbor atypical or borderline features warranting close monitoring or definitive treatment. Early detection and accurate classification influence patient prognosis and enable timely surgical and therapeutic interventions. When STUMP is diagnosed, hysterectomy is often recommended as definitive management to reduce recurrence or malignant transformation risk.

Keywords: uterine myoma, STUMP, histopathology, leiomyoma, leiomyosarcoma, incidental tumor, cesarean section, egg donation pregnancy

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Апстракт

Утериниte миоми се најчесто бенигни тумори на женскиот репродуктивен систем. Иако многу од нив се дијагностицираат предоперативно, некои се откриваат инцидентно за време на акушерски операции, како што е царскиот рез. Овој случај ја илустрира неопходноста секој ексцидиран утерин миом рутински да се испрати на хистопатолошка евалуација за да се утврди неговиот вистински биолошки потенцијал и да се води понатамошното менацирање.

Прикажуваме случај на 45-годишна примипарна жена (G1P0A1) со историја на ин витро фертилизација (ИВФ) и донација на јајце-клетка, хоспитализирана на 37+4 недели гестација за елективен царски рез. Постапката помина без компликации, но беа инцидентно забележани и ексцидирани повеќе мали интрамурални и субсерозни миоми. Хистопатолошката анализа откри тумор на мазни мускули со неизвесен малиген потенцијал (STUMP), карактеризиран со подрачја на фокална некроза, лесна цитолошка атипија и ниска митотска активност-

карактеристики што ја премостуваат границата помеѓу бенигниот леомиом и малигниот леимиосарком. STUMP претставува ретка хистолошка категорија која сочинува 0,3-0,9% од претпоставените фиброиди и има непредвидливо однесување. Стапките на рецидив варираат од 7% до 36%, со повремена прогресија во леимиосарком (медијана на време до рецидив околу 79 месеци) [1-5]. Поради оваа неизвесна прогноза, препорачавме следење со сликовни испитувања и мултидисциплинарна консултација. Постоперативната магнетна резонанца, проследена со хистеректомија, откри дополнителни субсерозни леомиоми и хронично грануломатозно воспаление. Со оглед на потенцијалниот ризик од прогресија, пациентката беше подложена на дефинитивна хистеректомија со зачувување на јајниците.
Овој случај ја нагласува клучната улога на хистопатолошката евалуација при инцидентно откриени утерини миоми. Дури и мали лезии можат да содржат атипични или гранични карактеристики кои бараат внимателно следење или дефинитивен третман. Раното откривање и точната класификација влијаат на прогнозата на пациентката и овозможуваат навремени хируршки и терапевтски интервенции. Кога ќе се дијагностицира STUMP, хистеректомијата често се препорачува како дефинитивен третман со цел намалување на ризикот од рецидив или малигна трансформација.

Клучни зборови: утерин миом, STUMP, хистопатологија, леомиом, леимиосарком;, инцидентен тумор, царски рез, бременост со донација на јајце-клетка.

Introduction

Uterine leiomyomas affect up to 70-80% of women by menopause and are the most frequent benign gynecologic tumors worldwide [6]. In rare cases (0.3-0.9% of presumed fibroids), histological review reveals variants such as STUMP-tumors with features intermediate between benign leiomyoma and malignant leiomyosarcoma [4,5]. The Bell criteria-cytologic atypia, mitotic count, and tumor cell necrosis-are used to distinguish between these entities [7]. Diagnosis is typically postoperative, as no reliable imaging modality definitively differentiates STUMP preoperatively [8,9]. Management protocols are not standardized due to rarity and heterogeneity; recurrence rates reported vary from 7% to 36%, occasionally with transformation into leiomyosarcoma [1-3,5].

Case Presentation

A 45 year old woman (G1P0A1) with secondary infertility and eight failed IVF cycles underwent successful pregnancy via IVF with egg donation. She was admitted at 37+4 weeks for elective cesarean delivery on June 24, 2024. During surgery, multiple small uterine myomas (largest ~3.5 cm) were incidentally located on the anterior and fundal aspects of the uterus. Nodules were excised en bloc and sent for histopathological evaluation per institutional protocol.

Histopathological findings:

- Smooth muscle tumor with focal tumor cell necrosis and mild to moderate nuclear atypia,
- Mitotic index: 3-4/10 high-power fields,
- Ki67 proliferation index: 5-7%,
- Immunohistochemistry: HMB45 negative, estrogen and progesterone receptor positive.

The combination of features met criteria for STUMP [7,8].

Postoperative imaging and management:
A contrast-enhanced pelvic MRI and CT scan revealed no extrauterine disease, but multiple additional subserous and intramural leiomyomas were noted. In light of the STUMP diagnosis, the uncertain natural history, and the patient's reproductive completion, a total abdominal hysterectomy with bilateral salpingooophorectomy (preserving ovaries) was performed. Final pathology demonstrated residual benign leiomyomas and chronic granulomatous inflammation without residual STUMP or malignancy.

Follow-up:
Eighteen months postoperatively, the patient remains disease-free, with no radiologic or clinical signs of recurrence.

Discussion

Prevalence and Natural History
STUMP accounts for approximately 0.3–0.9% of presumed leiomyomas [5]. The mean age at diagnosis is around 43-45 years [8], which was the case with our patient. Clinical presentation overlaps with that of benign fibroids-pelvic pain, bleeding, or incidental findings [8,9].

Imaging Limitations
Ultrasound and MRI lack sufficient specificity to differentiate STUMP from benign leiomyomas; heterogeneous echotexture, irregular margins, and cystic degeneration may be present, but are non-diagnostic [9,10]. In most series, >80% of STUMP lesions exceed 5 cm, while in our patient they were incidentally small (~3-4 cm), reinforcing that size alone is not predictive [8,11].

Histopathologic Diagnosis and Prognostic Markers

Diagnosis hinges on Bell's criteria:

- Coagulative necrosis
- Cytologic atypia
- Mitotic index

STUMP exhibits one or two positive features without fulfilling leiomyosarcoma criteria [7]. Prognostic markers affecting recurrence include high mitotic count, Ki67 > 20%, diffuse p16 expression, and epithelioid morphology [1]. Avoidance of unprotected morcellation is also critical, as it independently increases recurrence risk and reduces recurrencefree survival [1,12].

Recurrence Risk and FollowUp Strategy

Published recurrence rates range from 7% to 36%, with median time to recurrence around 79 months [1-3]. Some recurrences manifest as leiomyosarcoma, with potential metastases to lung, pelvis, or bone [1,3,13]. Surveillance protocols generally include pelvic exams and imaging (ultrasound or MRI) every 6 months for 2-3 years, then annually for at least 5-10 years [2,9].

Management Considerations

Hysterectomy is recommended for patients with completed fertility and STUMP diagnosis to minimize recurrence risk [2,3]. Fertilitypreserving management may be pursued under close surveillance in younger patients desiring childbearing [10,11], but patients should be counseled extensively on recurrence risk and the potential need for further surgery.

Table 1. Key Characteristics and Prognostic Data for STUMP

Feature	Published Data	Case Details
Incidence among presumed leiomyomas	0.3-0.9% [5]	Multiple small myomas (~3.5 cm)
Mean diagnostic age	43-45 years [8]	Patient age 45
Median tumor size	~7.5 cm (range 0.7-39 cm) [11]	Largest ~3.5 cm
Recurrence rate	7–36% (median recurrence at ~79 mo) [1,3]	None at 18 mo followup
Histologic risk factors for recurrence	High mitoses, Ki67 >20%, p16+, epithelioid, morcellation [1]	Low mitoses (4/10 HPF), Ki67 = 7%, no morcellation used
Common recurrence sites	Pelvis, lung, abdomen, bone [3,13]	No recurrence

Conclusion

This case demonstrates that even incidental, small uterine myomas encountered during cesarean section can harbor STUMP pathology. Given the unpredictable nature of STUMP, including substantial recurrence risk and rare malignant transformation, it is essential that all excised uterine tissues be submitted for histopathological analysis. Treatment should be tailored according to fertility desires and pathological risk factors; hysterectomy remains the definitive option in patients who have completed childbearing. Close long-term followup including periodic imaging is prudent. Adoption of routine histopathology submission protocols in obstetric practice can significantly improve early detection and patient outcomes.

Conflict of interests: None declared.

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Case report

SINUSITIS TREATMENT IN PREGNANCY- PERSONALISED AND INTEGRATED MEDICINE

ТРЕТМАН НА СИНУЗИТИС ВО БРЕМЕНОСТ – ПЕРСОНАЛИЗИРАНА И ИНТЕГРИРАНА МЕДИЦНА

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Abstract

Introduction. Sinusitis in pregnant patients is a disorder with incidence of around 3-4% worldwide, dependent from the impaired immune system. Long lasting symptoms are sometimes accompanied with nasal polyposis that is aggravated due to pregnancy hormones. The chronic condition has its relapses, with inflammatory or noninflamatory causes. Systematic analysis, diagnostic evaluations, treatment options must be personalized and dependent of the pregnancy trimester for a favorable pregnancy outcome with the help of integrated medicine.

Methods. We present a pregnant patient in the second trimester of her third pregnancy. The symptoms that occurred in the 17.5 week of gestational age included headache, high body temperature, fatigue, muscle cramps, loss of appetite, nasal congestion and discharge. After clinical examinations of microbiological samples, nasal endoscopy, mechanical vacuum suction, chronic sinusitis aggravated by nasal polyposis with propagation from maxillary sinus was diagnosed. The treatment according to antibiogram and FDA approval for the trimester included local topic treatment with diluted cephalosporins, corticosteroids (fluticasone propionate), inhalations, antibiotics, probiotics and vitamins per os.

Results and Discussion. Improvement of the subjective and objective symptomatology of the patient occurred after 5 weeks of treatment. Relapse occurred in the third trimester and two months postpartum. Immunopathohistologically, there is an antagonism of IgE, of interleukin IL-4, IL-5 and IL-13. The increase of IL-17 is proven for frequent exacerbations. Long lasting symptoms are sometimes accompanied with nasal polyposis that is aggravated due to pregnancy hormones.

Conclusion. The immune system in pregnancy changes, with exaggerated inflammatory reaction inadequate to recover from sinusitis for a shorter period of time. Therefore, detailed examination and adequate therapy is obligatory as soon as the diagnosis is settled. All corticosteroids are not allowed in the second trimester due to proven unfavorable outcome for the fetus. Mechanical treatments and topic antibiotics were main therapeutic solution. Modern medicine aims to combine genetics and detection of the phenotype for chronic type of inflammation and the type of the immune response in order to stratify patients for appropriate treatment.

Keywords: sinusitis, pregnancy induced, treatment, outcome

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Апстракт

Вовед. Синуситот кај бремените пациентки е заболување со инциденца од околу 3-4% на глобално ниво, поврзано со ослабениот имунолошки систем. Долготрајните симптоми понекогаш се придружени со носни полипози, кои се влошуваат поради хормоналните промени во бременоста.

Хроничната состојба има рецидиви, предизвикани од воспалителни или невоспалителни причини. Систематската анализа, дијагностичките процедури и тераписките опции мора да бидат персонализирани и да зависат од триместарот на бременоста, со цел да се обезбеди поволен исход на бременоста преку интегрирана медицина.

Методи. Прикажана е бремена пациентка во вториот триместар од нејзината трета бременост. Симптомите кои се појавиле во 17.5-тата гестациска недела вклучуваа главоболка, повисока телесна температура, замор, мускулни грчеви, губење на

апетит, носна опструкција и секреција. По клинички прегледи и микробиолошки испитувања, носна ендоскопија и механичко вакуумско чистење, дијагностициран е хроничен синусит, комплициран со носни полипози кои се проширile од максиларниот синус. Третманот, според антибиограмот и FDA препораките за овој триместар, вклучуваше локална терапија со разредени цефалоспорини, кортикостероиди (флутиказон пропионат), инхалации, антибиотици, пробиотици и витамини per os.
Резултати и дискусија. Подобрување на субјективната и објективната симптоматологија кај пациентката се случи по 5 недели терапија. Сепак, дојде до рецидив во третиот триместар и два месеци по породувањето. Имунопатолошките испитувања покажаа антагонизам на IgE, интерлеукините IL-4, IL-5 и IL-13, додека покачувањето на IL-17 е потврдено како фактор за чести егзацербации. Долготрајните симптоми понекогаш се придружени со носни полипози, кои се влошуваат поради хормоните од бременоста.
Заклучок. Имунолошкиот систем кај бремените жени се менува, што доведува до претерана воспалителна реакција и отежнато закрепнување од синусит во пократко време. Затоа, детален преглед и адекватна терапија се неопходни веднаш по поставувањето на дијагнозата. Сите кортикостероиди се забранети во вториот триместар поради нивниот негативен ефект врз фетусот. Механичките третмани и локалните антибиотици беа главните терапевтски решенија. Современата медицина се стреми кон комбинација на генетски испитувања и фенотипска детекција за хроничниот тип на воспаление и одговорот на имунолошкиот систем, со цел подобро да се насочи терапијата.

Клучни зборови: синусит, бременост, третман, исход

Introduction

The qualitative pathohistological evaluation of chronically inflamed sinus mucosa performed in our study indicated the existence of two different divergent pathohistological types: polypoid mucosal eosinophilia and glandular hyperplasia. The pathogenetic mechanism in the first entity, polypoid mucosa with eosinophilia, is associated with severe edema that causes obstruction of the narrow areas of the ostiomeatal complex, i.e. mechanical blockage of the natural sinus openings. Due to the chronic mucosal inflammation, the paranasal mucosal outgrowths forming nasal polyps. On the other hand, the released toxic substances eosinophil cationic protein (ECP) and major basic protein (MBP) cause damage to the epithelium of the sinus mucosa and thus suppression of ciliary activity. In the second type, glandular hyperplasia, the continuous increased secretion and production of mucus originating from hypertrophic and hyperplastically altered submucosal glands leads to obstruction of the paranasal openings.
Based on the inflammatory response, four main pathohistological types of chronic maxillary rhinosinusitis are distinguished: edematous or hyperplastic, infiltrative, fibrotic, and mixed type. The symptomatology can derive from intracranial problems, parafunctional habits, infections, sinusitis and many more. The secondary headaches need to be diagnosed meticulously since they derive from medical underlying conditions [1].
Group of authors refer that enlarged number of goblet cells are present at chronically inflammated mucosa of the maxillary sinus. Tos and Mogensen claimed that there are six times enlargement of the number and the density of submucosal glandular structures at chronic maxillary rhinosinusitis in comparison with group of patients without inflammation, which is a consequence of hyperplasia and productions of new glandular structures and widening of the glandular acinus elements. Another alert factor medical and dental staff should be trained for is the diagnosis of acute sinusitis. Acute sinusitis occurs six times more frequently in pregnant women and if left untreated many consequences can develop [2,3].
Besides making the pregnant women fell the difficulty breathing this symptom must be taken seriously at this time for the possibilities during pregnancy are limited [4].
Untreated sinusitis in pregnancy disease can lead to rare intracranial complications such as a subdural empyema. This chronic condition has its relapses, with inflammatory or noninflamatory causes. The patients can experience altered neurological status that might last for a different period of time if the patient doesn't take actions like visiting her doctors [5].
The etiology of sinusitis can have besides infectious, allergic factors can have odontogenic origin if the teeth are left untreated. Since the veins do not have valves and since in pregnancy the organism is succeptable to any infectious agents can be easily spread in the cranium or in the mediastinum if the origin is dental [6].
Systematic analysis, diagnostic evaluations, treatment options must be conducted with the help of personalized and integrated medicine dependent of the pregnancy trimester for a favourable pregnancy outcome.

Purpose

The purpose of this paper is to represent a case study of a pregnant patient with sinusitis treatment with the usage of personalised and integrated medicine.

Case report

A 32-year-old female, at the 17.5 weeks gestation

(second trimester) was administered to the University Clinic for Gynaecology and Obstetrics with a severe headache.
For the etiological factors causing the origin of the headache a team of specialist had conducted several medical examinations, such as the patients' gynaecologist, otorhynolaringologist, dentist and neurologist.
The patients was examined at the PHI University Clinic "St. Panteleimon" where at the examination it was proved that she does not have odontogenic infections.
The patients' major complaints adjacent to the headache were: loss of smell, nasal obstruction, thick yellow discharge, sinus pressure and difference in the brain functioning.
In the medical history of the patient there weren't found previous such complaints nor infections of her sinuses at that level. As from the severity of the pain the patient experiences a scale of pain in 4 points (none=0, mild=1, severe=2, intense=3) the patient has stated that her severity of pain felt in the frontal region of the head is very intense.
Diagnosis was pointed towards taking intravenous blood samples for detection of infectious agents. Leucotitosis, elevated neutropheles and eosinophils and CRP (resulted 86), and nasal and pharyngeal microbiological samples confirmed presence of Streptococcus pneumoniae.
Next the patient was administered to the University Clinic of Otorhinolaryngology where with the usage of flexible transnasal camera examination was conducted. The endoscopic evaluation discovered grapelike polipoid changes with dimension of 4 cm in the anterior and medium level parts of the maxillary sinus with airway obstruction of the osteoneasal complex. Immunopathohistologically analysis of the of IgE, and the increase of IL-17 were conducted in the blood samples of the patients on her controls.
Since Computer Tomography cannot be performed at this stage of pregnancy an Ultrasonographic examination was performed showing shades that prove the transnasal endoscopic evaluation.
After laboratory, clinically and endoscopically examinations have been performed bacterial sinusitis was confirmed for the pregnant patient.
After clinical examinations of microbiological samples, nasal endoscopy, mechanical vacuum suction, chronic sinusitis aggravated by nasal polyposis with propagation from maxillary sinus was diagnosed. The treatment according to antibiogram and FDA approval for the trimester included local topic treatment with diluted cephalosporins, corticosteroids, inhalations, antibiotics, probiotics and vitamins per os.
A treatment followed by local therapy using Cefriaxone 2 grames diluted in saline solution-nasal irrigation was performed twice a day for a period of two weeks. Topical corticosteroids were also used-Budesonide nasal spray (Category B) prescribed 1 spray per nostril twice a day for a period of 5 weeks.
Systemic antibiotic consisted of Cefuroxime of 500mg (FDA category B) twice a day for 21 days.
Improvement of the subjective and objective symptomatology of the patient occurred after 5 weeks of treatment. Relapse occurred in the third trimester and two months postpartum as acute exacerbation of the chronic findings.

Discussion

From the subjective symptomatology of the pregnant patient it was seen that her symptoms showed improvement after 7 days, however the complete resolution of the inflammation was diagnosed after 5 weeks of treatment.
It is of great importance when treating infections in pregnancy to exclude adverse effects on the mother or fetus, which has been proven in the studies of Goldstein G *et al* . [7].
Corticosteroids (e.g., budesonide) are recommended for nasal use in pregnancy due to low systemic bioavailability. Norjavaara E *et al*. state that budesonide is category B in pregnancy and thus it remains an agent for which the preponderance of safety data exists [8].
Studies have shown that oral decongestants may increase the risk of fetal gastroschisis, and also contribute to hypertension in the first trimester [9].
Usage of topical corticosteroids is shown by studies that in the second and third trimester can lead to possible fetal adrenal suppression, but clinically signifycant effects are rare [10].
Some studies show that miscarriage is common and can occur in any pregnancy for many different reasons, but the use of topical corticosteroids is not expected to increase the chance for miscarriage [11].
Briggs G *et al*. have shown that usage for oral antibiotics that do not harm the fetus may be used for acute rhinosinusitis (ARS) or acute exacerbations of chronic rhinosinusitits (CRS). Long-term macrolide or doxycycline use for CRS is not recommended during pregnancy. Penicillin and cephalosporin are the safest classes, and can be given when endoscopic evidence of purulence is present, which is in correspondence with the patient in this case study. Antibiotics that put the fetus at risk such as tetracyclines, aminoglycosides, trimethoprim-sulfamethaxazole and fluoroquinolones should not be used during pregnancy [12].
For nasal polipoids surgery may be considered prior to the pregnancy if they are discovered before the patients get pregnant. Lal D. state that in general, surgery that is not for a life threatening process should be avoided during pregnancy. The authors say that emergency surgery for complicated and acute/chronic sinusitis may be done with close anesthesia supervision. Also office procedures under local anesthesia may represent helpful alternatives in severely symptomatic CRS

pregnant patients, such as polypectomy, indicated balloon sinuplasty, and turbinate surgery under local anesthesia [13].

The patient in this study has her acute sinusitis turn into chronic type. Sinusitis in pregnant patients is a disorder with incidence of around 3-4%, dependent from the impaired immune system.

Immunopathohistologically, there is an antagonism of IgE, of interleukin IL-4, IL-5 and IL-13. The increase of IL-17 is proven for frequent exacerbations. Long lasting symptoms are sometimes accompanied with nasal polyposis that is aggravated due to pregnancy hormones, like the patient in this study [14,15].

Gevaert P. have reported that most patients with chronic rhinosinusitis with nasal polyps have a type 2 inflammatory pattern characterized by eosinophilia and elevated levels of interleukin-4, interleukin-5, and interleukin-13 which is also case in pregnancy proven in our patient laboratorically [16].

Chiarella E *et al*. have reported that the formation of the nasal polyp involves histologically well-identified mechanisms that rupture the mucosal epithelium, the proliferation of fibrous tissue through the damaged epithelium, the accumulation of extracellular matrix (ECM) with oedema and the proliferation of a granular tissue formed by thin-walled vessels and infiltration of inflammatory cells [17].

(For a proper recovery a systematic review of the literature guidelines and medicine evidence based recommendations are necessary). According g to FDA approvals, general recommendations as to which drugs should be avoided during pregnancy and then later on if the patient has sinusitis while breastfeeding.. For this controls to continue many follow ups should be done before, during pregnancy and after giving birth. Pregnant women and women breastfeeding must pay attention as to which drugs they can take topically, intraorally and intravenously [18].

Another chapter of diagnose is when genetics and phenotyping are taken in consideration for distinguishing the ethiology of chronic sinusitis [19,20].

The patient in this study was treated successfully and there weren't found any harmful effects on her baby. The polipose grape like structure in the patients' maxillary sinus two months after giving birth was not present.

Thus the personalized and integrated medicine treats each patient individually according to their etiological, genetical, phenotypical factors providing the best possible care for both the mother and the baby.

Conclusion

The immune system in pregnancy changes, with exaggerated inflammatory reaction inadequate to recover from sinusitis for a shorter period of time. Therefore, detailed examination and adequate therapy is obligetory as soon as the diagnosis has been obtained. All corticosteroids are not allowed in the second trimester due to proven unfavorable outcome for the fetus. Mechanical treatments and topic antibiotics were main therapeutic solution. Modern medicine is personalized and integrated and aims to combine genetics and detection of the phenotype for chronic type of inflammation and the type of the immune response in order to stratify patients for appropriate treatment.

Conflict of interests: None declared.

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УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски Медицински Преглед" (ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.

Списанието ги има следниве рубрики и категории на трудови:
1. Изворни трудови
2. Соопштувања за клинички и лабораториски искуства
3. Прикази на случаи
4. Од практика за практика
5. Едукативни статии
6. Вариа е (писма од редакцијата, општествена хроника, прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката ,,Во сеќавање,, и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови. Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП. Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот(ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет. Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

ТЕКСТ НА РАКОПИСОТ

Сите ракописи се испраќаат во електронска форма на електронската адреса (mld@unet.com.mk ; info@mld.mk) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол. Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. email); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот). Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и соопштувањата го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.
Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.
Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: **вовед** со целта на трудот, **методот, резултати** (со нумерички податоци) и **заклучоци**. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.
Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик.

Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) listata na Index Medicus.
Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).
Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.
Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните SI единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот методи.
Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем. Заклучоците треба да не бидат подолги од 150 зборови.

1. **ПРИЛОЗИ** Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации). Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).
Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата материјал и методи). Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по

смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

2. ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]. Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):

а) статија во списание (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: и сор.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

б) заеднички автор GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) без автор - анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).

г) поглавје во книга или монографија Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

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Адреса на Редакцијата Даме Груев бр. 3 Градски Sид блок II, 1000 Скопје,
Тел: ++ 389 02 3162 577
Електронска адреса (Е-маил): mld@unet.com.mk; ; info@mld.mk

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД – 3162 557.